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Plenary Lectures

Society for Endocrinology International Medal Lecture

PL1

Puberty: what are the neuroendocrine triggers for the biological end of childhood?

Ursula Kaiser
Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

The hypothalamic-pituitary-gonadal (HPG) axis controls puberty and reproduction and is tightly regulated by a complex network of excitatory and inhibitory neuroendocrine factors. Delayed or absent activation of the HPG axis results in delayed puberty or hypogonadotropic hypogonadism, whereas early activation results in central precocious puberty (CPP). In recent years, many genes have been identified in this complex network from genetic studies of human subjects with pubertal disorders, providing insights into the regulation of GnRH secretion and into disorders of reproduction and fertility. These new insights were heralded by the discovery of the kisspeptin system as a critical component for the activation of GnRH secretion, and followed by the discovery of the tachykinin, neurokinin B, and its role in puberty initiation, in turn, through regulation of kisspeptin secretion. More recently, we identified loss-of-function mutations in the maternally imprinted *MKRN3* gene, encoding makorin ring finger protein 3, as an important cause of CPP. *Mkrn3* is expressed at high levels in the mouse hypothalamus prepubertally and decreases prior to puberty onset, suggesting a role as a 'brake' or inhibitor of GnRH secretion and hence of puberty. Studies in cellular and animal models will help to elucidate the mechanisms by which MKRN3 regulates GnRH secretion and provide new insights into reproductive physiology.

DOI: 10.1530/endoabs.59.PL1

Society for Endocrinology Starling Medal Lecture

PL2

Hepatic fatty acid synthesis and partitioning: the effect of metabolic and nutritional state

Leanne Hodson
OCDEM, RDM, University of Oxford, Oxford, UK.

Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome encompasses a spectrum of conditions from hepatic steatosis through to cirrhosis; obesity is a known risk factor. It remains unclear why intrahepatocellular fat starts to accumulate, but it is likely to involve an imbalance between fatty acid delivery to the liver, fatty acid synthesis and oxidation within the liver and triglyceride export from the liver. Studying hepatic metabolism in humans is challenging as direct assessment can only be achieved by arteriovenous difference measurements, which are impractical in humans due to the inaccessibility of the portal vein. By using a combination of models and methodologies, such as *in vitro* cellular models and stable isotope tracers, there is the potential to gain insight into intra-hepatocellular lipid metabolism. Humans spend the majority of the day in a postprandial, rather than postabsorptive state and when dietary fat and carbohydrates are consumed, a series of complex metabolic processes ensures that these nutrients are absorbed, transported around the body and stored appropriately. As the liver plays a major role in regulating fat and carbohydrate metabolism, perturbations in these metabolic processes have the potential to impact on metabolic health. For example, whether fatty acids are partitioned toward oxidation or esterification pathways appears to be dependent on a number of metabolic factors; not least ambient insulin concentrations. Moreover, the nutrient content of the diet appears to play a key role in intrahepatic fatty acid partitioning. This talk will review insights gained from undertaking studies using *in vivo*, *ex vivo* and *in vitro* models of human liver metabolism and discuss how metabolic and nutritional state may alter hepatic fatty acid partitioning. The usefulness of these models in understanding the aetiology and development of NAFLD will be highlighted.

DOI: 10.1530/endoabs.59.PL2

Society for Endocrinology Medal Lecture

PL3

Endocrine systems are dynamic: Lessons from the hypothalamic-pituitary-adrenal axis

Stafford Lightman
University of Bristol, Bristol, UK.

Biological systems are invariably dynamic, with both stochastic interactions and deterministic processes across multiple timescales ensuring the maintenance of homeostatic regulation and allowing us to adapt to changes in both internal and external environments. It is no surprise therefore that the stress responsive hypothalamic-pituitary-adrenal (HPA) axis shows multiple levels of regulation which come together to regulate oscillating levels of glucocorticoid secretion with both diurnal and ultradian rhythmicity. I shall describe the mechanisms underlying the HPA pulsatility and how these interact with higher level circadian control by the hypothalamic suprachiasmatic nucleus. I will show how the adrenal adapts to pulsatile ACTH and how tissues respond to pulsatile changes in cortisol/corticosterone. The importance of this for optimal emotional and cognitive function in man will be described. Finally, I shall show how novel technology measuring dynamic changes in hormone levels in ambulatory subjects in their own homes/at work can be used to diagnose endocrine disease.

DOI: 10.1530/endoabs.59.PL3

Society for Endocrinology Transatlantic Medal Lecture

PL4

Circadian Clock Genes and the Transcriptional Architecture of the Clock Mechanism

Joseph Takahashi[1,2]
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The molecular mechanism of circadian clocks in mammals is generated by a set of genes forming a transcriptional autoregulatory feedback loop. The 'core clock genes' include: *Clock, Bmal1, Per1, Per2, Cry1* and *Cry2*. The discovery of 'clock genes' led to the realization that circadian gene expression is widespread throughout the body and that the clock is cell autonomous. The cellular autonomy of circadian clocks has raised a number of questions concerning synchronization and coherence of rhythms at the cellular level as well as circadian organization at the systems level. The role of clocks in peripheral tissues has a number of important implications for disease. In the circadian clock mechanism, CLOCK and BMAL1 activate the transcription of the *Period* and *Cryptochrome* genes. The PERIOD and CRYPTOCHROME proteins then feedback and repress their own transcription by interaction with CLOCK and BMAL1. In the mouse liver, CLOCK and BMAL1 interact with the regulatory regions of thousands of genes, which are both cyclically and constitutively expressed. These target genes are highly enriched for metabolic pathways and indeed all fundamental metabolic pathways in the cell are direct targets of CLOCK:BMAL1. In addition to transcriptional control, the circadian system impacts the timing of metabolism with respect to body weight regulation, aging and longevity. These topics will also be discussed.

References

1. Takahashi, J.S. 2017. Transcriptional architecture of the mammalian circadian clock. *Nature Rev Genet.* **18**: 164-179.
2. Acosta-Rodrıguez, V.A., M.H.M. de Groot, F. Rijo-Ferreira, C.B. Green and J.S. Takahashi. 2017. Mice under caloric restriction self-impose a temporal restriction of food intake as revealed by an automated feeder system. *Cell Metabolism* **26**: 267–277.

DOI: 10.1530/endoabs.59.PL4

Clinical Endocrinology Trust Visiting Professor Lecture

PL5

SIAD; a modern approach to diagnosis and management

Chris Thompson
Beaumont Hospital/RCSI Medical School, Dublin, Ireland.

The initial report of the syndrome of Inappropriate Antidiuresis (SIAD) was published as recently as 1960 in the American Journal of Medicine. Schwartz and colleagues described an elegant series of physiological studies, in which two patients with hyponatraemia and lung carcinoma were shown to have an inability to excrete a water load, and who responded to water restriction with a rise in plasma sodium concentration. They termed this syndrome SIADH; in the 60 years since then, the basic diagnostic requirements for SIAD – hyponatraemia, concentrated urine, elevated urine sodium concentration, euvolaemia, and exclusion of cortisol and thyroid hormone deficiency – remain the gold standard for definition of the syndrome. Neoplasia, particularly lung carcinoma, remains a major cause of the syndrome. In addition, all recent published guidelines

recommend that the treatment employed in these index cases – fluid restriction – should remain as first line therapeutic choice. However, much has changed. The development of RIA methods for measurement of plasma vasopressin (AVP) has led to more complex definition of SIAD, and molecular biology techniques have shown that AVP is produced ectopically in tumour tissue. Recent data has shown that cortisol deficiency is commoner than previously recognised as a cause of SIAD, and that the need to exclude hypothyroidism is of questionable value. Data has also questioned the clinical value of fluid restriction in the reversal of hyponatraemia; the AVP-receptor antagonists, the vaptans are clearly more effective clinically, though cost effectiveness remains an issue. The need to treat SIAD actively is emphasised by the prospective data which shows that SIAD is associated with increased mortality which cannot be attributed solely to co-morbidity. Finally, guidelines for management of acute hyponatraemia recommend bolus treatment with hypertonic saline rather than continuous infusion; clinical data shows this to be safe, and effective in restoring cognitive function.

DOI: 10.1530/endoabs.59.PL5

Clinical Endocrinology Trust Lecture

PL6

Sex, steroids and development – clinical research from the NHS

Gerard Conway
University College London, London, UK.

Reproductive endocrinology spans the interface between 'mainstream' endocrinology, paediatric endocrinology and gynaecology, with excursions into genetics and psychology. This subspecialty is a fertile ground for clinical research. The field of Turner syndrome – 'Turnerology' – is a perfect example of where an endocrinologist has a lot to contribute with knowledge of oestrogen physiology, diabetes, osteoporosis as well as cardiovascular disease, genetics and the care of individuals with long term conditions. Sex steroids form a major part of endocrine practice from hypopituitarism to gonadal dysgenesis, yet we know little of the correct dosing of replacement therapies. Oestrogen deficiency is probably under-treated in the majority of adolescents and young women. Furthermore, progesterone excess of adrenal origin in congenital adrenal hyperplasia often goes unrecognised. In both of these conditions, optimal sexual function and fertility is the casualty. Close collaboration with gynaecology and andrology is key to providing comprehensive care for a large proportion of endocrine patients. We are supremely privileged in the NHS in be able to construct truly patient centred care in our services. In comparison with other countries, we excel in the clinical expertise that arises from this structure. This is particularly evident in the care of chronic endocrine conditions. Simple clinical data collection and its analysis is essential to the understanding of our practice and should be embedded in our services. However, clinical research from an NHS post is becoming more of a challenge with the increasingly strict control over one's time. Short term goals of optimising service capacity are often counterproductive to patient care and particularly to research. To counteract this effect job planning must prioritise and ring fence research time – if necessary with creative accounting!

DOI: 10.1530/endoabs.59.PL6

British Thyroid Association Pitt-Rivers Lecture

PL7

How should we define optimal thyroid function?

Robin Peeters
Erasmus University Medical Center, Rotterdam, Netherlands.

It has been known for a long time that both hypo- and hyperthyroidism are associated with an increased risk of morbidity and mortality. In recent years, it has also become clear that minor variations in thyroid function, including subclinical dysfunction and even variation in thyroid function within the reference range, can have important effects on clinical endpoints, such as bone mineral density, depression, metabolic syndrome, and cardiovascular mortality. Serum thyroid parameters show substantial interindividual variability, whereas the intraindividual variability lies within a narrow range. This suggests that every individual has a unique hypothalamus-pituitary-thyroid axis setpoint that is mainly determined by genetic factors, and this heritability has been estimated to be 40–60%. In recent years, advances in genetic research have contributed to unraveling part of these genetic factors. In my presentation I will discuss the identification of important new genes contributing to the overall variation in TSH and FT4 levels, as well as the relevance of the optimal thyroid function set-point in specific examples such as aging and pregnancy.

DOI: 10.1530/endoabs.59.PL7

Society for Endocrinology Dale Medal Lecture

PL8

Disorders of Thyroid Hormone Action: insights into biological processes

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

Disorders of thyroid hormone action are classified broadly, to encompass conditions with defective cellular uptake, metabolism or nuclear action of thyroid hormones. We describe recent insights into two rare disorders of thyroid hormone action. Impaired conversion of T_4 to T_3 enables recognition of a multisystem disorder due to mutations in *SECISBP2* – a factor directing synthesis of 25 different human, selenocysteine-containing proteins that include deiodinase enzymes. We have discovered that progressive, aneurysmal, aortic dilatation is a life-threatening manifestation of this disorder. Cystic medial degeneration of the aorta, similar to that seen in other aortopathy syndromes (e.g. Marfan's, Loeys-Dietz), is associated with raised reactive oxygen species, oxidative damage and apoptosis in patient-derived aortic smooth muscle cells. Secisbp2 knockdown in zebrafish or vessel wall selenoprotein depletion in mice, recapitulate the human phenotype. How selenoprotein deficiency mediates vascular degeneration and whether antioxidants can inhibit this process, remains to be elucidated.

DOI: 10.1530/endoabs.59.PL8

Society for Endocrinology European Medal Lecture

PL9

Molecular mechanisms in primary aldosteronism

Maria Christina Zennaro[1,2,3], Fabio Fernandes-Rosa[1,2] & Sheerazed Boulkroun[1,2]
[1]INSERM, UMRS_970, Paris Cardiovascular Research Center, Paris, France; [2]Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [3]Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Génétique, Paris, France.

Arterial hypertension is a major cardiovascular risk factor. Detection of secondary forms of hypertension is key to targeted management and prevention of cardiovascular complications. Primary aldosteronism (PA) is the most common and curable form of secondary arterial hypertension and has an estimated prevalence of ~10% in referred patients and 5% in primary care. PA results from autonomous aldosterone production from the adrenal cortex, caused in the majority of cases by a unilateral aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). Whole exome sequencing has allowed identification of recurrent mutations in genes coding for ion channels (*KCNJ5, CACNA1D, CACNA1H, CLCN2*) and ATPases (*ATP1A1* and *ATP2B3)* in APA and familial forms of PA. Those proteins are responsible for maintaining intracellular ion homeostasis and membrane potential of zona glomerulosa cells. The current pathophysiological model for PA development involves modifications of intracellular ion homeostasis and membrane potential, leading to the activation of calcium signaling, the major trigger for aldosterone production. This presentation will summarize our current knowledge on the genetic basis of PA and discuss the pathogenic mechanisms leading to increased aldosterone production and cell proliferation. Perspectives for clinical management of patients and open questions to be addressed by future research will be discussed.

DOI: 10.1530/endoabs.59.PL9

Society for Endocrinology Jubilee Lecture

PL10

Ups and downs of nuclear receptor action

Malcolm G Parker
Institute of Reproductive and Developmental Biology, Imperial College London, Hammersmith Hospital, London W12 0NN, UK.

Nuclear receptors regulate many developmental processes and a vast array of physiological responses. They control the expression of subsets of specific genes by recruiting co-factors that can function either as co-activators or co-repressors to either stimulate or repress gene transcription. Using the ligand-binding domain of the estrogen receptor as bait we identified a receptor interacting protein of MW 140Kd that we called RIP140. Examination of RIP140 null mice showed two clear phenotypes: firstly, female mice were completely infertile due to ovulatory failure and secondly, both sexes were extremely lean even when fed a high fat diet. The failure to ovulate was caused by impaired amphiregulin signalling in cumulus cells leading to defective luteinisation. The resistance of the mice to obesity when fed a high fat diet was the result of fibre-type switching in muscle tissue and an increase in the number of brown/beige fat cells in adipose tissue, both of which led to an increase in energy expenditure. Clearly RIP140 regulates transcription of one or more genes involved in these physiological processes and much of my research in later years focussed on unravelling the underlying molecular mechanisms. One remarkable finding was that RIP140 could act as either a co-activator or a co-repressor in different biological processes. For example, in ovulation it functions as a co-activator to stimulate transcription from amphiregulin target genes in cumulus cells. On the other hand, in metabolic processes it functions as a co-repressor by competing with PGC1, a strong co-activator for PPAR receptors. Thus RIP140 emerged as a clinical target for interfering with ovulation or controlling obesity, but the complexity of the molecular mechanisms involved has hindered progress in this endeavour.

DOI: 10.1530/endoabs.59.PL10

Society for Endocinology Journal Awards

Society for Endocrinology Journal Award – Journal of Endocrinology

JA1

Conditional deletion of ELL2 induces murine prostate intraepithelial neoplasia

Laura E Pascal, Khalid Z Masoodi, June Liu, Xiaonan Qiu, Qiong Song, Yujuan Wang, Yachen Zang, Tiejun Yang, Yao Wang, Lora H Rigatti, Uma Chandran, Leandro M Colli, Ricardo ZN Vencio, Yi Lu, Jian Zhang & Zhou Wang.

Journal of Endocrinology 2017, **235**, 123–136 (DOI: https://doi.org/10.1530/JOE-17-0112)

DOI: 10.1530/endoabs.59.JA1

Society for Endocrinology Journal Award – Journal of Molecular Endocrinology

JA2

5-ALA Ameliorates Hepatic Steatosis through AMPK Signaling Pathway

Haoyong Yu, Mingliang Zhang, Yunqin Ma, Junxi Lu, Jiemin Pan, Pan Pan, Haibing Chen & Weiping Jia

Journal of Molecular Endocrinology 2017, **59**, 121–128 (DOI: https://doi.org/10.1530/JME-16-0260)

DOI: 10.1530/endoabs.59.JA2

Society for Endocrinology Journal Award – Endocrine-Related Cancer

JA3

Loss-of-function mutations in the CABLES1 gene are a novel cause of Cushing's disease

Laura C Hernández-Ramírez, Ryhem Gam, Nuria Valdés, Maya B Lodish, Nathan Pankratz, Aurelio Balsalobre, Yves Gauthier, Fabio R Faucz, Giampaolo Trivelli, Prashant Chittiboina, John Lane, Denise M Kay, Aggeliki Dimopoulos, Stephan Gaillard, Mario Neou, Jérôme Bertherat, Guillaume Assié, Chiara Villa, James L Mills, Jacques Drouin & Constantine A Stratakis

Endocrine-Related Cancer, 2017, **24** 379–392 (DOI: https://doi.org/10.1530/ ERC-17-0131)

DOI: 10.1530/endoabs.59.JA3

Society for Endocrinology Journal Award – Clinical Endocrinology

JA4

Increased circulating interleukin-8 in patients with resistance to thyroid hormone receptor α

Anne H van der Spek, Olga V Surovtseva, Saskia Aan, Anton TJ Tool, Annemarie van de Geer, Korcan Demir, Anja LM van Gucht, AS Paul van Trotsenburg, Timo K van den Berg, Eric Fliers & Anita Boelen

Endocrine Connections, 2017, **6** 731–740. (DOI: https://doi.org/10.1530/EC-17-0213)

DOI: 10.1530/endoabs.59.JA4

Symposia

Curing diabetes

S1.1

Immunotherapy for Type 1 diabetes

Colin Dayan
Cardiff University School of Medicine, Cardiff, UK.

It is nearly 100 years since the discovery of insulin and insulin is still the only treatment we have for type 1 diabetes (T1D). Using and adjusting insulin therapy is very difficult and demanding for patients and rarely allows perfect blood sugar control. Even with recent advances in insulin delivery, less than 30% of patients achieve levels of HbA1c that prevent long-term complications and many of those that do regularly experience hypoglycaemia. Furthermore, a significant number of patients find it difficult to engage with and fully comply with insulin therapy and monitoring, especially during teenage and young adulthood, putting them at risk of ketoaidosis and accelerated complications. An increasing number of safe and effective immunomodulatory biologic agents have transformed the management of other autoimmune diseases such as rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases. Five different immunotherapies have been shown to preserve beta cell function if given at diagnosis of T1D, and the persistence of even 5% of beta cell function has been shown to halve the rate of hypoglycaemia and allow 50% or more of patients to reach glycaemic targets. In particular, beta cell preservation is likely to be particularly beneficial for patients who find it difficult to engage with T1D, such as teenagers and young adults. This lecture summarises the most recent clinical trial and safety data, the portfolio of agents currently under study and the likely landscape over the next 5 years.

DOI: 10.1530/endoabs.59.S1.1

S1.2

State of the art in islet cell therapy: preclinical advances in graft revascularization

Willem Staels[1,2], Yannick Verdonck[1], Yves Heremans[1], Gunter Leuckx[1], Sofie De Groef[1], Carlo Heirman[3], Eelco de Koning[4], Conny Gysemans[5], Kris Thielemans[3], Luc Baeyens[1], Harry Heimberg[1] & Nico De Leu[1,6,7]
[1]Beta Cell Neogenesis (BENE), Vrije Universiteit Brussel, Brussels, Belgium; [2]Department of Paediatrics, Division of Paediatric Endocrinology, Ghent University, Ghent, Belgium; [3]Laboratory of Molecular and Cellular Therapy, Vrije Universiteit Brussel, Brussels, Belgium; [4]Department of Medicine, Section of Endocrinology, Leiden University Medical Center, Leiden, Netherlands; [5]Laboratory of Clinical and Experimental Endocrinology, Katholieke Universiteit Leuven, Leuven, Belgium; [6]Department of Endocrinology, UZ Brussel, Brussels, Belgium, [7]Department of Endocrinology, ASZ Aalst, Aalst, Belgium.

DOI: 10.1530/endoabs.59.S1.2

S1.3

Abstract Unavailable.

Big data and bone disease

S2.1

Osteoporosis Mega GWAS: Paths to causal proteins

Brent Richards
McGill University, Montreal, Canada.

Recent genome-wide association studies of estimated BMD (eBMD) have now included 426,000 individuals, identifying 518 genome-wide significant loci (301 novel), which explain 20% of the total variance in eBMD. Some of these loci are also strongly associated with risk of fracture in a GWAS meta-analysis of 1.2 million individuals. In this talk, I will discuss functional genomics methods that can use this information to identify proteins strongly enriched for known causal proteins. These same proteins have also been shown to have strong effects on the murine skeleton through a large-scale osteoporosis murine knock-out programs. They also are strongly enriched for expression in murine osteocytes. In-depth analysis of one such target gene, *DAAM2*, in an animal knock-out model and CRISPR studies on human cells, showed clear perturbation of osteoporosis-related metrics. These findings now enable a more clear identification of the causal proteins underlying GWAS associations and explain 66% more variance than the most recent GWAS for eBMD.
This comprehensive human and murine genetic atlas also provides new insights into osteoporosis pathophysiology and provides opportunities for drug development.

DOI: 10.1530/endoabs.59.S2.1

S2.2

Abstract Unavailable.

S2.3

How rare bone disease will advance bone biology (Role of the Musculoskeletal GeCIP)

Kassim J Javaid
University of Oxford, Oxford, UK.

The study of rare bone diseases has fundamentally informed our understanding of bone biology and led to the development of novel therapies in common diseases such as osteoporosis. The 100,000 Genomes Project is a landmark enterprise of whole-genome sequencing and included rare musculoskeletal disorders. This presentation will describe how studies of Van Buchem disease, hypophosphataemia and Osteogenesis Imperfecta have informed bone biology as well as the current research opportunities from the 100,000 genome project for clinicians and researchers.

DOI: 10.1530/endoabs.59.S2.3

Horizons in adrenal medicine

S3.1

Novel strategies in glucocorticoid replacement

Eystein Husebye
University of Bergen, Bergen, Norway.

Primary adrenal insufficiency (AI) is often a consequence of autoimmune destruction of the adrenal cortex, but a number of other causes have been reported, including genetic diseases, haemorrhage, infections, infiltration by tumour or metastasis, and medication. AI is rare with reported prevalence at 10–20 per 100 000 inhabitants. Before replacement therapy with corticosteroids became available, AD was invariably fatal. Accessibility to hydrocortisone and fludrocortisone was a revolution and offered patients near normal life expectancies, although mortality has been reported to be increased in some populations. Recent years have however revealed that despite state-of-the art treatment, many patients experience reduced health-related quality of life (HRQoL) and reduced ability to participate in the work force. A leading hypothesis has been that the unphysiological replacement regimens we offer is a major factor to explain these limitations. This has spurred development of alternative replacement strategies including extended release medication and subcutaneous administration of hydrocortisone by infusion. Despite these new tools, providing personalized treatment in AI is still a major challenge as we currently lack biomarkers to guide replacement therapy to the individual patient. Evolving evidence point to the fact that some patients retain the ability to produce significant amounts of corticosteroids despite many years of autoimmune AI. These patients might represent a subgroup with better HRQoL, fewer adrenal crises and could be subjects for regenerative treatment to partly or fully restore adrenocortical function. Taken together these novel developments is about bring care for AI patients into the era of personalized medicine.

DOI: 10.1530/endoabs.59.S3.1

S3.2

Urine steroid metabolomics in adrenal incidentaloma

Irina Bancos
Mayo Clinic, Rochester, New York, USA.

Adrenal masses are discovered in 5% of abdominal imaging scans and the diagnostic work-up has to address two major questions: does the adrenal mass overproduce hormones and, most important to the patient, does the adrenal tumour represent cancer? The reported incidence of adrenocortical carcinoma varies in reported series from 2 to 11%. However, the accuracy of currently available imaging tests to diagnose malignancy is poor. Urine steroid metabolomics is a combination of steroid profiling and machine learning-based data analysis, which was previously reported to diagnose adrenocortical carcinoma (ACC) with 90% sensitivity and specificity. We recently undertook a prospective international multi-center test validation study of urine steroid metabolomics, recruiting >2000 patients with newly diagnosed adrenal mass and employing high-throughput urine steroid metabolite analysis by tandem mass spectrometry prior to computational data analysis. Results demonstrate an excellent diagnostic performance of urine steroid metabolomics, superior to the performance of routine imaging, with an algorithm combining urine steroid metabolomics with two imaging parameters providing the best performance. We propose that urine steroid metabolomics should become part of the standard-of-care in the diagnostic work-up of patients with indeterminate adrenal tumors.

DOI: 10.1530/endoabs.59.S3.2

S3.3

Abstract Unavailable.

New treatments for bone disorders

S4.1

Abaloparatide Treatment for Osteoporosis

Felicia Cosman
Columbia University College of Physicians and Surgeons, New York, New York, USA.

Abaloparatide (ABL), a synthetic PTHrP(1–34) analogue (75% homology with PTHrP), has high affinity for the RG subtype of the PTH1R and low affinity for the R^0 conformation, resulting in a greater stimulus to bone formation vs resorption. In animals, ABL increases bone formation markers with minimal resorption marker increase, increases bone mass, improves microarchitecture and bone strength. In the Phase 3 Abaloparatide Comparator Trial in Vertebral Endpoints study (ACTIVE), 2463 postmenopausal women with osteoporosis (age 49–86, mean 69 years), were randomized to blinded daily subcutaneous ABL vs placebo or open label teriparatide (TPTD). At 18 months, spine BMD increased similarly with ABL and TPTD, however, in the Total Hip and Femoral Neck, BMD increments were faster and significantly larger with ABL. New vertebral fracture incidence (the primary endpoint) was 4.2% with placebo, 0.6% with ABL and 0.8% with TPTD (risk reductions: 86% for ABL and 80% for TPTD; both $P<0.001$). Time to first nonvertebral fracture revealed early separation between ABL and both placebo and TPTD. Over 18 months, nonvertebral fractures occurred in 4.7% of placebo, 2.7% of ABL and 3.3% of TPTD (risk reductions 43% with ABL, $P=0.049$, and 28% with TPTD, $P=0.22$). Participants from ABL and Placebo who completed ACTIVE (n=1139) were enrolled in an extension where all participants received alendronate (Aln) for 24 months. At the end of the 43-months, with Pbo/Aln, the new vertebral fracture rate was 5.6%, vs 0.9% with ABL/Aln (84% risk reduction; $P<0.001$). At 43 months, there was a sustained 39% risk reduction for nonvertebral fractures with ABL/Aln vs Pbo/Aln ($P<0.05$). Although all women received alendronate for 2 years of the 3.5-year trial, those who originally received ABL had significantly fewer fractures, suggesting persistent benefit. ABL represents a potent therapy for patients at high risk for fracture.

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S4.2

New treatments for rare bone disease

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We are living through an exciting period during which new medical treatments are emerging for a range of rare bone diseases. These include monoclonal antibodies, small molecules and repurposed as well as truly innovative drugs. Whilst underlying the use of them all is an increased understanding of some aspect of bone biology, presently each sits at a different point on the pathway from bench to bedside. Asfotase alfa (bone-targeted alkaline phosphatase) is licensed for the treatment of paediatric-onset hypophosphatasia and has transformed outcomes for perinatal disease in particular. In 2017 NICE determined that it should be available in England subject to a formal managed access agreement. Burosumab (monoclonal antibody against FGF23) is licensed for the treatment of X-linked hypophosphataemic rickets during growth with a determination by NICE pending at the time of writing this abstract. Various clinical trials are currently underway for new medical approaches to the treatment of other rare bone diseases such as osteogenesis imperfecta, achondroplasia, fibrodysplasia ossificans progressiva and fibrous dysplasia. These new treatments for rare disease have potential implications for service delivery, configuration and funding. The multidisciplinary nature of bone disease management presents particular challenges. One solution has been the designation of Highly Specialised Services in England for the management of osteogenesis imperfecta in children and of hypophosphatasia in adults and children. The range of emergent treatments and corresponding scope of rare bone diseases may ultimately require a broader framework of service delivery encompassing paediatric and adult centres with specialist expertise.

DOI: 10.1530/endoabs.59.S4.2

S4.3

Rare bone disorders: New genes, biology and therapeutic targets

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Genetic discoveries in patients and families with rare bone disorders have highlighted the complexity of molecular mechanisms and cellular pathways governing normal bone development and homeostasis. More than 400 different forms of skeletal dysplasia have been described. Most of them result from single-gene defects, involving genes that are of major importance for a particular cellular event in skeletal development. Studies aiming to identify the involved pathways can enable development of new therapeutic strategies for skeletal disorders. Previous studies have identified several forms of monogenic bone fragility that are directly or indirectly related to type I collagen. Importantly, other forms also exist, often with unique skeletal and extra-skeletal features and with variable inheritance patterns. The discovery of *LRP5* mutations in osteoporosis-pseudoglioma syndrome and in early-onset osteoporosis first indicated that the WNT-signalling pathway plays an important role in bone mass accrual. Several other studies thereafter, including our discovery of *WNT1* mutations in early-onset osteoporosis, have further highlighted the pathway's significance in various disorders of low and high bone mass and provided evidence for the potential of WNT-targeted therapies in osteoporosis treatment. The X-chromosomal osteoporosis caused by *PLS3* gene mutations is another example of novel monogenic forms of osteoporosis. PLS3 osteoporosis affects especially males and leads to severe progressive spinal osteoporosis; even females carrying the mutation may develop symptomatic osteoporosis. PLS3 may play a role in bone mineralization but the pathogenetic mechanisms are not fully understood. Careful clinical, radiological and biochemical profiling of the associated phenotypes, together with characterisation of the tissue-level pathology and the involved cellular events in these rare disorders are of great value. Such studies can lead to discoveries that will benefit not only patients with these particular disorders but may prove efficacious even in the treatment of more common skeletal disorders, such as postmenopausal osteoporosis or osteoarthrosis.

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Breast cancer

S5.1

Diving into the dark matter of the breast cancer genome

Luca Magnani

Recent years have seen an increasing effort to decode the cancer genome. Most of the studies have focused on the coding genome to identify cancer driver genes. My group is interested in the role of the non-coding genome and its potential contribution to the drive transcriptional aberrations in breast cancer patients. To do so we use a wide-spectrum of techniques including genomic, epigenomics in patient-derived samples. I will present the results of a couple of studies in which mapping the non-coding genome using epigenomic has yield novel insights on cancer progression in luminal breast cancer patients.

DOI: 10.1530/endoabs.59.S5.1

S5.2

Metabolic pathways regulating breast cancer in obesity

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Obesity is associated with an increased risk of hormone receptor positive breast cancer after menopause. The aromatase enzyme catalyzes the conversion of androgens into oestrogens and the breast adipose-specific expression of aromatase is hypothesized to be a major driver of breast cancer growth when ovarian oestrogen biosynthesis has ceased. We have found that aromatase is elevated in breast adipose stromal cells in relation to obesity and menopausal status. Furthermore, obesity-associated local and systemic factors were found to be important drivers of aromatase expression in the breast fat, in part via effects on metabolic pathways, including LKB1/AMPK, p53, HIF1α and PKM2. Importantly, these same factors and metabolic pathways have been shown to regulate energy homeostasis and the growth of breast cancer cells directly. Recently, we have discovered that the gut-derived peptide hormone ghrelin and its unacylated form, decreased in obesity, are potent negative regulators of aromatase expression in the breast fat and that they suppress the production of inflammatory mediators from adipose tissue macrophages, believed to be key drivers of aromatase and breast cancer growth in obesity. Moreover, unacylated ghrelin directly inhibits the growth of hormone receptor positive breast cancer cells that are sensitive and resistant to endocrine therapy. These findings support the hypothesis that we can harness our understanding of the mechanistic link between obesity and breast cancer to develop novel therapies for breast cancer.

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S5.3

The Estrogen Receptor chromatin binding landscape in human tumors

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Estrogen Receptor alpha (ER) is the key driver in the majority of all breast cancers, and considered the main target for therapy. However, resistance to treatment is common and biomarkers to facilitate optimal treatment selection are urgently needed. Even though the vast majority of breast cancer patients are female, breast cancer can develop in men as well. Using chromatin immunoprecipitation followed by massive-parallel sequencing (ChIP-seq), we identified the genome-wide chromatin binding profiles of ER in male and female breast tissue, which we compared with profiles found in cell lines. Interestingly, while in cell lines only $\sim$5% of ER chromatin binding sites are observed at promoter regions, a substantially higher promoter-occupancy of ER was found in tumor tissue from both sexes. By assessing inter-tumor heterogeneity of ER chromatin binding sites, a stronger conservation of promoter-binding by ER was found as compared to enhancer regions, which was directly compared with enhancer activity analyses in healthy breast tissue. By integrating both 'common' and 'unique' ER-bound enhancers with somatic mutation data and breast cancer risk SNPs, we aim to identify whether diversity of enhancer action and ER genomic selectivity between tumors may represent a driving factor in tumor development and progression.

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The most important nine months; impact of maternal health

S6.1

Abstract Unavailable.

S6.2

Impact of Maternal Obesity/Diabetes during Pregnancy and Child Health

Susan Ozanne
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Obesity prevalence is increasing across the globe. This includes women of childbearing age with recent statistics reporting that over half of women are now either overweight or obese during pregnancy in the UK. This is accompanied by an increased prevalence of gestational diabetes with some reports suggesting that one in seven babies in the world are born from a diabetic pregnancy. This is a major concern as evidence from humans and animal models suggests that developing in utero in an obesogenic or diabetic environment has a long-term impact on the metabolic and cardiovascular health of the child. This is termed the developmental origins of health and disease. The strongest evidence from humans to support the idea that development in utero in an obesogenic environment 'programmes' increased risk of obesity and cardio-metabolic disease comes from studies of siblings born before and after maternal bariatric surgery. These revealed that the sibling born post-surgery had reduced adiposity, lower blood pressure and increased insulin sensitivity compared to their sibling born prior to maternal weight-reducing surgery. We have used a mouse model of maternal diet-induced obesity to define the mechanisms by which obesity/impaired glucose tolerance during pregnancy impacts on the long-term cardio-metabolic health of the offspring. These studies showed that the offspring of obese dams, with impaired glucose tolerance during pregnancy, develop insulin resistance, cardiac dysfunction, hypertension and fatty liver even when the offspring are lean. The insulin resistance is associated with cell autonomous post-transcriptional programming of insulin signalling protein expression. In addition offspring of obese dams are more susceptible to diet-induced obesity. We identified maternal hyperinsulinaemia as a key 'programming' factor thus highlighting it as an important target of intervention studies such as those involving increased maternal physical activity.

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S6.3

Early-life stress increases vulnerability to develop cognitive and metabolic dysfunction: a focus on inflammation and nutrition

Kit-yi Yam, Eva Naninck, Maralinde Abbink, Silvie Ruigrok, Kitty Reemst, Paul Lucassen, Janssen Kotah & Korosi Aniko
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Early-life stress (ES) is associated with increased vulnerability to cognitive impairments as well as metabolic disorders like obesity later in life. We investigate the role of a synergistic effect of stress, metabolic factors, nutrition and the neuroimmune system in this early-life induced programming. We use an established model of chronic ES and expose mice to limited nesting and bedding material during first postnatal week and study the central and peripheral systems under basal and challenged conditions (i.e. LPS, amyloid accumulation, western style diet (WSD) and exercise) to gain further insight in the functionality of brain plasticity, microglia and adipose tissue. In addition, given the high nutritional demand during development, we propose that early nutrition is critical for programming of brain and body. We focus on essential micronutrients and fatty acids and propose that an early dietary intervention with a diet enriched with these nutrients might protect against ES-induced functional deficits. We show that ES leads to cognitive impairments associated with reduced hippocampal neurogenesis at basal conditions as well as in response to exercise, primed microglia with exaggerated response to LPS or amyloid accumulation. Metabolically, ES mice exhibit a leaner phenotype but they accumulate more fat in response to WSD. Finally, with an early dietary intervention with micronutrient or fatty acid we

were able to (at least partly) prevent ES-induced cognitive decline, likely mediated by modulation of microglia, without however affecting the ES-induced metabolic profile. These studies give new insights for the development of targeted dietary interventions for vulnerable populations.

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The microbiome in endocrine disease

S7.1

The gut microbiota in ageing and inflammation

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The gut microbiota are becoming increasingly recognised as key players in human health. As such strategies used to alter this microbial community hold the potential to impact on wellbeing. During the ageing process the gut microbiota undergoes changes, these changes are linked with low grade inflammation, sometimes termed inflammageing. Prebiotics and probiotics are two dietary methods used to positively alter our microbial communities. This talk, using *in vitro* and *in vivo* data will consider whether dietary intervention can positively impact on the microbiota reducing inflammation and potentially improving health status.

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S7.2

The role of the gut microbiome in obesity

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The gut microbiota is a major component of mammalian biocomplexity exerting a significant influence on the metabolic phenotype of the host. The genetic entourage of these intestinal residents, collectively termed the gut microbiome, encodes a diverse array of metabolic capabilities that far exceed the relatively limited host genome. Cross-talk exists between the microbiome and genome through a variety of mechanisms with implications for both host health and disease. Biochemical exchange is one such communication channel where microbial metabolites enter the metabolic system of the host and modulate endogenous and exogenous pathways. This has implications at the local gut level and also at the systemic level. Through such exchange the intestinal microbiome has been implicated in obesity *via* a variety of mechanisms. This includes altered energy harvest from the diet, modulation of appetite regulation, and modification of the enterohepatic circulation with downstream consequences for lipid digestion, metabolism and bile acid signaling pathways. Using powerful systems biology techniques such as metataxonomics, metabolomics/metabonomics, and transcriptomics, the dynamic and multidimensional interplay between the genome and microbiome is being characterised and the wide-reaching influence of the gut microbiota on host health is being understood.

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S7.3

A Role for the Microbiome in Graves' Disease and Orbitopathy?

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In Graves' disease (GD) thyrotropin receptor (TSHR) stimulating autoantibodies cause hyperthyroidism. Many GD patients develop Graves' orbitopathy (GO) characterized by orbital tissue remodelling including adipogenesis. Whilst progress has been made in understanding the processes causing expansion of orbital tissues, little is known about loss of tolerance to the TSHR target autoantigen. Mechanisms for triggering autoimmunity by microorganisms include molecular mimicry, but more recently the role of the gut microbiota in maintaining the balance between inflammatory Th17 and non-inflammatory Treg in the gut-associated lymphoid tissue has been recognised. Mothers transmit their genes and gut microbiota to their children. The microbial populations in the gut may affect metabolism; advances enable sequencing of microbial 16S rRNA genes, facilitating composition assessment of bacterial communities. We tested the hypothesis that in GD bacteria inducing tolerance (Treg) are under-represented or those generating pro-inflammatory cytokines are over-represented. I will present data from patients, untreated/within 6 weeks treatment commencing; GD ($n=65$) with no/minimal eye signs; GO ($n=56$), mild/moderate-severe and healthy controls ($n=42$) which demonstrate significant differences in phylum/genera composition between the three groups. Robust murine models would help delineate pathogenesis. Female BALBc mice, immunized with TSHR-A subunit expression plasmid/electroporation, generated a GD/GO model reproducible in London and Essen. Orbital disease was induced in both centres, but differences were apparent. We hypothesized that the gut microbiota influences the outcome and reproducibility of induced GD/GO. I will present data illustrating the significant differences in alpha, beta-diversity and taxonomic profiles observed in the two centres. Furthermore we identified disease-associated microbial taxonomies and correlation with ocular disease. Finally I will report preliminary findings of the effects of modifying the human and murine gut microbiota on spontaneous and induced disease outcomes achieved using probiotic (human and mouse), antibiotic or human GO faecal material transfer (in mice).

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Thyroid in pregnancy

S8.1

TABLET TRIAL – implications for targeted levothyroxine in pregnancy

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Hypothyroidism before and during pregnancy has been linked with adverse pregnancy outcomes. Observational studies have demonstrated that thyroid autoimmunity, characterised by the presence of thyroid peroxidase (TPO) antibodies, is associated with increased risks of miscarriage and pre-term birth. Small trials indicated that levothyroxine therapy could reduce such adverse outcomes, but the evidence was inconclusive. The TABLET trial is a multicentre, double-blind, placebo-controlled randomized trial to investigate whether levothyroxine treatment could increase live birth among euthyroid women with thyroid antibodies. Women were randomly assigned to receive 50 mcg per day of levothyroxine or placebo, commenced preconception and continued until the end of pregnancy. Women were given a twelve month period to conceive and the primary outcome was live birth at ^{3} 34 weeks gestation. 19,585 women were tested for thyroid antibodies and thyroid function across 49 UK hospitals. The overall prevalence of abnormal thyroid function was 4.8% (95% CI 4.5–5.1) and was overt in 0.4% (0.3–0.6) and subclinical in 3.6% (3.4–3.9). TPOAb positivity was found in 9.5% (9.1–9.9)) and was associated with euthyroidism in more than 90%. Women with higher BMI, subfertility and Asian ethnitiy were more likely to have thyroid dysfunction and autoimmunity. Using a lower (2.5 mIU/l) cut-off for serum TSH resulted in significantly increased rates of subclinical hypothyroidism (19.9% (19.3–20.5) vs 3.6% (3.4–3.9) for TSH >4.5 mIU/l). A total of 1420 women were eligible for the trial, of whom 952 were randomly assigned to receive either levothyroxine (476) or placebo (476). At the time of writing of this abstract the final outcomes are being analysed. We have identified specific subgroups of women at risk of thyroid dysfunction or autoimmunity in whom levothyroxine replacement may be beneficial. It is anticipated that the final outcomes of the TABLET trial will be available by the time of this presentation.

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S8.2

CATS Obstetric and development – implications for thyroid screening in pregnancy

Peter Taylor
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Low thyroid function in pregnancy is associated with adverse obstetric outcomes but it is unclear whether screening and initiation of levothyroxine during pregnancy is beneficial. The Controlled Antenatal Thyroid Study (CATS) was a randomised controlled trial which screened women for low thyroid function (subclinical hypothyroidism and isolated hypothyroxinemia) between 11 and 16 weeks gestation. CATS provides data on obstetric outcomes and offspring neurological development. These data are key to the crucial debate as to whether universal thyroid screening in pregnancy is beneficial. The original trial assessed offspring IQ at age 3, a follow on study (CATS II) assessed IQ and other cognitive

outcomes at age 9. Obstetric outcomes were obtained using data-linkage from the Secure Anonymised Information Linkage databank. The original CATS study found no difference in mean IQ between treated and untreated women with low thyroid function. Mean IQ scores were 99.2 and 100.0 in the screening and control groups, respectively (difference = 0.8; 95%CI (−1.1 −2.6) $P = 0.40$. The proportions of children with an IQ of less than 85 were 12.1% in the screening group and 14.1% in the control group $P = 0.39$. Similar results were seen at age 9. Children of 'over-treated' mothers displayed more ADHD symptoms than women with normal thyroid function. Potential benefits were seen in preventing fetal loss. Untreated women with low thyroid function had higher odds of fetal loss than women with normal thyroid function OR = 9.61 (95%CI 5.03, 18.4) $P < 0.001$. Untreated individuals also had a higher odds of miscarriage than those who received treatment OR = 4.07 (95%CI 1.14, 14.5) $P = 0.03$. No clear differences were seen for other obstetric outcomes. Screening for and treating low thyroid function at the end of the first trimester does not appear to improve neurological outcomes, however it may have a role in preventing fetal loss. Over-treatment should be avoided with monitoring.

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S8.3

Iodine supplementation in pregnancy and effect on offspring neurodevelopment

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Iodine is an essential component of thyroid hormones that are required for brain development. Severe iodine deficiency during pregnancy can result in cognitive impairment and lower IQ in the offspring. However, the effects of mild-to-moderate iodine deficiency on brain development and neurocognitive function are less well known, and this is important as mild-to-moderate deficiency is common in pregnancy in many European countries, including the UK. There are recommendations in some countries with mild-to-moderate iodine deficiency for pregnant women, lactating women, and those planning a pregnancy to take an iodine supplement. However, the evidence on which these recommendations are based is not strong. There are three non-randomised intervention studies with cognitive outcomes, two suggest a benefit of iodine supplementation but all have limitations that mean interpretation is difficult. Observational studies have found mixed results, with some studies even suggesting a negative effect on child neurodevelopment, either when the dose of iodine was relatively high (> 150 μg/day) or when iodine supplements were started during, rather than prior to, pregnancy. However, given their observational nature, these studies need to be interpreted with caution. There is a lack of evidence from randomised controlled trials (RCTs) in pregnancy; though a recent RCT in India and Thailand found no benefit of iodine supplementation on child cognition, the women recruited were only marginally iodine deficient. Thus further evidence from RCTs in pregnant women from regions of moderate iodine deficiency is required to strengthen the evidence base for public-health recommendations. However, it may become increasingly challenging to conduct such a trial, because it may be considered unethical to include a placebo group, especially in countries with official recommendations for iodine supplementation in pregnancy.

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Introduction and prevention of gonadal function

S9.1

How do I differentiate hypog hypog from constitutional delay?

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Constitutional delay is a common presentation to paediatric endocrine clinics. Most are boys who have been at the bottom of the normal range for height during childhood and then started to feel left behind as their peers develop in puberty. There is no agreed cut off age but most boys referred are 13–15 years old. Most boys with delay of puberty are healthy, although there is an association with chronic medical conditions (eg inflammatory bowel disease, juvenile rheumatoid arthritis, cystic fibrosis, etc). Distinguishing rare cases of hypogonadotrophic hypogonadism among the numerous referrals to paediatric endocrine clinics with pubertal delay is difficult. Baseline endocrine testing is unhelpful. GnRH tests can give information but rarely completely confirm the diagnosis. MRI scans or genetic testing might confirm a diagnosis but only for a proportion of those affected. It is not justified to intensively investigate every child with pubertal delay so most clinicians will do basic tests at presentation and then observe progress. Treatment to induce puberty can be of considerable psychological benefit. There is a limited range of sex steroid formulations which can be used in low doses, and published data are limited. Gonadotrophins are not often used as the main agent to induce puberty. There is discussion of whether induction of spermatogenesis at the same time as induction of pubertal development will help future fertility in individuals with hypogonadotrophic hypogonadism, but not much evidence to support this. Most individuals with constitutional delay will start to progress in endogenous puberty when treated, so if there is no sign of endogenous puberty (testicular enlargement) with treatment, hypogonadotrophic hypogonadism becomes a more likely diagnosis.

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S9.2

Induction of Spermatogenesis

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Hypogonadotrophic hypogonadism (HH) is the only form of infertility that is directly treatable with hormone replacement, either in the form of gonadotrophin injections, or pulsatile GnRH if the underlying defect is hypothalamic and pituitary function is intact. However, men with HH face a complex and confusing journey to access treatment: misinformed that they are irredeemably infertile, struggling to find a clinician with relevant experience and authorisation to prescribe gonadotrophins, or even denied funding outright as not explicitly commissioned by local NHS structures. Despite its physiological elegance, GnRH is not available in the UK and many other countries. Indeed, for men with adult-onset HH, fertility is often restored by substituting hCG for testosterone (T). The hCG dose is titrated to achieve normal range serum T levels (levels within the testes are upto 100x higher), without abnormally raising estradiol level or haematocrit. However, hCG-alone rarely achieves sperm in the ejaculates of men with congenital HH (CHH), even after 10 years' treatment; these men require combined hCG and FSH treatment. Nevertheless, almost ¼ fail to develop sperm in the ejaculate even after 12–36 months' combined therapy. For those having smaller testes (< 4 ml) and history of bilateral cryptorchidism – evidencing absent perinatal minipuberty, during which Sertoli cell proliferation would normally occur– prognosis is even poorer; only ⅓ developing sperm. Outcomes are slightly better when serum FSH levels > 4 IU/l are achieved, but a more radical approach re-thinks the gonadotrophin initiation sequence. Classical regimens begin with an arbitrary phase of hCG-monotherapy before introducing FSH; a sequence largely informed by regulatory requirements of drug-licensing studies and lacking scientific underpinning. Having missed minipuberty, CHH males have a depleted population of immature Sertoli and germ cells, and their testis should logically receive a phase of FSH-mediated cell-proliferation prior to these cells being matured through exposure to hCG-stimulated T.

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S9.3

Abstract Unavailable.

Pancreatic NETs – an update

S10.1

Managing Pancreatic Neuroendocrine Tumours in MEN1

John Newell Price
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Pancreatic neuroendocrine tumours (pNET) in patients with MEN1 pose a particular and challenging clinical problem. Whilst patients with a pNET and clear clinical and biochemical evidence of hormonal hypersecretion are usually candidates for some form of surgical or medical therapy, the decision-making is far harder for those who are found to have a non-functioning tumour on

surveillance imaging. There is a lack of knowledge of the differing biological behaviour between pNETs in MEN1 vs. sporadic disease, although some data suggest a more aggressive phenotype for MEN1. The clinical conundrum is that the main intervention, pancreatic surgery, carries significant morbidity and mortality, whilst there remains risk of metastatic disease and increased mortality for patients with known pNETs managed expectantly. Thus the risk-benefit ratio for any given individual is a fine decision needing MDT discussion and influenced by several factors including: size and position of tumour; general co-morbidities; risk of morbidity from intervention; and, importantly, patient preference. It is essential to take into account the experience that the patient has of outcomes for other members in the family who have been affected by MEN1, as this will have a key influence on their views. Sufficient consultation time is needed to explore these issues, to ensure a fully informed joint-decision making process. Survey data suggest that patients have insufficient information for this to be satisfactory. There are no long-term data for the use of somatostatin analogues in patients with MEN1 with non-functioning pNETs who are receptor-positive, but this may be a reasonable approach in some. For those with metastatic disease treatments may be based on current paradigms used for sporadic pNETs, and include the use of radionuclide therapy, and depending on the proliferation index or behaviour tyrosine kinase inhibitors, mTOR inhibitors and other parentral and oral chemotherapy, but MEN1-specific data are needed.

DOI: 10.1530/endoabs.59.S10.1

S10.2

Advances in endoscopic ultrasound and endotherapy for pancreatic neuroendocrine tumour

Stephen Pereira
University College London, London, UK.

Pancreatic neuroendocrine tumours (PNETs), although reported with increasing frequency through increased use of abdominal imaging, are rare and uncommon tumours (1 per 100,000 population) representing 1–2% of all pancreatic neoplasms. Preoperative diagnosis is important since a solitary small tumour without evidence of metastatic spread may be suitable for pancreatic preserving surgery such as enucleation or middle segment resection rather than more extensive resection. However, preoperative localisation can be difficult, as these tumours are frequently smaller than 2 cm in diameter and conventional imaging methods such as trans-abdominal ultrasound, computed tomography and magnetic resonance imaging may fail to accurately localise the tumour in up to 40–70% of patients. Endoscopic ultrasound (EUS) has been reported to be highly accurate for the preoperative localization of PNETs, mainly primary insulinomas which frequently are negative on somatostatin receptor scintigraphy. PNETs are identifiable by EUS in 79–95% of suspected cases, and usually appear hypoechoic, round and homogenous, although they may be isoechoic or hyperechoic with irregular margins. EUS guided fine needle aspiration (EUS-FNA) or biopsy (EUS-FNB) can confirm the diagnosis pathologically and provide information to guide the type of surgical intervention. Radiofrequency ablation (RFA) causes thermal coagulative necrosis through the administration of a high-frequency current. Recently new monopolar RFA probes have been developed that can be placed down the working channel of a linear echoendoscope, enabling RFA to be administered under EUS guidance. To date this technique has been shown in several case series to be effective and safe in the management of patients with functional PNETs who have failed multiple medical therapies and cannot undergo surgery due to co-morbidities. Long-term outcome data and further experience are required but EUS-guided RFA and other novel ablative approaches may now be considered for selected cases.

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S10.3

The genomic landscape of pancreatic neuroendocrine tumours

Chrissie Thirlwell
Royal Free Hospital NET Unit and UCL Cancer Institute, London, UK.

In recent years the genomic landscape of pancreatic neuroendocrine tumours (PNETs) has been elucidated through unbiased exome, whole genome and ingrated genomic analyses. Most commonly mutations in the epigenetic machinery occur – *ATRX / DAXX / Menin* affecting 40–45% of cases. Alongside this, mutations occur less frequently in the mTOR pathway and DNA repair genes. It has also been determined that 17% of cases have an underlying germline mutation. Recent developments in integrated genomic analysis and molecular profiling of PNETs will be presented with discussion of how these findings might be introduced in to clinical practice.

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Early Career Symposia

Navigating the academic

EC2.1

The scientific fellowship route

David Hodson
University of Birmingham, Birmingham, UK.

In the present presentation, I will discuss the options open to researchers wishing to pursue a career in academia via the scientific fellowship route. Particular attention will be paid to establishing strong early career foundations, managing expectations, as well as appropriately timing career stage with any application. Finally, the pros and cons of this career track will be highlighted.

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EC2.2

Early Careers: navigating the academic pathway. The clinical academic route

Victoria Salem

I will talk about my own experience pursuing a PhD, postdoctoral research and ultimately an Intermediate Clinician Scientist Fellowship alongside training in Diabetes and Endocrinology with GIM. I will talk about the particular barriers and challenges commonly reported by clinical academics and how universities and funding bodies are working to provide tailored support to help the furious juggle of research, grants, papers, on-calls, clinics and, yes, a home life.

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EC2.3

Abstract Unavailable.

EC2.4

Surviving academia: The lectureship route

Matthew Simmonds
School of Life Sciences, College of Science, University of Lincoln, Lincoln, UK.

Within any scientific career there is one constant… change. Moving from PhD through to postdoctoral positions we have to constantly evolve to establish ourselves as independent researchers with our own unique research area and group. Academia poses several challenges for early career scientists including obtaining fellowships in an ever increasingly competitive environment, grant funding running out and short term contracts making it difficult to plan life events. Whilst there is no 'one size fits all' pathway to achieving a long-term career in academia, obtaining a lecturer position, for many, is a natural next step in cementing a permanent academic position. With lectureship positions becoming increasingly competitive this talk will discuss some of the ways in which you can get appropriate experience to put yourself in an ideal position to apply for these roles whilst still ensuring that you continue to maintain a strong research career and publications, which is vital for any young researcher. I will discuss some of the ways in which you can get teaching experience both through traditional routes, such as undertaking lectures and small group teaching, but also through alternative routes, for anyone who may not have access to these more traditional opportunities. This talk will also provide some insights into what different Universities look for when recruiting lecturers and importantly some of things to look out for when trying to find lectureship positions which will provide you with the best environment to support both your research and teaching ambitions. I will also discuss some of my own experience of how I found the first few years of undertaking a lectureship, including some of the challenges and successes along the way, which will hopefully provide you with some insights into whether the lectureship route within academia could be a suitable career path for you.

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EC2.5

Abstract Unavailable.

Clinical Management Workshops

Workshop 1: Aggressive pituitary tumours

CMW1.1

How and when to use temozolomide in pituitary tumours

Ben Whitelaw
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Temozolomide (TMZ) is an oral chemotherapy first used for pituitary tumours in 2006. Over the past 12 years experience and confidence using this treatment has increased. Temozolomide is effective: with about 50% of cases showing a tumour response. This figure rises to 70% if stable disease is regarded as a tumour response. The effectiveness appears to be similar in both aggressive adenoma and carcinoma. Functioning tumours show a better response as compared with non-functioning. Recent publications demonstrate temozolomide improves overall survival and the use of TMZ has been incorporated into guidelines on aggressive tumour management. TMZ is an oral treatment normally given as a monotherapy for cycles of 5 days every 28 days (200 mg/m^2). It is safe and well tolerated. The common side effects are nausea, vomiting and fatigue. Myelosuppression (thrombocytopaenia / neutropenia) occurs in 7–17% of cases. The decision to initiate temozolomide should be made by a pituitary MDT who have, or can access, the appropriate knowledge and experience. Often TMZ is used for about 12 months but the optimal duration of treatment is an area of uncertainty and relates to the specific circumstances. There is evidence TMZ potentiates radiotherapy. Combination with other agents such as capecitabine has been recommended by some. Most, but not all, series show MGMT depleted tumours (as assessed by immunohistochemistry) have a better clinical response to TMZ as compared with MGMT replete tumours. It is widely accepted that temozolomide should be used to treat pituitary carcinoma and should be used as a salvage treatment in aggressive adenomas refractory to surgery and radiotherapy. Using TMZ earlier in the treatment pathway, such as prior to radiotherapy; or on the basis of anticipated aggressive behaviour is a more controversial area currently being explored.

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CMW1.2

When to intervene in recurring pituitary tumours: the role of revision surgery

Caroline Hayhurst
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The clinical course of pituitary adenoma is highly variable. Aggressive adenoma subtypes may require multimodal therapy with multiple operations. Even standard adenoma exhibit a relatively high long term recurrence rate and delayed intervention is often required. The indications for revision surgery in the endoscopic era are expanding for both functioning and non-functioning tumours, including access to the medial and lateral cavernous sinus and intracranial compartments. Although revision surgery can be challenging anatomically, it has been demonstrated to be safe and effective. Risk factors for complications in repeat surgery include prior radiotherapy. Therefore, the question of early radiotherapy in pituitary adenoma remains controversial. Increasing understanding of pituitary tumour biology will facilitate individualised treatment and surveillance protocols, with early intervention in high risk adenoma subtypes.

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CMW1.3

Proton Beam Therapy: The future of radiotherapy?

Yen Ching Chang

This talk aims to explain:

- What is proton beam therapy (PBT)
- How it is delivered
- Clinical indications for PBT
- Evidence for its use
- Challenges
- UK service – current and future

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Workshop 2: Endocrine emergencies

CMW2.1

Adrenal crisis: prevention and management

Mark Sherlock
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Acute adrenal insufficiency, also termed adrenal crisis, is a life-threatening endocrine emergency due to a lack of production of the adrenal hormone cortisol (and also aldosterone in primary adrenal insufficiency). Patients with both primary (PAI) and secondary adrenal insufficiency (SAI) are at risk of adrenal crisis. PAI is caused by loss of function of the adrenal gland itself resulting in both glucocorticoid and mineralocorticoid deficiency. SAI is caused by alterations in the regulation of adrenal cortisol production due to a reduction in ACTH secretion by the pituitary gland and results in glucocorticoid deficiency but maintained mineralocorticoid secretion (which is controlled by the Renin-Angiotensin-Aldosterone system). While patients with adrenal crisis due to PAI and SAI present similarly, there are some differences in presentation. Identifying patients at risk of adrenal crisis and prompt management can be lifesaving. In addition to 'classical causes' of AI it has become increasingly evident that patients receiving exogenous glucocorticoids even as inhalers, steroid creams or nasal sprays can lead to SAI. This presentation will highlight the importance of patient and clinician education in the prevention of adrenal crisis. The presentation will also highlight the differences in presentation between PAI and SAI and discuss the optimum management of adrenal crisis.

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CMW2.2

A phaeochromocytoma crisis

Ruth T Casey
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A phaeochromocytoma is a catecholamine secreting tumour arising from the adrenal medulla and a paraganglioma refers to its extra adrenal counterpart, which can develop from sympathetic or parasympathetic tissue anywhere from the skull base to the pelvis. Presenting symptoms of these rare tumours are most commonly related to catecholamine excess, and include headache, palpitations, paroxysmal hypertension, anxiety, abdominal pain and excessive sweating. A phaeochromocytoma crisis is a life-threatening endocrine emergency defined as catecholamine-induced hemodynamic instability including; labile blood pressure, tachyarrhythmias and the risk of subsequent cardiovascular collapse. Although catecholamine crises are rare with an estimated incidence of 11% (1), the associated pooled mortality rates are significant at approximately 15% (2). Severe complications of a catecholamine crisis include cardiomyopathy, myocardial infarction, pulmonary oedema, cerebrovascular accident and ischaemic ileus (1). A phaeochromocytoma is regarded as the 'great mimicker' and therefore early consideration of this diagnosis should be given to those patients presenting with unexplained cardiovascular or hemodynamic compromise. Early cautious treatment with alpha-blockade remains the first line treatment option for a catecholamine crisis. However, invasive pressure monitoring and cross-specialty input from cardiology, endocrinology, intensive care and surgical colleagues is often crucial in achieving the best patient outcomes. This management session will involve a cased-based and interactive discussion focusing on: (i) potential presenting symptoms of a phaeochromocytoma crisis; (ii) risk factors and precipitants of a crisis; (iii) complications of a crisis; and, (iv) suitable management strategies.

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CMW2.3

Thyrotoxic crises

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Thyroid storm is a rare medical emergency with high mortality and is difficult to diagnose and treat. The optimal treatment regimen is not clear, and options include combinations of beta blockade, high dose anti-thyroid drugs, potassium iodide, dexamethasone, iodinated contrast agents, plasmapheresis and dialysis. Patients with severe, uncontrolled thyrotoxicosis, unresponsive to anti-thyroid drug therapy, represent a group of patients in whom treatment can be particularly challenging, especially if co-morbidities such as cardiac disease or myopathy are present. In this session I will summarise the literature on thyrotoxic crises and, based on this and personal experience, provide a suggested treatment algorithm for these patients.

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Workshop 3: How do I... (1)

CMW3.1

How Do I....Manage Diarrhoea in Patients with NETs

Mark Strachan
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Diarrhoea is a common symptom in patients with neuroendocrine tumours (NETs), especially metastatic small bowel NETs. Diarrhoea substantially impairs quality of life, as increased frequency of bowel moments with associated urgency, cause social embarrassment and constrain diet and the ability to leave the house. Diarrhoea, with associated electrolyte disturbance, was a major cause of premature death in patients with NETs prior to the advent of medical therapies. It is important to remember that diarrhoea in patients with NETs is not necessarily hormonally-mediated. Other causes include short-bowel syndrome (due to surgical resection of bowel), exocrine pancreatic insufficiency (following pancreatic resection and as a side effect of somatostatin analogue (SSA) therapy), small bowel bacterial overgrowth (due to 'blind loops' following certain surgical procedures) and bile acid malabsorption (due to terminal ileal disease). Anti-motility agents (e.g. loperamide and codeine) are the mainstay of management of short-bowel syndrome and can be effective in other forms of diarrhoea too. Exocrine pancreatic enzyme supplements, cyclical courses of antibiotics and bile acid sequestrants (e.g. colestyramine) should be considered in relevant situations. Hormonal causes of diarrhoea in NETs include serotonin (small bowel carcinoids), vasoactive intestinal peptide (rare pancreatic NETs) and calcitonin (medullary thyroid cancer). SSAs are the key treatment in the management of hormonally-mediated diarrhoea in patients with NETs. SSAs can transform quality of life and also have anti-tumour properties. Intractable diarrhoea, despite optimum SSA therapy, should prompt evaluation for non-hormonal causes as above, but if symptoms persist then additional anti-cancer treatments may improve diarrhoea by reducing hormone section. Options include peptide receptor radionuclide therapy, multi-kinase inhibitor therapies and local cyto-reduction techniques. Telotristat is an inhibitor of tryptophan hydroxylase, one of the key enzymes in the serotonin synthesis pathway. Trials have shown that it can reduce the frequency of diarrhoea in patients with diarrhoea due to serotonin excess.

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CMW3.2

Abstract Unavailable.

CMW3.3

Abstract Unavailable.

CMW3.4

Abstract Unavailable.

CMW3.5

Abstract Unavailable.

CMW3.6

Abstract Unavailable.

Workshop 4: Treating troublesome menopausal symptoms

CMW4.1

HRT: Efficacy and Safety

Nick Panay

The adverse outcomes seen in The Women's Health Initiative (WHI) combined hormone therapy trial were mainly due to an over-dosage of hormone therapy (HT) in a relatively elderly population. However, fundemental differences exist between conjugated equine estrogens and 17 beta estradiol and between medroxyprogesterone acetate and other progestogens. It is likely that these differences also contributed to the adverse outcomes in WHI, which were contrary to the cardiovascular benefits seen in previous observational trials. In addition to binding to the progesterone receptor, many progestogenic compounds also bind to the glucocorticoid, mineralocorticoid and androgen receptors. This can lead to unwanted effects such as unfavourable glucose metabolism, fluid retention, acne, weight gain**.** Recent studies of cardiovascular risk markers in younger women have therefore been designed using predominantly 17 beta estradiol and progesterone or dydrogesterone as primary interventions. Menopause societies are now advising that natural progesterone and dydrogesterone may have more favourable metabolic and breast effects compared to synthetic progestogens. Natural progesterone and dydrogesterone do not attenuate the beneficial effects of estradiol in reducing insulin resistance and arterial compliance. There also appear to be differential effects of progesterone and progestogens on breast tissue. Progesterone has a neutral and dydrogesterone a pro-apoptotic effect on breast epithelial cells, whereas androgenic progestogens such as medroxyprogesterone acetate appear to have a proliferative effect, possibly through non-specific effects on the glucocorticoid receptors and gene expression. This might explain the small increase risk in breast cancer promotion in some studies when synthetic progestogens are combined with estrogen. Observational data such as the French E3N cohort and the Finnish registry cohort suggest that women using natural progesterone and dydrogesterone are not at increased risk of breast cancer within the first 5 years of use; ideally these data will be confirmed in the future by definitive long term, randomised prospective studies.

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CMW4.2

Non-hormonal therapies for climacteric symptoms

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The National Institute of Clinical Excellence (NICE) Menopause Clinical Guidelines, November 2015, has reinstated Hormone Replacement Therapy (HRT) for the average fit & healthy woman in her fifties, the clinical model used. Some women require alternatives for either medical or personal reasons,. Few complementary and alternative treatment options have evidence of efficacy yet several are mentioned by NICE as having possible roles. In symptomatic women with a contra-indication to estrogen progestogens have been a popular alternative to HRT. Some randomised controlled trials (RCT) show a modest benefit over placebo, but effective doses carry an increased risk of venous thrombo-embolism. The increased risk of breast cancer seen in combined HRT, and not estrogen alone, suggests a role in causation although, progestogens behave differently in breast tissues; it is not a class effect. Women often use complementary therapies as they are perceived to be safe alternatives to HRT. However, drug interactions and side-effects, especially St Johns Wort, calls this into question. The current regulation of complementary and alternative medicine is inadequate. A European Union Directive implemented in the UK in Oct 2005 on traditional herbal medicinal products does not cover products bought elsewhere. Phyto-estrogens either from Soy or Red Clover sources have the best evidence base and have been subjected to a Cochran Database Review. Non-hormonal prescribables include Clonidine (the only one licensed for vasomotor control), Gabapentin, Selective Serotonin re-uptake inhibitors (SSRIs) and Serotonin Nor-adrenaline re-uptake inhibitors (SNRIs). SSRIs have the potential to interact with Tamoxifen and adversely effect libido more than SNRIs. RCT data shows a small benefit, but in short duration trials with low numbers. Clinicians need familiarity with non-hormonal treatments to inform and guide women as to which options are most beneficial for them.

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CMW4.3

Neurokinin B antagonism – novel therapy for menopausal flushing

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Hot flushes affect 70% of menopausal women and often severely impact physical, psychosocial, sexual, and overall wellbeing. Hormone replacement therapy is effective but is not without risk. Neurokinin B signalling is increased in menopausal women, and has been implicated as an important mediator of hot flushes in animals. We carried out a phase 2, randomised, double-blind, placebo-controlled, single-centre, crossover trial assessed the effectiveness of an oral neurokinin 3 receptor antagonist (NK3R antagonist) on menopausal hot flushes. Participants received 4 weeks of an NK3R antagonist (40 mg, orally, twice daily) and placebo (orally, twice daily) in random order separated by a 2 week washout period. The primary outcome was the total number of hot flushes during the final week of both treatment periods. Analyses were by intention to treat and per protocol using generalised linear mixed models and standard crossover analysis. 28 participants completed the trial and were included in a per-protocol analysis. The NK3R antagonist significantly reduced the total weekly number of hot flushes by 45 percentage points (95% CI 22–67) compared with the placebo (intention-to-treat adjusted means: placebo 49·01 [95% CI 40·81–58·56] vs NK3R antagonist 19·35 [15·99–23·42]; adjusted estimate of difference 29·66 [17·39–42·87], $P<0·0001$). Treatment was well tolerated. Three participants developed a transaminase rise (alanine aminotransferase 4·5–5·9 times the upper limit of normal) with a normal bilirubin 28 days after starting the NK3R antagonist, which normalised within 90 days (1,2). Treatment with a neurokinin 3 receptor antagonist could be practice changing as it safely and effectively relieves hot flush symptoms without the need for oestrogen exposure.

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Workshop 5: How do I...(2)

CMW5.1

How do I manage endocrinopathies in HIV patients?

Alison Wren
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Endocrinopathy is common in patients with HIV and presents a distinct series of challenges. Polypharmacy is common (both of prescribed and non-prescribed drugs) with the potential for drug-drug interactions and endocrine adverse effects of longterm medication. Structural pathology is also commoner than in the general population with the potential for both tumours and atypical infections affecting endocrine organs. Altered binding proteins are common, particularly high SHBG, affecting interpretation of total hormone assays. Autoimmune endocrinopathy is also common, particularly with the immuno-reconstitution that occurs in the months after commencing anti-retroviral therapy. I will share some cases, experience gained and tips from working with a large HIV unit.

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CMW5.2

How do I manage Paget's disease

Stephen Gallacher
Queen Elizabeth University Hospital, Glasgow, UK.

Paget's disease of bone is the second most common metabolic bone disease after osteoporosis. It is a condition characterised by abnormal bone cellular activity resulting in the formation of disorganised (and weaker) bone. Paget's disease can affect single or multiple bones. In many cases it may be asymptomatic, however it can often be associated with pain affecting the pagetic bone or there may be 'peri-pagetic' pain related to altered biomechanics due to changes in bone shape or to stress put on adjacent joints leading to the development of osteoarthritis. The primary pathological change is an increase in bone turnover. This increase in turnover can be assessed by measurement of alkaline phosphatase which often correlates with both the extent of the pagetic bone load and the degree of pagetic activity. Aside from pain, Paget's disease can be associated with a variety of complications. These include bone deformity and fractures, compressive neurological problems leading to e.g. spinal stenosis and deafness. Cardiovascular and metabolic complications are rare and transformation to osteosarcoma is particularly rare. The primary aims of treatment are to manage pain and/or associated complications. Antiresorptive treatment is the mainstay of therapy with IV zoledronic acid being the treatment of choice. Antiresorptive therapy will both reduce bone vascularity and be associated with falls in alkaline phosphatase. There has been some recent interest in other bone turnover markers as tools to assess pagetic activity however the role for these markers remains uncertain. It had been hoped that aggressive targeting of alkaline phosphatase suppression might be associated in less in the way of longer-term pagetic complications but data from PRISM and PRISM-EZ studies suggest this approach is probably not beneficial.

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CMW5.3

How do I manage thyroid eye disease?

Petros Perros
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Evidence is emerging from the UK and elsewhere that: (a) endocrine clinics are reservoirs of undiagnosed thyroid eye disease (TED); (b) the interval from onset of symptoms of TED to diagnosis and treatment often exceeds 1 year; (c) simple interventions that can be initiated in the endocrine clinic can reverse mild TED and prevent progression; (d) immunosuppressive treatments work best in the first 9 months. Early detection of TED is a fundamental part of management and can be achieved by a simple, easy and rapid clinical evaluation. Management in the endocrine clinic consists of meticulous attention to achieving and maintaining euthyroidism, avoidance of radioiodine, selenium supplements, artificial tears and close monitoring for progression. Patients who progress should be referred to a Joint Thyroid Eye Clinic offering specialist care by a team of experienced endocrinologists

and ophthalmologists. Access to Joint Thyroid Eye Clinics should be rapid as there is an inverse relationship between efficacy of medical treatments and duration of TED. High dose intravenous pulses of methylprednisolone are the mainstay of medical treatment for active, moderate to severe TED and for optic nerve compression. Orbital irradiation has a modest beneficial effect in patients with vertical diplopia. Newer medical treatments include biologics, but their role is still under investigation. Surgical management plays an important part in patients with optic nerve compression and more commonly for rehabilitative purposes. Variation in access to surgical services for TED in the UK is high, and an area where improvement is needed. TEAMeD (Thyroid Eye disease AMstErdam Declaration implementation group) was established in 2009 to promote the Amsterdam Declaration, which pledged to improve care for people with TED. 'TEAMeD-5', is a campaign to promote better care for patients with TED and provides easily accessible guidance and support for endocrinologists on how to manage TED: *http://www.btf-thyroid.org/projects/teamed/332-teamed-5*.

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CMW5.4

Abstract Unavailable.

CMW5.5

How do I know which non-diabetic patients could benefit from a GLP-1 analogue

Barbara Mc Gowan
Guy's & St Thomas Hospital, London, UK.

The physiological effects of glucagon-like peptide (GLP-1) are of great interest because of their potential clinical relevance. GLP-1 is secreted by the L-cells of the distal ileum and colon in response to nutrient ingestion. It acts as an incretin hormone and augments glucose-stimulated insulin secretion in the pancreas. The use of GLP-1 agonists for the treatment of Type 2 Diabetes (T2DM) is well established. However, GLP-1 has several other physiological functions. It acts as satiety hormone by its direct effects on appetite inhibition through GLP-1 receptors expressed within the hypothalamus. Peripherally, GLP-1 inhibits gastric emptying, acid secretion and motility. This session will discuss the use of the GLP-1 agonists as weight loss agents in patients with obesity without T2DM. It will highlight potential metabolic benefits including remission of pre-diabetes and obstructive sleep apnoea. The results of recent Phase-2 clinical trials for new and more powerful GLP-1 agonists will be discussed, including how these agents may bridge the gap between lifestyle and metabolic surgery for the treatment of obesity in the near future.

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CMW5.6

How Do I...Investigate Sweating

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Sweating in the absence of any physiological precipitant can be extremely distressing and unpleasant. Primary hyperhydrosis, usually affecting the palms of the hands, soles of the feet and the axillae, usually presents in teenage years and is managed by dermatologists. Secondary hyperhydrosis usually develops later in life, is more generalised and may be associated with flushing. The differential diagnosis is very long and includes systemic illness (such as lymphoma and chronic infections), neurological disorders (such as Parkinson's syndrome and neuropathies), drugs (including SSRIs and tricyclic antidepressants) and withdrawal from certain drugs (including SSRIs). Endocrine disorders may also be associated with secondary hyperhydrosis and the typical list includes oestrogen defciency in women, thyrotoxicosis, acromegaly, carcinoid syndrome and phaeochromocytoma. General practitioners have generally excluded all the common causes of secondary hyperhydrosis by the time a referral is made. Endocrinologists are then left with exclusion of rarities and, of course, the reality is that endocrine investigations are invariably unremarkable. Although sweating is a recognised symptom of carcinoid syndrome and phaeochromocytoma, in practice these conditions rarely (if ever) present with this symptom in isolation and usually their diagnoses are made in other contexts. In many people with unexplained secondary hyperhydrosis, there is a prior history of significant weight gain. Treatment of unexplained hyperhydrosis is challenging. Usually by the time of referral, simple measures (such as lifestyle change and anti-perspirants) have already been explored. Botulinum toxin injections and iontophoresis (with or without glycopyrrolate) can be very effective for axillary and palmar/plantar hyperhydrosis respectively. Surgery and microwave ablation therapies are also available. Anti-cholinergic agents (such as propantheline and oxybutynin) can be tried for generalised hyperhydrosis, but their efficacy is often limited by side effects. Beta-blockers and clonidine are also sometimes used.

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Applied Physiology Workshop

GPCRS: hotspots and complexes

APW1.1

Calcium-sensing at 25 years

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This year marks 25 years since the calcium-sensing receptor (CaSR) was first identified in bovine parathyroid and the receptor has since emerged as a fundamental contributor to extracellular calcium (Ca^{2+}_e) homeostasis, by regulating parathyroid hormone release and urinary calcium excretion. The CaSR is a class C GPCR that is functionally active as a homodimer. It couples to multiple G-protein subtypes to activate intracellular calcium mobilisation and mitogen-activated protein kinase signalling, induce membrane ruffling and suppress cAMP pathways. The importance of the CaSR in the regulation of Ca^{2+}_e has been highlighted by the identification of >230 germline loss- and gain-of-function CaSR mutations that give rise to disorders of calcium homeostasis, including familial hypocalciuric hypercalcaemia (FHH) and autosomal dominant hypocalcaemia (ADH). Functional studies of these disease-associated mutations have demonstrated that CaSR signals in a biased manner and have revealed specific residues important for receptor activation. Furthermore, allosteric modulators targeting the CaSR represent a potential therapy for patients with symptomatic forms of FHH and ADH, and their specific actions on distinct signalling pathways may offer a precision medicine approach to treatment. In the last decade, the genetic heterogeneity of FHH and ADH has emerged, with mutations in the $G\alpha_{11}$ protein, by which CaSR signals, and the adaptor protein-2 sigma subunit, by which CaSR is endocytosed, being revealed as additional contributors to calcaemic disorders. Studies of these mutations have uncovered novel mechanisms by which CaSR is internalised, and demonstrated that CaSR can signal by an endosomal pathway. Additionally, non-calcitropic roles have emerged for the receptor in inflammation, bronchoconstriction, wound healing, gastro-pancreatic hormone secretion, hypertension, and glucose metabolism. Understanding the mechanisms by which these novel signal pathways and non-calcitropic roles arise are likely to provide continued insights into the CaSR for years to come.

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APW1.2

FSH, Body Fat, Bone Mass and Biological Aging

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Pituitary hormones have long been thought solely to regulate single targets. Challenging this paradigm, we found that both anterior and posterior pituitary hormones, including FSH, had other functions in physiology. We have shown that FSH regulates skeletal integrity, and, more recently, find that FSH inhibition reduces body fat and induces thermogenic adipose tissue in wild type mice, phenocopying genetic haploinsufficiency for the FSH receptor. A polyclonal antibody raised against a short, receptor–binding epitope of FSHβ was found not only to rescue bone loss post–ovariectomy, but also to display marked anti–obesity and pro–beiging actions. Questioning whether a single agent could be used to treat two medical conditions of public health importance – osteoporosis and obesity – we developed two further monoclonal antibodies against computationally defined receptor–binding epitopes of FSHβ. We show that both monoclonal antibodies reduce body weight and fat mass and cause beiging in mice on a high-fat diet. They also increase cortical thickness and trabecular bone volume, and microstructural parameters, in sham–operated and ovariectomized mice, noted on microcomputed tomography, as well as inhibit osteoclastic bone resorption and stimulate osteoblastic bone formation. These effects were exerted in the absence of alterations in serum estrogen in wild-type mice. Our study provides the framework for the future development of FSH–based therapeutics that could potentially target both bone and fat.

References

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APW1.3

The nanodomain organization of GPCR signalling: lessons from TSH receptors and beyond

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My group investigates the basic mechanisms of G protein-coupled receptor (GPCR) signalling and their alterations in endocrine disease, which we study using innovative microscopy methods such as fluorescence resonance energy transfer (FRET) and single-molecule microscopy. Using these methods, we have demonstrated that GPCRs do not only signal via cyclic AMP at the cell surface but also at intracellular sites (Calebiro et al., PLoS Biology 2009). We have shown that this is required for the biological effects of hormones like TSH and LH. Moreover, we have demonstrated for the first time that this occurs via retrograde trafficking of the internalized receptors to the trans-Golgi network (TGN), where they induce local cAMP signalling (Godbole et al., Nat Commun 2017). In parallel, we have developed an innovative single-molecule microscopy approach to investigate receptor interactions on the plasma membrane with unprecedented spatiotemporal resolution. Using this approach, we could demonstrate that GPCRs from transient complexes that differ considerably in size and location among receptors (Calebiro et al., PNAS 2013) Very recently, we were the first to directly visualize individual receptors and G proteins as they interact and signal in living cells (Sungkaworn et al., Nature 2017). This has revealed 'hot spots' for G protein signalling on the plasma membrane, which we hypothesize confer speed and specificity to GPCR signalling. Altogether, the most recent findings by our and other groups suggest that GPCR signalling is highly organized in time and space, which likely plays a key role in determining signal specificity downstream of this important family of membrane receptors. These findings also have major implications for drug discovery, as they might provide a new basis to precisely modulate GPCR activity, and, thus, develop innovative drugs with improved efficacy and tolerability for diseases such as diabetes or heart failure.

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Metabolites as hormones

APW2.1

Metabolic and microbial investigation of weight loss surgery

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Bariatric surgery, in particular, Roux-en-Y gastric bypass (RYGB), is the most effective treatment for morbid obesity. The restricted gastric capacity and reduced absorption of nutrients cannot account for all the metabolic benefit we observe post-operation. Therefore, we applied metabolic and microbial profiling approach to investigate the potential mechanisms of RYGB surgery. Metabolic profiling strategy is widely applied in the discovery and development of metabolic biomarkers of disease and therapeutic intervention in personalized healthcare, as well as for characterizing host-gut microbial metabolic interactions. We carried out RYGB surgery in a range of rodent models and applied metabolic, microbial and microRNA profiling to study systemic responses of the body to RYGB surgery. All these rodent models showed a significant weight loss in the RYGB-operated animals and significant increases in the gut hormones, e.g. PYY and GLP-1. Consistent changes in tricarboxylic acid cycle intermediates and host-microbial co-metabolism were also found and these changes are independent of the reduced food intake or weight loss post-operatively. The faecal bacterial composition also shifted from Firmicute-dominant to Proteobacteria-dominant community. We also observed that 14 circulating microRNAs differentially expressed post RYGB, which could be associated with increased energy expenditure post-surgery. In human cohorts, we also observed significant changes in host-microbial co-metabolites and decreased branched-chain amino acids in serum of the RYGB patients. Our studies showed that RYGB surgery induced changes in both local and global metabolic activities. These findings aid our understanding of the metabolic phenotype of bariatric procedures and can facilitate development of alternative treatments for obesity-related diseases.

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APW2.2

Short chain fatty acid signalling in human health and disease

Edward Chambers
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Prospective studies and clinical trials have repeatedly demonstrated that high intake of dietary fibre reduces the incidence of metabolic diseases and their risk factors. An increased intake of dietary fibre raises the amount of undigested material available for fermentation by the gut microbiota and the production of short chain fatty acids (SCFA). SCFA have been shown to regulate energy homeostasis through various metabolic pathways and receptor-mediated mechanisms. The majority of the available evidence to support a role of SCFA in metabolic regulation has been obtained from animal models. The presentation will provide an overview of translational human research that has investigated the impact of SCFA on hormone release at different organ sites.

DOI: 10.1530/endoabs.59.APW2.2

APW2.3

Abstract Unavailable.

Early Career Prize Lectures

ECP1.1

Neurokinin 3 receptor antagonism – the magic bullet for hot flushes?

Julia Prague
Department of Investigative Medicine, Imperial College, London, UK.

Seventy percent of menopausal women experience vasomotor symptoms (hot flushes/night sweats), which can be highly disruptive and persist for years; 10% describe them as intolerable. Hormone replacement therapy (HRT) and other available treatments have variable efficacy and/or side effects. A novel therapeutic could therefore benefit 10 million in the UK alone, and particularly those who have a contraindication or aversion to HRT. Neurokinin B signalling is upregulated in menopausal women secondary to oestrogen deficiency, and over recent years, together with its receptor (the neurokinin 3 receptor (NK3R)), has increasingly been implicated as an important mediator of menopausal hot flushes. We recently completed the first clinical trial of an NK3R antagonist in a randomised, placebo-controlled, double-blind, crossover study, and showed that hot flush frequency can be reduced by 73% compared to baseline as early as day 3 of treatment (51 percentage point reduction compared to placebo) as well as reducing hot flush severity, bother, and interference. Subsequent work investigating LH pulsatility in a sub-group using mathematical modelling has challenged the long held scientific dogma regarding the hormonal aetiology of vasomotor symptoms; and investigating single nucleotide polymorphisms in the NK3R gene has uncovered further mechanistic detail of hot flush experience and aetiology.

DOI: 10.1530/endoabs.59.ECP1.1

ECP1.2

The Importance of Local Steroid Action in the Regulation of Fertility

Douglas Gibson
University of Edinburgh, Edinburgh, UK.

In women, establishment of pregnancy is dependent upon 'fine-tuning' of the endometrial microenvironment which is mediated by differentiation (decidualisation) of human endometrial stromal fibroblasts (hESF). Using a robust *in vitro* model of decidualisation we have demonstrated an important role for local steroid metabolism in regulating hESF, something previously considered a solely endocrine-mediated process. We have conducted detailed time-course profiling of the steroidogenic capacity of hESF during decidualisation and established that expression of aromatase, the key enzyme required for synthesis of estrogens, as well as enzymes that convert precursor androgens into active testosterone and dihydrotestosterone (AKR1C3; SRD5A1) are altered in a time-dependent manner. Expression of these enzymes results in increased biosynthesis of potent steroid receptor agonists (estrogens and androgens) that in turn regulate expression of genes important for endometrial receptivity and immune cell-mediated vascular remodelling. Our recent studies demonstrate that bioavailability of circulating precursors including dehydroepiandrosterone, as well as sulfated steroids, also contribute to local tissue steroid concentrations and impact on decidualisation. Collectively, these findings represent a paradigm shift in our understanding of the importance of local sex steroid action in the endometrium during the establishment of pregnancy, highlighting new therapeutic targets for reproductive health and disease.

DOI: 10.1530/endoabs.59.ECP1.2

Meet the Expert Sessions

What the Endocrinologist Needs to Know about Gentics

MTE1

What the endocrinologist needs to know about genetics?

Marta Korbonits
Centre for Endocrinology, WHRI, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

Prevention of disease or severe complications is the intended hallmark of modern medicine. Currently available diagnostic methods allow the early recognition of an increasing number of diseases allowing timely treatment and hopefully better long-term outcomes. The best examples of this strategy are genetic diseases and every week the genetic cause for another disease is identified. Therefore, the understanding of the practicing clinician the nature and pitfalls of genetic testing is greater than ever. In general, the threshold for genetic testing lies at least in the range of 2–10% positive results, but of course is influenced by the clinical impact a diagnosis makes on the future health of a patient and the patient's family. Genetic testing should only be recommended if there is either evidence or logical support that it will reduce morbidity or mortality for the patient or other family members or significantly would affect life choices. Often the benefit of testing will be rather in cascade family screening of, to date, unaffected individuals than for the patient itself. In other cases, there are treatment decisions that are influenced by genetic testing. Understanding the various genetic terms are crucial for the interpretation of the test result and the correct advice for the patient. The power of newer types of genetic testing also brings the problem of interpretation of rare variants into the clinical setting. In this interactive session we will systematically go through the most important issues an endocrinologist should understand and will illustrate the points with examples from endocrine genes and diseases.

DOI: 10.1530/endoabs.59.MTE1

GC Metabolic Health

MTE2

Glucocorticoids in metabolic health: Effects of selective GR modulators

Onno Meijer
Leiden University Medical Center, Leiden, Netherlands.

Endogenous glucocorticoids help to mobilize energy to prepare for daily activity and to deal with stressors, e.g. by catabolic effects on muscle and stimulation of the release of glucose and fat from the liver. Chronic overexposure to glucocorticoids has strong deleterious effects, in medical glucocorticoid and in Cushing's disease. It is less clear to what extent glucocorticoid signalling may be used as a therapeutic target in the much more frequent consequences of the metabolic syndrome. We have tested new GR antagonists and selective GR modulators in mouse models of metabolic syndrome. Selective modulators combine antagonism on some GR-mediated processes with (partial) agonism on others. In a series of experiments, we have found that selective receptor modulation can have pronounced benefits over full antagonism in these models. E.g. some level of anti-inflammatory efficacy may be beneficial. Selective GR modulator C118335 in mice had very pronounced effects on hepatic liver accumulation. Due to its GR agonism on VLDL production, but lack of agonism on lipid uptake by the liver, this compound can fully prevent and reverse hepatic liver accumulation in mice after 6 weeks on high fat diet. These data suggest that the glucocorticoid receptor is a valid target, and that selective modulation, by interfering with GR-stimulated metabolic fluxes, may have advantages over full antagonism of the GR.

DOI: 10.1530/endoabs.59.MTE2

Biochemistry Masterclass

MTE3.1

Insulin assay

David Halsall
Cambridge University Hospitals Trust, Cambridge, UK.

Quantitation of insulin in human plasma was first achieved by Berson and Yallow in 1960, as reported in their seminal paper describing radio-immunoassay (J Clin Invest. 1960(7)39:1157). Despite the wider availability of insulin assays, improvements in immunoassay design and the advent of mass-spectrometric methods to quantitate insulin, insulin assays are used far less than other hormone assays in endocrinological investigations. This is largely due to the dynamic nature of insulin *in vivo* and the complex relation between insulin concentration and relevant clinical correlates. The investigation of hypoglycaemia is the most widely accepted application for insulin assay. The endocrinologist needs to be vigilant when interpreting insulin concentration in this context as most commercial assays do not detect all synthetic insulins or biologically active but partially processed insulin such as proinsulin. Some assays do not have the required analytical sensitivity to measure insulin at low concentration. Mass-Spectrometric assays offer the promise for better detection of insulin analogues, but these are not yet widely available. Whilst useful in a research context, insulin assays are not routinely used to diagnose insulin resistance due to limited clinical utility. A notable exception is the diagnosis of severe insulin resistance syndromes where features like lipodystrophy are present or characteristics of insulin resistance are either extreme or disproportionate to habitus. Hirata syndrome is a rare condition caused by insulin autoantibodies; such antibodies can confound both the measurement of biologically active insulin and the diagnosis of hypoglycaemia. Patients usually present with very high plasma insulin. The situation becomes more complex when anti-insulin antibodies coexist with diabetes. Whilst anti-insulin antibodies are often detected in diabetes, in rare cases both insulin pharmacokinetics and our ability to detect biologically active insulin are affected.

DOI: 10.1530/endoabs.59.MTE3.1

MTE3.2

Insulin-like growth factor-1 (IGF-I) assays

Gwen Wark
Berkshire and Surrey Pathology Services, Royal Surrey County Hospital, Guildford, UK.

Insulin-like growth factor-1 (IGF-I) is a 70-amino acid peptide hormone which is the principal mediator of the effects of growth hormone (GH). Pituitary GH is secreted in a pulsatile manner and is subjected to various environmental and physiological stimuli. In contrast, IGF-I is synthesised in a more stable manner and has a longer half-life therefore it is a more reliable biomarker of GH status. Hence IGF-I measurements are essential for the diagnosis and treatment of GH deficiency and GH-excess conditions such as acromegaly. Traditionally, IGF-I has been measured by using commercial immunoassays but an alternative platform for serum IGF-I quantification is liquid-chromatography mass spectrometry (LC-MS). Nevertheless the mainstay for IGF-I analyses in the UK remains the use of automated immunoassays supplied from principally three manufacturers: Siemens Healthineers, DiaSorin and Immunodiagnostic Systems (IDS). Although a WHO international standard (IS) for IGF-I (IS 02/254) is available for the calibration of IGF-I immunoassays, there are still significant method related differences observed for IGF-I results. This short presentation will use clinical examples to highlight factors that contribute to IGF-I assay differences such as; the effect of insulin-like growth factor binding proteins (IGFBPs), the need for establishing appropriate reference values etc to demonstrate their impact on IGF-I result interpretation and patient care.

DOI: 10.1530/endoabs.59.MTE3.2

MTE3.3

Abstract Unavailable.

Brown Adipose Tissue

MTE4

Brown adipose tissue: A neuroendocrine target

Jan Nedergaard
The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden.

Brown adipose tissue presently attracts broad interest due to the possibility that it may have the potential to counteract development of obesity and may have other positive metabolic effects, e.g. on glucose and lipid handling. As brown adipose

tissue is found, to different extent, in nearly all humans up to middle age, the possibility to affect its activity may be of significance for human health. Brown adipose tissue is affected by several (neuro)endocrine factors. Best studied are the effects of the sympathetic nervous system; the released norepinephrine not only directly induces the thermogenic processes in the tissue but also promotes the differentiation process and, uniquely, also cell proliferation and anti-apoptosis. The interaction with thyroid hormone is not well understood. Apparently, the effects of centrally administered thyroid hormone on body metabolism are mediated via a stimulation of the sympathetic nervous system whereas the increased metabolic rate observed after peripheral thyroid hormone treatment is not dependent on brown fat thermogenic activity. At thermoneutrality, glucocorticoid treatment diminishes the thermogenic capacity of brown adipose tissue but the increased obesity observed during such treatment is not due to the inactivity of the tissue. There is no direct effect of leptin on brown adipose tissue activity but leptin increases body temperature if given to leptin-deficient mice; this is an effect directly on the apparent set point for the body temperature. The hormonal basis for the increased recruitment and activity of the tissue seen during so-called diet-induced thermogenesis is still not identified.

DOI: 10.1530/endoabs.59.MTE4

Non-surgical Management of Incurable Thyroid Cancer
MTE5

Non-surgical management of incurable thyroid cancer

Maria Alevizaki
Kapodistrian University, Athens, Greece.

The majority of differentiated thyroid cancer (DTC) cases will be successfully treated with surgery usually (but not always) followed by radioiodine (RAI). The large majority have excellent prognosis. 10% of DTC may present disease progression: local relapse and/or distant metastases. 25–50% of these will slowly loose the capacity to take up radioiodine – RAI refractory cases. Further management includes loco-regional therapies such as surgical excision of lesions causing symptoms, chemoembolization, external irradiation of bone or mediastinal lesions and radiofrequency ablation. When these modalities fail to restrain tumour growth, multi tyrosine kinase inhibitors (TKIs) are used, which are oral antineoplastic agents targeting the molecular pathways activated during tumorigenesis. With these agents a substantial proportion of patients will have at least stabilization of disease. However these agents also have significant side-effects; furthermore, 'escape' from their antitumour effect may be observed at follow-up. An interesting agent that may restore the capacity of iodine uptake in the tumour has been reported; relevant clinical trials are now running. Medullary thyroid cancer (MTC) may also present at advanced stage or progress rapidly after surgery. The management of progressive disease includes locoregional therapies as in the case of DTC. Furthermore, agents that target the molecular pathways involved in its pathogenesis - TKIs - have been used. Two of these agents (Vandetanib and Cabozantinib) have been approved in the USA and in Europe for use in MTC patients with progressive disease. These agents are associated with significant increase in the progression free survival. They stabilize disease in the majority of cases. The optimal timing of initiation of such treatments in both types of thyroid cancer has not been clearly defined and should be individualized. The management of these difficult cases requires expertise and a team approach.

DOI: 10.1530/endoabs.59.MTE5

Gender Dysphoria
MTE6

Gender dysphoria: Treatment and out comes

Leighton Seal[1,2]
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[2]GIC Tavistock abd Poertman NHS Foundation Trust, London, UK.

Introduction
The incidence of people presenting to gender services is increasing rapidly the case load appears to double every 5 years.This equates to a an estimated incidence of between 1:7440(10) to 1:30,000 for natal males and 1:31,153(10) to 1:10000 for natal females making this a relatively common disorder. The aim of therapy is threefold to suppress the production of the natal sex steroids, provide sufficient hormone levels for the development of the secondary sexual characteristics of the desired gender and finally in the longer term to prevent the consequences of hypogonadism following gonadectomy. Hormone therapy is undertaken in the context of a multidisciplinary team who assess and diagnose the gender dysphoria psychologically and advise on the suitability of the individual for treatment. For Trans women oestradiol valarate in increaseing dose to achieve follicular phase oestradiol levels in combination with a GnRH analogue is the mainstay of hormone treatement.The major risk of oestrogen therapy, as in natal females, is that of thromboembolism. For Transmen the use of standard male testosterone therapy is usually sufficient to suppress ovarian function without the need for a GnRH analogue. The current data suggest that long-term treatment with testosterone in transmen is not associated with any increased risk of cardiovascular disease and the standard mortality ratio of this patient population is one, which is to say there is no increase in mortality. Hormonal therapy being continued lifelong and the target levels for that hormone replacement are the same as for the general male population. I will also discuss the treatment of non-binary people.
Key learning points
Indications for treatment, Effects of cross sex hormone therapy in both genders, Side effects of therapy, Aims and monitoring of cross sex hormone treatment, Long term outcomes, Common regimens used.

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A Year in Thyroid
MTE7

Abstract Unavailable.

Circulating Tumour Cells in NETS
MTE8

Abstract Unavailable.

Pituitary Ion Channel Activity in Health and Disease
MTE9

Abstract Unavailable.

Service Improvements
MTE10.1

GIRFT (Getting It Right First Time) for Endocrinology, NHS England

John A. H. Wass, Professor of Endocrinology, University of Oxford and Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford OX3 7LJ, United Kingdom
John Wass
Oxford University, Oxford, UK.

The GIRFT (Getting It Right First Time) visits, about which we have consulted the membership of the Society for Endocrinology and had positive feedback from many members, have now started. We have done four pilots in Birmingham, Leicester, Oxford and York. The objectives are to try to introduce a quantitative approach to help demonstrate best practice. It will explore surgical outcome data

and complication rates with regard to thyroid, parathyroid, adrenal, pituitary and neuroendocrine surgery where applicable. It is also looking at the number and experience of endocrinologists and surgeons. Evidence suggests that high volume surgeons deliver better outcomes, but there is still over x% of operations done by surgeons doing less than y operations a year. We need to reduce the number of low volume surgeons in terms of adrenal, pituitary and less frequently thyroid. To improve quality nationally, there also has to be a focus on correctly coding activity, which is highly variable across the UK and this will improve the profile of the specialty. Differentiating specialised from non-specialised endocrinology will help promote the importance of the specialty and improve funding. We are looking also to improve the delivery of outpatient care in endocrinology especially for those travelling long distances in terms of the steadily rising numbers of outpatients. Lastly we need to make sure there are adequate multidisciplinary tier 3 services for patients with an obesity problem in every hospital. Currently only 50% of the population is covered. Next year we aim to publish a review of the data jointly with the Society for Endocrinology which together will provide a national report.

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MTE10.2

The Society for Endocrinology peer review scheme

Antonia Brooke
Royal Devon and Exeter Foundation Trust, Exeter, UK.

Society for Endocrinology peer review is in its 16th year. In 2018 the format has been updated and single centre reviews are now being carried out. The catchment area of hospitals reviewed has varied from 280 000 to 2.5 million. A review helps to highlight a centre's strengths and help focus on areas for development. It is a qualitative deep dive into a service which includes benchmarking against other similar services. The review is conducted by a team of clinical endocrinologists and specialist nurses with a similar profile to the trust being reviewed. It is mutually beneficial to centres and reviewers and a good benchmark for quality of care. This talk will explain the benefits of the scheme, provide examples of good practice from recent reviews and innovative ways of networking to support continued improvements in endocrinology in the future.

DOI: 10.1530/endoabs.59.MTE10.2

MTE10.3

Optimising patient outcomes and time management: the perfect MDT

Helen Simpson
UCLH NHS Foundation Trust, London, UK.

Multidisciplinary working is key to working as an endocrinologist. MDTs can be formal, such as in an oncology context, or a looser working arrangement of health care professional across different specialties and roles providing care to patients, often with multisystem or rare endocrine conditions. They can range from an MDT with no patients present, to a multidisciplinary or joint clinic. I will discuss some different models of multidisciplinary working and ideas on how to develop multidisciplinary working. I will also discuss challenges and disadvantages of MDTs.

DOI: 10.1530/endoabs.59.MTE10.3

Skills

Skills 1: Presentation skills

SK1.1

How to write an Abstract

Paul Newey
University of Dundee, Dundee, UK.

The scientific abstract provides the researcher with an opportunity to communicate their research efforts concisely to a wider target audience. Most commonly, this is as part of a research article or submission to scientific meeting, and in each situation, the preparation of a well-written abstract will enhance the likelihood of a successful outcome (e.g. an article being sent for peer-review, or conference abstract being accepted for oral presentation). Indeed, a well-structured abstract frequently provides reassurance to the reader as to the mindset of the researcher and the likely quality of their research. Thus, the abstract should be viewed as a critical component of the scientific process that requires careful consideration, rather than a quick task immediately prior to submission. This presentation will address many of the key considerations required for successful abstract writing. In particular, it will focus on the essential elements of a strong abstract, as well as providing tips on how to ensure it reaches its target audience.

DOI: 10.1530/endoabs.59.SK1.1

SK1.2

Abstract Unavailable.

SK1.3

Abstract Unavailable.

SK1.4

Abstract Unavailable.

SK1.5

How do I respond to peer review?

Colin Farquharson
Roslin Institute, University of Edinburgh, Edinburgh, UK.

Having spent many months, if not years, obtaining and analysing your data you are ready to submit your manuscript to your preferred Journal. There is one step though that is often over-looked; responding to reviewer's comments *i.e.* the peer review process. This can be challenging to all but especially those who have not experienced the process before. There are however some golden rules, that if followed can make the process easier and result in your goal of getting your manuscript accepted for publication. The outcome of the review process can be rejection before (at triage) or after review, major or minor revision or, on the rare occasion, accept. If you are given the chance to revise your manuscript, view the reviewer's comments as a positive opportunity to improve your submission. The majority of reviewers want to help, not criticise and their reports are vital in enabling you to improve your paper to make it the best it can be. Acknowledge what can be improved and be prepared to do more studies/analysis. The reviewer's reports may contain comments that you strongly disagree with, or you consider simply wrong. First, get over it and control your anger and resist the temptation to reply in an aggressive tone. Rather, seek first to understand what the reviewer wants and this will make it easier for you to respond. Respond completely, politely but avoid conflict and don't escalate. Where possible look for compromise however, you can disagree with the reviewer's comments and suggested edits provided you can explain and preferably backed up with evidence. In your final rebuttal, provide a detailed, point-by-point response detailing changes made and where in your manuscript and consider carefully the comments of the Senior Editor. Remember what you want, winning vs publishing. Pick your battles!

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Skills 2: How do I pass the SCE

SK2

How Do I pass the SCE Exam?

Graham Leese
University of Dundee, Dundee, UK.

This presentation will look at specific samples of SCE exam questions. The rationale of the questions and the thinking behind the question writing will be explained. The background and rationale of the exam will be explained in terms of this being an 'exit' exam in Endocrinology and Diabetes to test clinical discernment and understanding within a practical context. It is linked with the JRCPTB specialty training curriculum, to enable a CCT to be awadred in awarded in Endocrinologya nd Diabetes. The detail of how the exam is constructed and the quality assurance around the exam questions will be explained. The key documents that the exam refers to will be mentioned, before running through a series of questions in detail. There will be plenty of time for questions and answers.

DOI: 10.1530/endoabs.59.SK2

Master Class

Masterclass 1: PCOS

MC1.1

Polycystic ovary syndrome; The role of androgen excess in disease pathogenesis and metabolic dysfunction

Michael O Reilly
University of Birmingham, Birmingham, UK.

Insulin resistance and androgen excess, alongside anovulatory infertility, are the cardinal clinical and biochemical features of polycystic ovary syndrome (PCOS). Circulating androgen burden and metabolic dysfunction in PCOS are closely correlated, but an independent contribution of androgens *per se* to metabolic and other complications of PCOS remains poorly characterised. My work since 2012 has focused on delineating the distinct impact of androgens on metabolic function, with a particular focus on adipose tissue and insulin resistance. Adipose tissue is capable of androgen activation, and has a complex network of activating and inactivating enzymes. One of these enzymes, aldoketoreductase type 1 C3 (AKR1C3), activates the androgen precursor androstenedione to more potent testosterone. AKR1C3 expression is upregulated in subcutaneous adipose tissue from women with PCOS compared to BMI-matched controls. Using adipose tissue microdialysis, we have shown that PCOS women have significantly increased adipose concentrations of the active androgens testosterone and dihydrotestosterone compared to controls. Furthermore, using *in vivo* and *in vitro* studies, we have demonstrated direct effects of intra-adipose androgens on adipocyte lipid biology, with increased *de novo* lipogenesis and suppression of lipolysis promoting adipocyte hypertrophy. In other aspects of the presentation, I will discuss the relative contribution of the 11-oxygenated androgen synthesis pathway to circulating androgen burden and metabolic dysfunction in PCOS, which traditionally has been understudied in PCOS and other disorders of androgen excess. Data from a number of population-based studies will also be presented, which we have used to delineate the independent effects of androgen excess on metabolic disorders such as diabetes and non-alcoholic fatty liver disease, as well as on less well characterised potential complications of androgen excess such as obstructive sleep apnoea and idiopathic intracranial hypertension.

DOI: 10.1530/endoabs.59.MC1.1

MC1.2

Polycystic ovary syndrome: management

Stephen Franks
Imperial College London, London, UK.

Polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility, menstrual disturbances and hirsutism. PCOS is also associated with a metabolic disturbance characterised by hyperinsulinaemia and insulin resistance. Women with PCOS are at increased long-term risk of developing type 2 diabetes (T2DM) and carry a significant risk factor profile for cardiovascular disease. Obesity amplifies both reproductive and metabolic dysfunction. A growing body of evidence also highlights the high prevalence of anxiety and depression amongst women with the syndrome. The diagnosis of PCOS is made principally on clinical grounds, supported by a small number of biochemical investigations. The choice of investigations in women with PCOS depends primarily on the mode of presentation. Treatment should be tailored to the presenting complaint. For example, in infertile women, induction of ovulation can be achieved in most cases by the use of antioestrogens. Weight reduction in obese subjects with PCOS not only increases the chance of fertility but will also improve the long-term prognosis with regard to development of diabetes. Symptoms of androgen excess (hirsutism, persistent acne) are best managed by suppression of ovarian androgens, using a combined oral contraceptive, supplemented, if necessary, by androgen receptor blockade. Insulin sensitizing drugs such as metformin have a place in regulation of menses and in reducing risk of T2DM. Psychological support may be needed for those with anxiety and depression.

DOI: 10.1530/endoabs.59.MC1.2

Debate

This house believes that the gut is the conductor of the endocrine orchestra

D1.1

Abstract Unavailable.

D1.2

Abstract Unavailable.

Nurse Session

Nurse Session 1: Pituitary adenomas; beyond surgery

N1.1

Abstract Unavailable.

N1.2

The role of gamma knife in the management of pituitary adenomas

John Newell Price
University of Sheffield, Sheffield, UK.

Pituitary radiotherapy plays an important role in the overall management of pituitary disease, but needs discussion at an expert regional pituitary MDT. Repeat surgical exploration is increasingly performed either as an alternative to radiotherapy or to further reduce tumour bulk ahead of radiotherapy. Careful discussion with the patient on the risks and benefits of radiotherapy, and all the other options, is essential. It is best to consider the control of tumour growth and any hormonal hypersecretion separately – use of radiotherapy to control an expanding tumour in one patient with no hypersecretion, or in a patient with a tiny tumour volume but in whom there is excess hormone secretion and for whom other medical therapies may be used. If there is pre-existing hypopituitarism there is 'less to loose' by radiotherapy, but even when pituitary function is intact it is essential to control tumour growth. The choice between the different modalities of radiotherapy is governed primarily by the anatomy of the tumour target. Modern fractionated radiotherapy over 5–6 weeks is highly conformal to the tumour target but the gamma knife offers single dose radiotherapy to the tumour volume (targeting accuracy 0.2 mm) with minimal radiation to surrounding structures. The main limiter to the use if the gamma knife is the distance to the optic apparatus so that dose is kept to <8Gy to that structure. Although it is commonly thought that gamma knife has a lower risk of late onset hypopituitarism our experience at the National Centre for Stereotactic Radiosurgery in Sheffield in over 340 patients (125 with acromegaly) is that the rates are not dissimilar to fractionated radiotherapy, but it is highly effective for control of hormonal hypersecretion and our 30 y follow data indicate no evidence of increased risk of other long term CNS sequelae, such as stroke.

DOI: 10.1530/endoabs.59.N1.2

N1.3

Abstract Unavailable.

N1.4

Gamma Knife Surgery – a Patient's Perspective

1. Introduction and a bit about me
2. My tumour and surgical treatment
Explanation of how my tumour presented and was diagnosed. Description of how I was treated with transsphenoidal surgery, the results of that, and subsequent craniotomy. Immediate endocrine effects.
3. Recurrence and its treatment – Radiotherapy vs Radiosurgery
Monitored with MRI scans, recurrence detected. Broad observations on what were the possible treatments for the recurring tumour, how the treatments work, which one I chose and why.
4. How Gamma Knife Radiosurgery treatment works
A layman's explanation of how Gamma Knife treatment works.
5. Having the treatment
Description of the process of Gamma Knife treatment, use of a metal frame attached to the skull, scan and planning. How I experienced the treatment and how it felt for me.
6. How I have been since
How my tumour and treatment has affected my life, and what I have been able to achieve. How my endocrine position has changed over the years, and thoughts about how this may have affected me as a person.

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Nurse Session 2: Adrenal crisis & steroid education; raising the safety bar

N2.1

Abstract Unavailable.

N2.2

National Education Programme for Patients with Chronic Adrenal Insufficiency

Gesine Meyer
Goethe-University Hospital, Frankfurt, Germany.

Appropriate hydrocortisone adjustment by the patient himself in situations of increased demand, e.g. in gastrointestinal or febrile infections, is indispensable to prevent adrenal crises (AC). Previous studies revealed a lack of knowledge concerning self-management in patients with AI. A comprehensive patient education is one of the key measures to avoid life-threatening AC. In November 2014, a working group of the adrenal section in the German Endocrine Society (DGE) met to develop a structured and consistent patient education programme. Starting from nine participating centres, a growing number of teams, each comprising an endocrine nurse and an endocrinologist, completed the teachers' training program. Up to now, more than 70 German centres have been qualified to offer the DGE-certified education to their patients. The patient programme provides general information on AI, encourages and enables patients to increase their hydrocortisone medication in critical situations and instruct them how to self-inject hydrocortisone in case of emergency. The structured education consists of a two-hours group training with 4–10 participants, including patients and their relatives or spouses. All standardised training materials are updated regularly and are available to all qualified teaching teams via an internet-based platform. To evaluate the education programme, $n=399$ patients from eight certified centres completed questionnaires comprising questions on individual course and perception of AI as well as knowledge questions, each before, shortly after and 6–9 month after training. Data show a significant gain of knowledge on AI and an increased willingness and self-confidence to manage AC after participation. At present the program is freely offered but not compensated by health care providers. A future aim is financial reimbursement similar to education programmes for other chronic diseases such as diabetes in order to empower more patients for the prevention of AC.

DOI: 10.1530/endoabs.59.N2.2

N2.3a

Adrenal Crisis-not always the obvious-Case Study 1

Anne Marland

This case study is part of the Nurses session -Adrenal Crisis and steroid education.The incidence of Adrenal Crisis in secondary Adrenal Insufficiency is high and associated with substantial mortality. However the etiology is not always obvious. Advances in comprehensive patient education including self-administration of hydrocortisone is crucial to eliminate death from Adrenal Crisis. Other advances in the United Kingdom have been implemented to assist allied health care professionals in the identification of patients at risk. This case study will explore unusual etiology and examine current resources available to help to identify patients at risk.

DOI: 10.1530/endoabs.59.N2.3a

N2.3b

Adrenal crisis, not always the obvious – Case study

Lisa Shepherd
University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Delay in establishing a diagnosis of adrenal insufficiency can lead to adrenal crisis. An adrenal crisis is a potential life-threatening complication of adrenal insufficiency, and can lead to increased morbidity and mortality if not treated appropriately. Adrenal crises have been defined as 'acute disturbances of physiology that happen when the circulating levels of adrenal steroid hormones are insufficient for physiological requirements'. Adrenal crisis related deaths can occur in patients with undiagnosed adrenal insufficiency. It is recognised that some pharmaceutical preparations can provoke adrenal insufficiency and thereby increase the risk of adrenal crisis. Therefore, a high degree of clinical suspicion, and early recognition of presenting signs and symptoms of adrenal insufficiency is required to prevent deterioration. Identification of factors that can trigger an adrenal crisis is also imperative. This presentation will highlight a case that demonstrates the importance of recognising the impact medication can have on the hypothalamic-pituitary-adrenal axis. Subsequent management and the role of the nurse throughout the patient's pathway will also be discussed.

DOI: 10.1530/endoabs.59.N2.3b

Senior Endocrinologists Session

SE1.1

Abstract Unavailable.

SE1.2

Plasma Steroid Bioavailability: Hormones, Precursors and Metabolites

Geoffrey Hammond
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Steroid bioavailability is delineated by the "free hormone hypothesis" and its underlying tenet that only steroids not bound by plasma proteins enter cells. Steroid hormones, as well as their unconjugated precursors and metabolites, circulate bound by several unrelated plasma proteins, including albumin, orosomucoid, sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG), while the more water soluble sulphated steroid conjugates are bound largely by albumin. The amounts and physicochemical properties of these proteins collectively determine the plasma distribution of their respective steroid ligands and how much of them exists in the nonprotein-bound or 'free' fraction that is accessible to cells. The tissue localization and extravascular disposition of plasma steroid-binding proteins varies considerably and is not well understood in the context of determining steroid bioavailability. With the exception of aldosterone, biologically active steroid hormones and some of their immediate precursors and metabolites are bound primarily by one of the high affinity binding proteins, SHBG or CBG, and this limits their metabolic clearance and bioavailability. Many steroid hormone precursors or metabolites are bound primarily by albumin and their non-protein bound concentrations in the blood approach or even exceed those of the active hormones, and this underpins the importance of their local metabolic 'intracrine' conversion into active sex steroids. Genetic differences that alter the production and function of SHBG and CBG have been identified and have confirmed these proteins are the main determinants the plasma concentrations of their respective steroid ligands, and some have been linked to specific clinical conditions. Pharmaceutical interventions to increase plasma SHBG levels have been used to treat symptom of androgen excess in women, and non-steroidal ligands that competitively occupy the steroid-binding sites of SHBG and CBG may provide a means of enhancing the biological activities of their natural steroid hormone ligands.

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SE1.3

Why did the Queen die?

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In 1547 Henry VIII died, and was succeeded by his young son from his marriage to Jane Seymour; the boy was only 9 years old, and became Edward VI. However, he was a sickly child, and only survived to the age of 15 years, probably dying of TB. With no living male heir, there was an attempt at continuing with a Protestant monarch, but this lasted only 9-days with the unfortunate Lady Jane Grey. The crown then fell to Mary, the child of the marriage of Henry to Catherine of Aragon, whose failure to produce an heir had led to Henry breaking off relations with the Church of Rome and forming the Church of England, with himself at its head. Henry's divorce led to his expropriation of all church lands, which were enormous in extent, although this vast influx of wealth was, as is the nature of many later dictators, handed out to his followers as a form of patronage. However, Mary's ascent to the throne, and her difficult relationship with her father, led to a reaffirmation of Catholicism, with the execution, often by burning, of many 'heretics'. Mary married Phillip II, scion of the Hapsburg dynasty: Phillip was less than enamoured with Mary, and while she appeared to adore him he treated this as a political move designed to establish Spanish hegemony over England. Mary's death at the age of 42, without an heir, led to the crowning of Elizabeth I in 1558, and was the first step in the ascendance of English power, the English Enlightenment, and European dominance. Had Mary lived, the future would have been very different: so, why did she die so young?

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Oral Communications

Translational Highlights

OC1.1

Resilient reproductive, bone and adrenal function in Expedition Ice Maiden, the first all-female, unassisted Antarctic crossing

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Higher short-term exercise-associated reproductive, psychological and bone health-related outcomes have been reported in women than men, although the reasons for this are poorly understood. The first, all-female transantarctic expedition provided a unique opportunity to perform an observational study examining concurrent effects of extreme exercise on pertinent hormonal axes to reproductive dysfunction and associated pathology. Body composition was measured by dual-energy xray absorptiometry (DXA) one and two months before and 15 days after the expedition. Basal metabolic and endocrine markers and 1-hour dynamic adrenal and pituitary gonadotroph tests, were conducted before, and 4–5 and 15–16 days after the expedition. Monthly hair cortisol was measured before and during the expedition. Basal bone turnover markers (BTMs) and high-resolution peripheral quantitate computerised tomography (HRpQCT) were assessed before and after the expedition. Six women (median (range) 32.7 (28.6–36.1) years) hauled 80 kg sledges 1700 km in 61 days, becoming the first all-female team to complete an Antarctic traverse. Mean (SD) weight loss was 9.37 (2.31) kg, entirely constituting fat mass; lean mass was unchanged. Basal sex steroids, corticosteroids and metabolic markers were largely unaffected by the expedition, except leptin and vitamin D, which fell during the expedition and recovered after 11 days. LH reactivity was suppressed prior to and during the expedition, recovering after 11 days, while FSH did not change during or after the expedition. Cortisol reactivity did not change during or after the expedition, although the HPA axis demonstrated marked sensitivity to central suppression. Monthly average cortisol was elevated during the expedition. BTMs revealed uncoupling before and during the expedition, resolving after 11 days. Tibial stiffness and fracture threshold were unchanged after the expedition. This study is unprecedented in women, demonstrating marked resilience in reproductive function, the HPA axis and bone, suggesting that female biological capacity for extreme endurance exercise is greater than anticipated.

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OC1.2

Vitamin D insufficiency and elevated vitamin D metabolite ratios (VMR) are associated with increased risk of injuries: Results from the british army lower limb injury prevention (ALLIP) study

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Introduction
British Army recruits suffer from musculoskeletal injuries (MSI) during initial training. Up to 10% suffer skeletal stress fracture (SFx) resulting in lost training days and medical attrition. There is evidence to suggest that vitamin D deficiency is prevalent in the army. Our aim was to determine vitamin D metabolites (VDM) in recruits upon starting training, and health outcomes after a 14-week training programme.
Methods
940 of 2252 healthy army recruits, age 18–32 yrs were included in the analysis (ClinicalTrials.gov ID: NCT02416895). Excluded were those who took calcium/vitamin D supplements and with prior injuries. Serum 25OHD/ $24,25(OH)_2D$, $1,25(OH)_2D$ and PTH were tested across all seasons. The co-primary endpoints were incidence of SFx, MSI, infections and days lost in rehabilitation (DLR) in relation to VDM.
Results
38% of participants identified as vitamin D insufficient (25OHD $<$ 50 nmol/L) were associated with increased risk(OR): SFx(1.03), medial tibial stress syndrome (MTSS)(1.26), upper limb trauma (1.02), respiratory infections (1.13); and highly significant risk of upper limb overuse injuries(3.18) and subsequent DLR(3.49). 25OHD:$24,25(OH)_2D$ VMR was significantly increased at 25OHD $<$ 50 nmol/L ($P<0.001$). There was no significant relationship between $1,25(OH)_2D$ and 25OHD, the distribution of $1,25(OH)_2D$:$24,25(OH)_2D$ VMR showed an exponential negative correlation with 25OHD ($y=1525.8\times^{-0.983}$, $r^2\text{Exp} = 0.582$, $P<0.001$). PTH was significantly higher ($P>0.001$) in subjects with high $1,25(OH)_2D$:$24,25(OH)_2D$ VMR and low 25OHD than those at the opposite. Cosinor-fit curves revealed circannual rhythm on all VDM and VMR except for $1,25(OH)_2D$. Baseline BMD was not associated with any health outcomes.
Conclusion
Vitamin D insufficiency is strongly associated with training-related injuries and lengthened rehabilitation. By using VMR models we demonstrated possible underlying mechanisms preceding the accelerated injury.

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OC1.3

Novel insights into the genetic architecture of thyroid disease

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Introduction
There has been a substantial increase in our knowledge of the genetic architecture of thyroid function, with numerous variants associated with TSH and/or FT4 levels. However, our knowledge of the genetic variants associated with thyroid disease is more limited.
Methods
Data was obtained from the Neale laboratory† which provided a case-control study to identify single nucleotide polymorphisms associated with a diagnosis of hypothyroidism or hyperthyroidism. From this data there were 337,159 participants in UK Biobank, 16,376 with a diagnosis of hypothyroidism and 2,547 witha diagnosis of hyperthyroidism.
Results
We note 79 independent variants associated with hypothyroidism, several of which were novel. Novel genome-wide significance associations ($P<5\times10^{-08}$) were seen in variants in or near: *C12ORF42, EDARADD, ELMO1, HIPK1, LINC00271, MIR1208, MIR6711, MIR7-3, MIR8071, NR1P1, PDE4A, PDX1, PLGRKT, PPP4R3B, RAD51B, SGK223,* and *SLC1A2*. A novel variant in *NRIP1* (a thyroid hormone repressor) appears to be an expression quantitative trait locus. Genome-wide levels of association were also seen for the first time in variants previously implicated in thyroid disease including *TLR3, STAT1, TBX21, AAK1, RASGRP1, MIR3188* and *LPP*. Variants in *PDE8B, CAPZB* and *FOXE-1,* previously associated with TSH, were also associated with hypothyroidism. We also note 4 independent variants near *PTPN22*, *CTLA4, TSHR* and *HLADQB1* at genome-wide levels of significance for hyperthyroidism; all were demonstrated in previous studies.
Conclusion
The substantial polygenic nature of the associations seen in multiple potential pathways with thyroid disease may explain its high prevalence. This work has also identified potential pathogenic pathways in genes associated with thyroid cancer and identified novel insights into thyroid disease. Intriguingly, few of the genetic variants associated with altered TSH and FT4 levels in the normal population were strongly associated with developing overt thyroid disease.
†(http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank)

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OC1.4

Whole genome sequence analysis establishes correct diagnosis for a syndromic form of hyperuricaemia

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Whole genome sequencing (WGS) has the potential to identify nearly all forms of genetic variation. In complex disorders with multiple manifestations WGS can establish a definitive diagnosis that may change clinical management (Stavropoulos *et al.* 2016 *Genomic Med*). Here, we report on the utility of WGS in establishing the correct diagnosis in a family with hyperuricaemia. Hyperuricaemia may occur as: part of a syndromic disorder (e.g. Lowe syndrome, renal coloboma syndrome (RCS), and familial juvenile hyperuricaemic nephropathy (FJHN)); or as an isolated non-syndromic disease. The proband, presented with gout and had hyperuricaemia, with reduced fractional excretion of uric acid (FEUA), and later developed chronic kidney disease and secondary hyperparathyroidism, consistent with FJHN. The proband's brother had gout, hyperuricaemia and reduced FEUA, and father had chronic renal failure. Genetic studies had not detected mutations in the *UMOD* or *REN* genes, which cause FJHN. WGS was therefore undertaken in the two siblings after obtaining informed consent. This identified a heterozygous c.226G > C variant in the paired box 2 gene (*PAX2*), that predicted a missense mutation pGly76Arg. This mutation co-segregated with hyperuricaemia and disrupts an evolutionarily conserved amino acid. A different missense change at this same residue (p.Gly76Ser) has been reported in RCS patients (Devriendt *et al.* 1998 *Human Genet*). RCS is characterized by abnormalities in renal structure and function in >90% of patients, and anomalies of the optic nerve and retina in >75% of patients, while hyperuricaemia is reported in only <1% of patients. These genetic findings prompted ophthalmological examination of the hyperuricaemic patients that revealed the presence of optic pits, consistent with coloboma, in the proband and his affected brother. The diagnosis was therefore revised to RCS, a syndromic form of hyperuricaemia. Thus, our results demonstrate the importance of WGS analysis in establishing diagnosis in disorders that may have multiple aetiologies.

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OC1.5

In vivo and *ex vivo* metabolomics in succinate dehydrogenase deficient tumorigenesis

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Mutations affecting the mitochondrial enzyme succinate dehydrogenase (SDH) are associated with a wide spectrum of tumours. SDH deficient tumours have a unique tumour metabolome due to the interruption of the citric acid cycle and accumulation of the 'oncometabolite' succinate, which drives tumourigenesis. Investigating the tumour metabolome of SDH deficient tumours has potential translational application. MRI spectroscopy (^{1}H-MRS) was used for *in vivo* metabolomics analysis and a nuclear magnetic resonance spectroscopy technique; high resolution magic angle spinning, was employed for *ex vivo* analysis. *Ex vivo* analysis was performed on 40 tumours (8 gastrointestinal stromal tumours (GIST), 32 phaeochromocytoma/paraganglioma (PPGL)). Targeted metabolomics analysis of succinate, demonstrated that succinate was several folds higher in SDH deficient tumours compared to wild type (wt) tumours ($P < 0.001$). Untargeted metabolomics analysis demonstrated that concentrations of lactate, glutamate, aspartate and branch chain amino acids, were significantly lowered in *SDH* mutated tumours compared to wt tumours. The detection of 2 hydroxyglutarate (2HG) accumulation in a single paraganglioma, heralded the subsequent discovery of a somatic *IDH1 (R132C)* mutation in that tumour. *In vivo* metabolomics analysis was performed on 12 patients (6 GIST, 5 PPGL, 1 non-functioning pituitary macroadenoma) A succinate peak was detected for 8/12 (66.7%) patients and succinate detection correlated with SDHB immunohistochemistry and or germline genetic status in 11/12 (92%) cases. ^{1}H-MRS identified a succinate peak in two patients with metastatic GIST without a germline *SDHx* mutation but an identified somatic *SDHC* epimutation. Finally, we demonstrated that *in vivo* metabolomics has a role as a surrogate biomarker to validate therapeutic strategies in malignant SDH deficient disease as succinate accumulation was identified in a patient with a metastatic paraganglioma and a germline *SDHB* mutation before treatment with lutetium labelled peptide receptor radionuclide therapy, but no succinate was detectable in the same tumour deposit after four cycles of treatment.

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OC1.6

Germline CYP2W1*6 and CYP2B6*6 polymorphisms as predicting markers of sensitivity to mitotane treatment in advanced adrenocortical carcinoma: a multicentric ENSAT study

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Adrenocortical carcinoma (ACC) is a rare tumor with poor prognosis and the only approved drug for advanced disease is mitotane. The cytochromes P450 (CYP) 2W1 and 2B6 are proposed predicting markers of sensitivity to mitotane treatment. Aim of the study was to evaluate the relationship between CYP2W1 and/or CYP2B6 polymorphisms and response to mitotane in ACC.

Methods

We performed a multicentric retrospective study including 182 ACC patients (F/M = 121/61) treated with mitotane monotherapy in adjuvant ($n = 103$) or palliative ($n = 79$) setting. CYP2W1*6 (p.P448L) and CYP2B6*6 (p.Q171H) were genotyped and sequenced in leukocyte DNA. Response to therapy was evaluated by time to progression (TTP) from the start of mitotane.

Results

Patients with advanced ACC and CYP2W1*6 CT/TT showed a worse response to mitotane compared to wild-type (wt) group (median TTP 3 vs 8 months, $P = 0.019$, HR = 2.10), also after adjustment for ENSAT stage ($P = 0.031$, chi-square = 4.67), and presented a higher rate of progression (71% vs 38%; $P = 0.01$, chi-square = 6.95). Moreover, 76% of CYP2W1*6 CT/TT patients did not achieve the mitotane target levels compared to 52% of wt ($P = 0.051$, chi-square = 3.79). Oppositely, a higher percentage of patients with CYP2B6*6 GT/TT achieved the target levels than wt (54% vs29%, $P = 0.027$, chi-square = 4.951), as well as had higher mitotane levels after 6 months of treatment ($P = 0.005$). Combining these polymorphisms, 61% patients with GT/TT CYP2B6*6-CYP2W1*6 wt achieved target levels vs 21% with CT/TT CYP2W1*6–CYP2B6*6 wt and 32% with both CYPs wt ($P = 0.02$ and $P = 0.037$, respectively). No relevant results were observed in adjuvant setting.

Conclusion

We demonstrated that patients with advanced ACC and CYP2W1*6 CT/TT are less sensitive to mitotane and CYP2B6*6 correlates with mitotane levels after 6 month-treatment. We suggest that the association of CYP2W1*6 and CYP2B6*6 may predict the individual response to mitotane treatment, avoiding useless drug administration leading to toxicities.

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The Best of the Best

OC2.1

24-hour adrenal steroid rhythms are readily detected by ULTRADIAN automated ambulatory microdialysis in man

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Background

Hormones oscillate in circadian and ultradian rhythms. Single time point samples are difficult to interpret and high frequency measurements are time consuming, expensive and invasive. We developed a minimally invasive technique of

ambulatory, automated microdialysis. This allows frequent 24-hour sampling of interstitial fluid while participants continue normal daily activities.
Methods
Healthy volunteers (age 18–68, no regular medications, no active medical conditions, BMI 16–29) were recruited for 24-hour hormone profile analysis. A 20 kDa linear microdialysis sampling catheter was inserted in abdominal subcutaneous tissue. Catheters were perfused at 1 microl/min using a portable CMA107 microdialysis pump attached to our novel fraction collector (U-RHYTHM) worn in an elasticated waist band. Microdialysate samples within the fraction collector were separated by air bubble every 20 minutes. During sampling, participants were free to continue their normal routine. Multiplex analysis of steroid concentrations was achieved using triple quadrupole mass spectrometry.
Results
We present 24-hour profile data for 10 participants. 72 consecutive 10 microL samples were analysed for each participant. The following steroids are presented: cortisol (F), cortisone (E), aldosterone (A), dehydroepiandrosterone sulfate (DHEAS), corticosterone (CCS), 18-OH-cortisol (18-OHC), 18-OH-corticosterone (18-OHCCS). All 24-hour profiles demonstrated circadian and/or ultradian rhythms.
Conclusions
Ambulatory microdialysis using U-RHYTHM in combination with high precision mass spectrometry can reliably and accurately detect dynamic fluctuations in steroid physiology during normal daily activities, without the need for hospitalisation.

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OC2.2

Comparison of acute effects of corticosterone versus cortisol (hydrocortisone) infusion in adults with congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is associated with poor health outcomes. This is, in part, because doses of glucocorticoid sufficient to suppress excess adrenal androgens are also associated with adverse metabolic effects such as insulin resistance. This toxicity occurs with efficacious doses of all commonly prescribed glucocorticoids (hydrocortisone, prednisolone and dexamethasone). However, the glucocorticoid corticosterone may have an improved therapeutic index because of its unusual susceptibility to export from cells by ATP-binding cassette (ABC) transporters. ABCB1 is expressed in the brain and exports cortisol (hydrocortisone), prednisolone and dexamethasone, limiting their potency at suppressing ACTH. However, corticosterone is not exported by ABCB1 but is exported by ABCC1. Expression of ABCC1 is relatively low compared to ABCB1 in brain, however it is expressed in the absence of ABCB1 in adipose tissue, muscle and bone, potentially limiting corticosterone action in these tissues. We hypothesised that corticosterone may be more efficacious at suppressing ACTH and adrenal androgens but with less metabolic toxicity than hydrocortisone. Fourteen adults with classic CAH due to 21-hydroxylase deficiency were recruited to a double-blind randomised crossover study comparing intravenous infusions of placebo, hydrocortisone and deuterated (D8) corticosterone. Subjects attended after omitting their usual glucocorticoid for 12h and were administered glucocorticoid/placebo for 5.5 hours in a two-step infusion designed to achieve concentrations of 400 and 800 nM. Blood samples were collected regularly. Circulating D8-corticosterone concentrations were approximately 30% higher than hydrocortisone. D8-corticosterone suppressed ACTH, androstenedione and 17-hydroxyprogesterone to a greater extent than hydrocortisone. However, hydrocortisone increased circulating insulin compared with D8-corticosterone and placebo (10.0 ± 1.3 vs 8.3 ± 1.2 vs 7.2 ± 1.3 mU/l respectively, $P < 0.05$). Blood pressure and FFAs were similar between phases. Thus, corticosterone acutely suppresses ACTH and adrenal androgens in CAH patients without causing hyperinsulinaemia. Corticosterone may be a better glucocorticoid replacement than hydrocortisone for the treatment of CAH.

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OC2.3

Prospective serum thyroid function and cognitive decline in the very old: the Newcastle 85+ study

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Context
Perturbations in thyroid function are common in older people, and subclinical hyperthyroidism has been associated with increased risk of dementia in people aged 55 years and above. The significance of subtle perturbations of thyroid function in the very old remains poorly understood.
Objective
This study sought to determine if subtle abnormalities of thyrotropin and variations of free thyroid hormones within the reference range correlate with cognitive impairment in the very old, using data from the Newcastle 85+ study.
Design
A cohort of 85-year-old individuals was assessed for their health status and thyroid function. Cross-sectional and prospective data (up to 5 years follow-up) were analysed using linear mixed and regression models for global and memory-specific cognitive performance in relation to baseline and 3-year changes in serum thyrotropin (TSH), free T4 (FT4) and free T3 (FT3).
Setting and participants
Six hundred and forty-two 85-year-olds with TSH ranged between 0.1–10 mU/l, normal FT3/FT4 levels and who were not taking thyroid-interfering medication were included.
Results
After adjusting for age, sex, years of education and smoking, cognition (MMSE and memory sensitivity index) was associated with baseline log-transformed TSH ($P = 0.012$) and free T3 ($P < 0.01$). After additional adjustment for potential confounders, including depression, physical activity and chronic disease status, both baseline log-TSH and FT3 remained significantly associated with global cognition ($P < 0.05$), with lower log-TSH and FT3 correlated with worse cognitive outcome. Reduction in TSH over the initial 3 years increased the odds of cognitive impairment at 60-month (OR 1.60 (95% confidence interval 1.14–2.24), $P = 0.006$).
Conclusions
Individuals aged 85 years with low but unsuppressed TSH or low normal free T3 had a significantly worse cognition at baseline. We show, for the first time, that a decreasing TSH trajectory anticipates the development of cognitive decline in later life.

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OC2.4

Biochemical analysis of radioiodine uptake enhancement in endocrine cancer

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The most common form of endocrine cancer is differentiated thyroid cancer (DTC). Outcomes of DTC largely depend on radioiodine treatment, which is mediated the sodium-iodide symporter (NIS). However, many tumours exhibit NIS dysregulation, resulting in a poorer prognosis. Since breast cancer can also overexpress NIS, albeit of limited function, radioiodine treatment may be a promising treatment option. Our previous data show that overexpression of the pituitary tumor-transforming gene-binding factor (PBF) is partially responsible for the reduced function of NIS in thyroid and breast cancer. The interaction of PBF with NIS leads to an alteration of NIS localisation away from the plasma membrane. Binding of NIS requires a C-terminal PBF tyrosine residue 174 (Y174) to be phosphorylated by the tyrosine kinase Src. To address the mechanistic interactions between NIS, PBF and Src we used CRISPR/Cas9 to knock PBF out in TPC1 and Nthy-ori thyroid cells, as well as in MDA-MB-231 and MCF7 breast cell lines. Endonuclease screening, Western blotting and DNA sequencing identified successful PBF knock out with at least two different guide RNAs (gRNA) in TPC1 and N-thy-ori thyroid CRISPR cell lines. Knockout of PBF in TPC1s was associated with a 50.33% (gRNA#1) and 49.13% (gRNA#2) increase in radioiodide uptake compared to parental lines expressing NIS, whilst Nthy-ori cells showed a 75.04% (gRNA#1) and 45.12% (gRNA#3) increase. Transfection of Src into CRISPR- PBF versus parental lines resulted in a similar magnitude of radioiodide uptake repression. Thus, PBF is directly implicated in the intrinsic activity of NIS in vitro, but it is likely that Src phosphorylates

additional targets to PBF, which are also able to directly or indirectly repress iodide uptake.

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OC2.5

Using integrative lipid systems biology to understand the role of Liver X receptors (LXRs) in male reproduction

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Introduction
LXRs are transcription factors that regulate cholesterol homeostasis and likely modulate other aspects of lipid metabolism. In the testis, tightly regulated lipid metabolism is crucial to maintain fertility. Testicular LXRs are highly expressed but their role in regulating lipid homeostasis is not fully understood. *Lxrα/β* double knockout male mice (*Lxrα/β* DKO*)* are sterile by 7 months of age, with aberrations in lipid metabolism.
Aim
To identify specific disrupted cellular lipids and candidate target genes in the testes of *Lxrα/β* DKO mice using integrated wide platform studies.
Methods
RNA-seq, quantitative mass spectrometry and mass spectrometry imaging (MSI) were combined to study whole testicular tissues from *Lxrα/β* DKO mice compared to age and strain matched controls. cDNA libraries were prepared for sequencing using NextSeq-500 and lipid extracts for LC-MS analysis with SONAR acquisition, based on an *m/z* isolation range of the quadrupole. Results were analysed using LipidMaps and ProgenesisQI for normalised quantitation. For MSI, the MALDI SYNAPT G2-S*i* was equipped with an ion mobility cell and experiments performed using Waters High Definition Imaging (HDI) 1.4 and MassLynx.
Results
Histological assessment confirmed abnormal seminiferous tubules, germ-cell loss and lipid deposition in *Lxrα/β* DKO mice. Quantitative lipidomics analysis confirmed statistically significant differences in lipids compared to controls. Retrieved curated targets were mapped with KEGG pathway analysis. Alterations in cholesterol, triglyceride, sphingomyelin and ceramide metabolism were identified. From RNA-seq, 1161 genes ($\log^2$ FC -3.49 to $+2.17$, $P<0.01$) were differentially expressed in the *Lxrα/β DKO* with genes relevant to pathways identified from lipidomic data. Finally MSI confirmed deposition of specific lipid species and a visualisation of their location within the testis.
Discussion
An integrative approach using lipidomic analysis with mRNA transcript studies provides data implicating LXRs in novel lipid pathways critical for male reproductive function.

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OC2.6

Overexpression of *SKAP2* in familial *AIP* mutation negative somatotrophinomas

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Background
Germline mutations in the aryl-hydrocarbon receptor interacting protein (*AIP*) gene have been implicated in the tumorigenesis of patients with familial isolated pituitary adenoma (FIPA). Around 25% of FIPA patients have an identified *AIP* mutation; in the remainder of FIPA patients, molecular mechanisms involved in pituitary tumorigenesis have yet to be elucidated.
Aims
To identify the genes and molecular mechanisms involved in the pituitary tumorigenesis of *AIP* mutation negative FIPA patients (*AIP*mut negative),
Methods
Gene expression analysis of FIPA *AIP*mut negative (*AIP*mut negative, $n=5$), FIPA *AIP*mut positive (*AIP*mut positive, $n=4$), normal pituitary (NP, $n=5$), sporadic somatotrophinoma (Acro, $n=3$) and non-functioning pituitary adenoma (NFPA, $n=4$) tumour samples were carried out using the Affymetrix Gene-Chip HG-U133 plus 2.0 array. Five significantly differentially expressed genes were selected for validation using RT-qPCR with standard curve method data analysis. Independent *AIP*mut negative ($n=1$), Acro ($n=5$), NFPA ($n=4$) and NP ($n=3$) samples were also validated.
Results
Among differentially expressed genes in *AIP*mut negative tumours compared to NP, Src Kinase Associated Phosphoprotein 2 (*SKAP2*) was identified as upregulated, which has been implicated in tumour metastasis and in the inhibition of actin polymerisation. *SKAP2* was overexpressed in *AIP*mut negative tumours staining positive for growth hormone (*AIP*neg-Acro, $n=3$) compared to NP ($n=6$; 3.09 ± 0.82 vs 1.00 ± 0.10). *SKAP2* is expressed similarly in Acro ($n=9$) compared to NP (1.33 ± 0.30 vs 1.00 ± 0.10) and underexpressed in NFPA ($n=9$) and non-functioning familial *AIP*mut negative tumours ($n=2$) versus NP (0.16 ± 0.30 vs 1.00 ± 0.10; 0.37 ± 0.03 vs 1.00 ± 0.10).
Conclusions
SKAP2 is overexpressed in *AIP*neg-Acro compared to NP, NFPA and familial *AIP*neg NFPA. *SKAP2* plays a role in tumour metastasis and may explain the tendency of these tumours to invade locally only. *SKAP2* is therefore a novel candidate in pituitary tumorigenesis and target for protein expression and functional studies.

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Obesity & Diabetes

OC3.1

Kisspeptin stimulates insulin secretion and modulates serum metabolites in humans

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Background
Limited data exists on the hormonal mediators connecting metabolism and reproduction. Animal studies show that the reproductive hormone, kisspeptin, may also be important in metabolism. We investigated the effects of kisspeptin on human metabolism for the first time, to explore possible kisspeptin-mediated links between reproduction and metabolism.
Methods
We performed intravenous glucose tolerance tests (IVGTTs) in 15 healthy men (age 25 ± 1y, BMI 22.3 ± 0.5 kg.m^{-2}); during 1 nmol.kg^{-1}.hr^{-1} kisspeptin infusion and vehicle infusion. Blood samples were collected pre- and during infusions (pre-glucose load/pre-meal), when kisspeptin levels had plateaued, to determine kisspeptin's effects on serum metabolites. Static incubation experiments were performed using human donor islet cells ($n=6$) and a human pancreatic β-cell line (EndoC-βH1 cells), to assess *in vitro* effects of kisspeptin on glucose-stimulated insulin secretion (GSIS).

Results
During IVGTTs, GSIS was higher with kisspeptin infusion compared to vehicle (mean serum insulin concentration kisspeptin minus vehicle: 4.1 $\mu U.mL^{-1}$, $P=0.01$; disposition index: kisspeptin 2768 ± 484 vs vehicle 2061 ± 255, $P<0.05$). Consistent with this and providing mechanistic information, kisspeptin elicited dose-dependent increases in insulin secretion *in vitro,* in human islet and EndoC-βH1 cells. Compared to vehicle, kisspeptin resulted in changes in serum metabolites, including alterations in lysophosphatidylcholines, phosphocholines and sphingomyelins, which are associated with insulin secretion.
Conclusions
This is the first study to examine the effects of kisspeptin on metabolism in vivo in humans. We demonstrate that kisspeptin increases GSIS and produces changes in circulating metabolites, providing evidence for novel kisspeptin-mediated connections between reproduction and metabolism. This has significant implications for the ongoing development of kisspeptin-based therapies: in addition to treating reproductive disorders kisspeptin may also have positive effects on associated metabolic dysfunction (for example in men with type 2 diabetes, up to 40% of whom have associated hypogonadism).

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OC3.2

Glucose regulates pancreatic β cell Ca^{2+} dynamics and connectivity *in vivo* in the anterior chamber of the mouse eye

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Background and Aims
β cell connectivity is a feature of pancreatic islets *in vitro* but its existence in vivo, when innervated and continuously perfused with blood, has not yet been demonstrated. We imaged islets engrafted in the anterior chamber of the mouse eye (ACE) to explore this question.
Methods
Mouse (C57BL6, Ins1Cre::GCaM6m$^{f/f}$) or human islets infected with adenovirus to express GCaMP6m, were engrafted and Ca^{2+} imaging performed under anaesthesia. Glucose or insulin were administered intravenously to achieve low glucose (4–6 mM) or high glucose (25–30 mM) conditions Data were collected on a spinning disc confocal microscope using a 20×, 1.0 NA water immersion objective (3 Hz). Following movement correction, Ca^{2+} traces were analyzed with Image J. Connectivity analysis was performed with custom-built scripts in Matlab.
Results
Ca^{2+} waves spreading across the islet in 5/5 animals were observed. Even at low glucose concentrations, β cells form a highly connected syncytium. Increasing glucose concentrations augmented the proportion of connected β cells from 65 to 86% ($n=5$; $P=0.02$) and correlation strength (Pearson R with bootstrapping) from 0.34 ± 0.07 to 0.46 ± 0.08 ($n=5$; $P=0.05$). Granger causality analysis indicated that cells which responded first during Ca^{2+} pulses were causally linked to the activity of the largest number of other β cells in the islet. Moreover, the presence of a super-connected β cell subpopulation (8.7 ± 3.6% of cells) was revealed by signal binarisation and Monte Carlo randomization. Pearson connectivity was increased from 58.3% to 63.9% ($n=1$ animal) in engrafted human islets
Conclusions
We demonstrate intercellular connectivity between β cells within the islet *in vivo* under conditions of normal islet perfusion and innervation. These findings are consistent with the existence of islet pacemaker cells which coordinate Ca^{2+} dynamics and possibly pulsatile insulin secretion in the physiological setting.

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OC3.3

Staging of non-alcoholic fatty liver disease through LC-MS/MS analysis of the urinary steroid metabolome

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Introduction
The development of accurate non-invasive markers to diagnose and stage non-alcoholic fatty liver disease (NAFLD) is of high importance to reduce the need for an invasive liver biopsy. These markers help to stratify patients at highest risk of hepatic and cardio-metabolic complications and allow tracking of disease progression and treatment response. We have previously described alterations in glucocorticoid metabolism that are differentially regulated across the NAFLD spectrum (simple steatosis, steatohepatitis (NASH), fibrosis, cirrhosis) using gas chromatography-mass spectrometry (GC-MS) coupled with machine-learning analysis. However, GC-MS is time-consuming and labour intensive, which can limit its utility. Here we compare GC-MS derived data with high-throughput liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis in patients with NAFLD.
Methods
GC-MS and LC-MS/MS were used to analyse 26 distinct steroid metabolites in spot urine samples (corrected for creatinine) from 71 patients with biopsy-proven NAFLD, including 55 with NAFLD cirrhosis. Machine learning-based analysis (generalised matrix-learning vector quantisation, GMLVQ) was used to determine NAFLD stage and diagnostic performance of GC-MS and LC-MS/MS, respectively.
Results
GMLVQ analysis achieved excellent separation of early from advanced NAFLD fibrosis. Performance was almost identical using GC-MS (AUC-ROC = 0.87) and LC-MS/MS (AUC-ROC = 0.86), respectively. Significantly, this performance was superior to published, validated non-invasive markers (Fib-4 and NAFLD Fibrosis scores, AUC-ROC = 0.80 for both). Additionally, there was very good separation of non-cirrhotic compared to cirrhotic patients (GC-MS AUC-ROC = 0.82; LC-MS/MS AUC-ROC = 0.77).
Conclusion
Unbiased GMLVQ analysis of the urinary steroid metabolome appears to be a robust non-invasive risk stratification tool in patients with NAFLD and is potentially superior to existing established non-invasive markers. We show also that LC-MS/MS analysis, a more cost- and time-efficient methodology, performs similarly to established GC-MS profiling. With further development and validation, this LC-MS/MS platform has potential to be adopted into large-scale clinical practice to enhance patient care.

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OC3.4

Knockout of glucocorticoid receptor on AgRP/NPY/GABA (ANG) neurons identifies a potential role for this neuronal population in mediating glucocorticoid–induced insulin resistance in female mice

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Glucocorticoids (Gcs) are used in the treatment of inflammatory disorders including asthma and rheumatoid arthritis. However, long-term use can cause metabolic side-effects including obesity and diabetes. Previous studies have shown that Gcs increase *Agrp* expression and that AgRP/NPY/GABA (ANG) neurons can regulate appetite and insulin sensitivity. To investigate the effects of chronic Gc treatment directly on ANG neurons, we crossed *AgRP-IRES-Cre* with *GR$^{Flox/Flox}$* mice to generate *AgRP-Cre/GR$^{Flox/Flox}$* (GR/ANG KO) mice where GR is deleted in ANG neurons only. Female GR/ANG KO mice, their

AgRP-Cre/GR$^{Flox/+}$ (Cre) and *GR*$^{Flox/Flox}$ (GR Flox) littermates (controls) were treated with corticosterone (Cort-) or vehicle-supplemented drinking water for 3 weeks after which phenotypic, biochemical and neurohormonal characteristics were assessed. Mice with GR deleted from ANG neurons did have increased *Agrp* expression, which was present in control strains. Further, although Cort increased food intake in both GR Flox and Cre strains compared to their vehicle controls, GR/ANG KO mice were partially protected from Cort-induced hyperphagia. Cort increased body weight and adiposity in control strains and GR/ANG KO mice to a similar extent. However, Cort-treated GR/ANG KO mice had reduced hepatic lipid accumulation compared to Cort-treated control mice and although control mice were hyperinsulinaemic after 3 weeks, circulating insulin was not elevated in GR/ANG KO mice. Additionally, in Cort-treated GR/ANG KO mice there was no decrease in skeletal muscle *Irs1* expression or increase in expression of *P85a* in skeletal muscle or liver, in contrast to the controls. Loss of the glucocorticoid receptor on ANG neurons ameliorates the acute hyperphagia induced by Cort. In addition, the changes in circulating insulin, liver and muscle seen in GR/ANG KO mice suggest that ANG neurons appear to have a role in mediating Gc-induced hyperinsulinemia and insulin resistance.

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OC3.5

Hypothalamic arcuate glucokinase and its downstream pathways are critical in glucose homeostasis

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As the nation gets fatter, the incidence of diabetes is also rising. The brain is now emerging as a critical mediator of blood sugar control, re-directing focus away from the traditional pancreas-centred model. The enzyme glucokinase (GK) acts as a glucose sensor in many tissues including glucose-sensitive neurones within the hypothalamic arcuate nucleus. However, the role of GK here is unclear. We investigated the role of arcuate GK in glucose homeostasis in both healthy and overweight models. We used a recombinant adeno-associated vector (rAAV) expressing either GK (iARC-GK) or antisense GK (iARC-ASGK) to increase or decrease GK activity specifically in the arcuate nucleus of rats. We investigated the subsequent effects on glucose homeostasis. Increased glucokinase activity significantly improved glucose tolerance (7.43 ± 0.23 mmol/L iARC-GFP vs 6.4 ± 0.27 mmol/L iARC-GK, $P < 0.05$). Insulin secretion was also significantly increased (2.68 ± 0.38 ng/ml iARC-GFP vs 3.94 ± 0.33 ng/ml iARC-GK, $P < 0.001$). Conversely, decreased glucokinase activity significantly worsened glucose tolerance (7.27 ± 0.34 mmol/L iARC-GFP vs 8.5 ± 0.34 mmol/L iARC-asGK, $P < 0.05$) and insulin secretion was significantly lower (3.63 ± 0.12ng/ml iARC-GFP vs 2.89 ± 0.20 ng/ml iARC-asGK, $P < 0.05$). The effect of glucokinase upregulation was maintained in a rodent model of Type 2 diabetes. Interestingly, these obese models were also more sensitive to centrally administered sulphonylureas compared with healthy controls. However, the same sulphonylureas were ineffective when administered peripherally. These results demonstrate a role for arcuate nucleus GK in systemic glucose homeostasis. Increasing glucokinase activity improved blood glucose levels and increased insulin secretion in both healthy and metabolically dysregulated models thereby making it an attractive potential therapeutic target. Furthermore, centrally acting sulphonylureas appear to be more effective in correcting hyperglycaemia than peripherally administered sulphonylureas. This effect is particularly marked in obese models. Hence development of centrally active ligand-directed glucokinase activators or central sulphonylureas working via the glucokinase activation pathway, may herald a new era in anti-diabetic therapy.

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OC3.6

5β-reductase (AKR1D1) is a potent regulator of hepatic insulin sensitivity, carbohydrate and lipid metabolism *in vitro* and *in vivo*

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Steroid hormones and BAs are established regulators of metabolic phenotype. 5β-reductase (AKR1D1) is highly expressed in the liver where it inactivates steroid hormones and catalyses a fundamental step in bile acid (BA) synthesis. We have hypothesised that AKR1D1 plays a crucial regulatory role in hepatic metabolic homeostasis. Genetic manipulation of AKR1D1 was performed in human liver HepG2 and Huh7 cells. Expression changes were confirmed by qPCR and western blotting, with parallel alterations in cortisone clearance, tetrahydrocortisone generation and BA production, measured using GC-MS technology. RNA sequencing analysis following AKR1D1 knockdown identified discrete dysregulated metabolic pathways, notably those impacting upon insulin action and fatty acid (FA) storage and utilization. Insulin sensitivity was enhanced with increased insulin-stimulated phosphorylation of AKT and mTOR, following AKR1D1 knockdown. Endorsing our cellular observations, hepatic AKT, mTOR and INSRβ protein levels were higher in AKR1D1 knockout (KO) male mice than in wild type (WT) controls. *In vitro*, AKR1D1 knockdown increased glucose transporter mRNA expression with an associated decrease in extracellular glucose concentrations ($P < 0.05$) and increased intracellular glycogen accumulation ($P < 0.05$). In addition, FASN and ACC1 expression were increased, resulting in enhanced ACC phosphorylation and increased intracellular triglyceride accumulation ($P < 0.01$). Consistent with our *in vitro* findings, we also observed a significant increase in total ACC levels in KO male mice. Mass spectrometry analysis of lipid composition demonstrated increased palmitic and palmitoleic acid synthesis, indicative of increased *de novo* lipogenesis and fatty acid saturation. Cell media 3-hydroxybutyrate levels were reduced ($P < 0.01$). Pharmacological manipulation of BA receptor activation prevented the induction of lipogenic genes, suggesting that the observed metabolic phenotype is likely to be driven through BA rather than steroid hormone availability. In conclusion, AKR1D1 is able to regulate hepatocyte insulin sensitivity, carbohydrate and lipid metabolism, and may therefore have an as yet unexplored role in metabolic disease.

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Clinical Highlights

OC4.1

Targeted molecular analysis in adrenocortical carcinomas: a strategy towards improved personalized prognostication

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Background

Adrenocortical carcinoma (ACC) has a heterogeneous prognosis and current medical therapies have limited efficacy in its advanced stages. Genome-wide multi-omics-studies identified molecular patterns associated with clinical outcome. Here, we aimed at identifying a molecular signature useful for both

personalized prognostic stratification and druggable targets, using methods applicable in clinical routine.
Methods
117 tumor samples from 107 ACC patients were analyzed. Targeted next-generation sequencing of 160 genes and pyrosequencing of 4 genes were applied to formalin-fixed paraffin-embedded (FFPE) specimens to detect point mutations, copy number alterations and promoter region methylation. Molecular results were combined with clinical/histopathological parameters (tumor stage, age, symptoms, resection status, and Ki67) to predict progression-free survival (PFS).
Results
In addition to known driver mutations, we detected recurrent alterations in genes not previously associated with ACC (e.g. *NOTCH1, CIC, KDM6A, BRCA1, BRCA2*). The association of age $\geq$50 years, tumor- or hormone-related symptoms, ENSAT tumor stage, resection status and ki67 proliferation index (modified GRAS classification) could prognosticate recurrence risk ($P<0.0001$; $\chi^2=49.0$). However, best prediction of PFS was obtained integrating molecular results (>1 somatic mutation, alterations in Wnt/β-catenin and p53 pathways, high methylation pattern) and clinical/histopathological parameters into a combined score ($P<0.0001$, χ^2 68.6). Accuracy of prediction for early disease progress was 83.3% (area under the ROC curve: 0.872, 0.80–0.94). Furthermore, 17 potentially targetable alterations were found in 64 patients (e.g. in *CDK4, NOTCH1, NF1, MDM2, EGFR* and in DNA repair system).
Conclusions
This study shows the feasibility of DNA analysis on FFPE tumor tissues in the clinical practice. We demonstrate that clinical/histopathological parameters might predict the clinical outcome of ACC patients. However, the combination with specific molecular alterations increases the power of the prognostic stratification and may identify new potential drug targets. Our findings might pave the way to a precision medicine approach in ACC.

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OC4.2

Kisspeptin- a novel clinical test of hypothalamic function in men with hypogonadotrophic hypogonadism

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Background
Hypogonadotrophic Hypogonadism (HH) is characterised by hypogonadism in the context of low gonadotrophin levels, frequently due to a defect in hypothalamic function e.g. Kallman's syndrome. However, no direct test of hypothalamic function currently exists. Kisspeptin is a hypothalamic neuropeptide that stimulates endogenous GnRH release. Thus, we investigated whether kisspeptin could be used to interrogate hypothalamic function in men with HH.
Methods
Men with HH (low testosterone/LH/FSH, normal MRI pituitary, absent puberty, unprimed by pulsatile GnRH; $n=4$) and healthy eugonodal men ($n=20$) received either an intravenous bolus of GnRH (100mcg), or kisspeptin-54 (6.4 nmol/kg), on two study visits $\geq$1 week apart. Serum gonadotrophins were measured every 15mins for 6hrs following injection. Increases in serum gonadotrophins from baseline following GnRH/kisspeptin in eugonadal men and HH were compared by unpaired *t* test.
Results
Mean increase in serum LH from baseline was $+8.2\pm3.8$i U/L in eugonadal men and $+0.12\pm0.13$ iU/L in HH ($P=0.0003$) following kisspeptin. All men with HH had an LH-increase <1.5i U/L following kisspeptin, whereas all eugonadal men had an LH-increase >1.5i U/L. By contrast, mean increase in serum LH from baseline following GnRH was $+6.2\pm3.2$i U/L in eugonadal men and $+2.2\pm3.8$ iU/L in HH ($P=0.062$). Whilst kisspeptin-induced mean LH increase effectively discriminated men with HH from eugonadal men (area under ROC 1.0), GnRH-induced mean LH increase was less discriminatory (area under ROC 0.82). In eugonadal men, the maximal increase in LH following kisspeptin significantly predicted the maximal increase in LH following GnRH (univariate linear regression, $r^2=0.45$; $P=0.0013$), however this relationship was lost in men with HH ($r^2=0.03$; $P=0.83$).
Conclusion
This provides 'proof of concept' that a novel kisspeptin test of hypothalamic function better discriminate men with HH from eugonadal men than GnRH. These findings have significant implications for managing patients with HH.

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OC4.3

A novel non-invasive short synacthen test validated in healthy adult and paediatric populations

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Introduction
Worldwide the Short Synacthen Test (SST) is the most popular investigation for adrenal insufficiency (AI). Its invasivity make it resource-intensive. Salivary cortisol is a well-established alternative to serum. We have developed a non-invasive alternative to the SST, using a novel formulation of Synacthen (containing a drug enhancer, chitosan) administered nasally and utilising saliva to measure glucocorticoid response.
Methods
Four open-label, sequence-randomised, cross-over pharmacokinetic studies and a repeatability study were conducted in dexamethasone suppressed participants. Twelve healthy adult males were recruited to each study, 6 re-recruited for the repeatability study and 24 children (12F) aged 4–14 years participated in the paediatric study. The intravenous comparator was 250mcg or 1mcg synacthen. Nasal formulations were administered using a mucosal atomiser device. Fourteen paired blood and saliva samples were taken and measurements of plasma Synacthen (ACTH EIA), serum cortisol (chemiluminescent immunoassay) and salivary cortisol and cortisone (LC-MS/MS) made.
Results
The addition of chitosan and dose escalation improved bioavailability and cortisol response. The Nasacthin003 formulation was selected based on superior bioavailability and serum cortisol responses. Administration of nasal synacthen was highly reproducible. The mean plasma cortisol Cmax in children compared with adults was 568 nmol/L ($\pm$79) versus 558 ($\pm$110), 406 ($\pm$77) versus 400 ($\pm$89) and 630 ($\pm$54) versus 615 ($\pm$51) for Nasacthin003, 1mcg IV and 250 mcg IV respectively. Salivary cortisol and cortisone samples were closely correlated with their paired serum samples ($r=0.88$ and 0.90 respectively). Salivary cortisone was the more sensitive marker of adrenocortical response at lower serum cortisol values. Nasal Synacthen was well tolerated with no unexpected adverse events.
Conclusions
We have validated a non-invasive SST, with PK parameters demonstrating Nasacthin003 stimulation leading to an indistinguishable glucocorticoid response in both serum and saliva compared to high and low-dose IV synacthen in adults and children.

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OC4.4

An intravenous insulin protocol designed for pregnancy reduces neonatal hypoglycaemia after betamethasone administration in women with gestational diabetes

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Introduction
Neonatal hypoglycaemia (NH) is common in infants born soon after betamethasone administration, and may be reduced by at-target peri-partum glycaemic control. A Pregnancy-specific Intravenous Insulin-Glucose Infusion (PIIGI) protocol was introduced at a tertiary hospital in June 2017, replacing a generic Adult IntraVenous Insulin protocol (AIVI) not designed for pregnancy, without change in indication for IV insulin (initiated with any BGL > 6.7 mmol/L following betamethasone, and continued for 24 hours after the final dose of betamethasone). Capillary glucose levels are measured every 30–60 minutes whilst on infusion.
Patients and methods
A prospective audit June 2017-May 2018 captured all uses of PIIGI following betamethasone in women with gestational diabetes ($n = 65$), and compared to a similar retrospective cohort treated with AIVI ($n = 86$). Primary outcome was percentage of on-infusion time at target (BGL 3.8–7 mmol/L). Secondary outcomes were percentage time with critical hyperglycaemia (BGL > 10 mmol/L) or hypoglycaemia (BGL < 3.8 mmol/L), and incidence of NH (BGL < 2.7 mmol/L in first 48 hours if betamethasone given within 2 days of birth). As this was a real-world analysis of practice, a waiver of consent was granted by the Human Research Ethics Committee.
Results
On-infusion time at target was 68% (95%CI 64–71%) for PIIGI compared to 55% (95%CI 50–60%) for AIVI ($P = 0.0002$). Critical hyperglycaemia was lower with PIIGI compared to AIVI (2% vs 5%, $P = 0.006$), with no change in rate of hypoglycaemia (0.1% vs 0.5%, $P = 0.09$). NH occurred with 11/31 (35%) of births following PIIGI, compared to 29/48 (60%) births following AIVI ($P = 0.03$). A multiple logistic regression model adjusting for potential confounders gave an odds ratio for NH with PIIGI of 0.30 (95%CI 0.11–0.82, $P = 0.02$).
Conclusions
An infusion protocol designed for pregnancy effectively controlled maternal hyperglycaemia following betamethasone. This is the first protocol to show reduction in betamethasone-associated NH associated with optimum maternal glycaemic control.

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OC4.5

Hypothalamic-pituitary adrenal axis recovery rate of patients with glucocorticoid-induced adrenal insufficiency (GC-induced AI)

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Aim
To evaluate the recovery rate, characteristics and factors that might help predict the HPA axis recovery of patients with glomerulonephritis (GN) and GC-induced AI.
Study Design
A retrospective study involving all GN patients referred from January 2014-December 2016 with a confirmed diagnosis of GC-induced AI with a planned weaning from conventional Prednisolone (Pred) immunosuppression and switch onto Hydrocortisone (HC). Data collected up to November 2017.
Patients
There were a total of 38 patients (23 male) included in the study; median age of 53.
Methods
Review of demographic data, Pred lowest dose exposure (PredTime) and their detailed adrenal function assessments (short synacthen test (SST)), $Test_0$ up to $Test_6$ (follow up period, 7–42 months) with corresponding HC switched dosage.
Results
25 (66%) recovered their HPA axis, median of 9 months (7–13 months). HC switched dosage, 15 vs 20mg daily revealed 9.3% vs 7.0% chances of recovery, respectively ($P = 0.008$). PredTime and demographic variables were not statistically significantly different. The cortisol 30 min value, increment and ratio of the initial SST ($Test_0$) were found to be predictors of recovery with a P value of 0.005, 0.001 and 0.007 respectively.
Conclusions
HPA axis recovery was achieved frequently in patients at approximately 9 months. A lower HC dose may influence recovery and cortisol response during a SST may be independent predictive factors for the recovery of adrenal function. A well-controlled prospective study in a larger cohort with GC-induced AI is required to strengthen the observed correlation of HC dose and cortisol response during a SST with potential recovery.

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OC4.6

^{11}C-Methionine PET/MRI is superior to MRI for localisation of functioning prolactinomas and may facilitate targeted intervention

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Background
Prolactinomas are the commonest hormone-secreting pituitary adenomas. First-line treatment is dopamine agonist (DA) therapy. However, side-effects are increasingly recognised, leading to an increasing consideration of transsphenoidal surgery (TSS) and/or radiotherapy. Co-registration of 11C-methionine Positron Emission Tomography (Met-PET) imaging with Spoiled Gradient Recalled Acquisition MRI (SPGR MRI), referred to in combination as Met-PET/MRI, can aid accurate localisation of de novo or residual/recurrent adenomas, directing targeted intervention. We compare this modality with MRI alone for localisation of prolactinomas.
Methods/patients
23 patients (10 male, 13 female; 10 microadenoma, 13 macroadenoma) with a confirmed prolactinoma (single centre, 2010–2018) were identified. 16 with de novo tumours underwent initial DA titration but failed this primary medical therapy. Seven failed medical therapy for residual/recurrent disease after transsphenoidal resection. Each then had Met-PET/MRI and standard MRI to localize functional tumour.
Results
Medical therapy failed predominantly due to development of DA side effects, of which dizziness and behavioural changes were commonest (38% of the cohort each). Met-PET/MRI demonstrated focal tumour uptake in 20 patients with hypersecretion at time of scanning. Three patients on medical therapy had a serum prolactin within reference limits at the time of PET scanning, which did not demonstrate active tumour in these cases. In comparison, MRI alone only located tumour confidently in 8/23 patients. For the subgroup with a prior surgical procedure, residual active tumour was detected by PET in all (7/7) cases, whereas MRI alone identified tumour in just 4/7. Six patients (4 macroadenomas, 2 microadenomas) have to date undergone TSS guided by Met-PET/MRI. All demonstrated significant biochemical improvement postoperatively, with three attaining remission.
Conclusion
Met-PET/MRI can be used as an adjunct to conventional MRI in prolactinoma with failed medical therapy, with greater sensitivity than conventional MRI alone, thereby potentially facilitating targeted surgery/radiotherapy.

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Adrenal

OC5.1

Timed urinary steroid profiling of patients with different degrees of cortisol excess: a proposal for a new test for the diagnosis of Cushing's syndrome

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Background
Cushing's syndrome (CS) is caused by endogenous cortisol excess and is associated with significant morbidity. Twenty-four-hour urinary cortisol is one of the most useful tools to diagnose CS although it has limitations, especially in "mild" and "subclinical" forms of cortisol excess. We hypothesized that given the diurnal rhythm of physiological cortisol secretion, night-time urinary glucocorticoid excretion should be lower than day-time excretion, which could facilitate more sensitive detection of cortisol excess with an overnight urine collection.
Methods
Prospective study comparing the urinary steroid profiling of patients with different degrees and aetiologies of cortisol excess to controls. Subjects provided an overnight urine collection and a day-time urine collection. Urine samples were analysed by liquid chromatography-tandem mass spectrometry quantifying 15 distinct adrenal steroids. The night-time and day-time steroid excretion rates were compared to the conventional 24-h urine excretion.
Results
We included patients with overt CS ($N=11$), mild autonomous cortisol excess (MACE) in the context of adrenal incidentaloma ($N=17$), nonfunctioning adrenal incidentalomas ($N=22$), and sex- and age-matched healthy controls ($N=28$). Steroid excretion in controls reflected the diurnal pattern of adrenal steroid secretion, with lower night-time than day-time excretion of glucocorticoid metabolites and 11β-hydroxyandrosterone, the metabolite of the major adrenal androgen 11β-hydroxyandrostenedione. Overt CS showed significantly increased night-time urinary cortisol excretion and, in contrast to 24-h cortisol excretion, no overlap between overt CS, MACE and controls. Both patients with overt adrenal CS and MACE had significantly decreased night-time androgen excretion in comparison to ACTH-dependent CS.
Conclusions
The timed overnight urinary collection performs equivalent to the current reference standard 24-h collection, with improved performance of urinary cortisol in patients with overt CS. The simultaneous analysis of multiple adrenal steroids is a promising tool for the stratification of patients with different degrees of cortisol excess and for the differential diagnosis of CS.

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OC5.2

Residual adrenal function in autoimmune addison s disease effect of dual therapy with rituximab and depot tetracosactide

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In patients with autoimmune Addison's disease (AAD), exogenous glucocorticoid (GC) therapy is an imperfect substitute for physiological GC secretion; patients on long-term steroid replacement have increased morbidity, reduced life expectancy and poorer quality of life. Recent early-phase studieshave demonstrated that some endogenous steroidogenic function – Residual Adrenal Function (RAF) - is maintained at the point of diagnosis in a proportion of AAD patients; this can be harnessed and exploited with novel therapies. The RADS2 (rescue of addison's disease 2) study examined the impact of B-lymphocyte depleting immunotherapy and trophic stimulation on steroidogenic function in AAD for the first time. Dual therapy with rituximab and depot tetracosactide was administered in 13 subjects (9 female, 4 male; aged 19–64 years) with new onset AAD within 4 weeks. A detailed assessment of serum and urine GC, mineralocorticoids (MC) and androgens was performed at baseline and at regular intervals throughout the 72-week follow-up period (during temporary cessation of exogenous steroid replacement). 10/13 (77%) subjects had evidence of RAF on trial entry (detectable cortisol on short synacthen testing (SST); range 26-265 nmol/L). Following intervention, 7/13 (54%) subjects had an increase in stimulated cortisol measurement, with a peak response of 325 nmol/l at Week 18 in 1 patient, which facilitated weaning of exogenous GC replacement to hydrocortisone 5mg daily. Increased urinary excretion of steroid metabolites, assayed by GC-MS at baseline, Week 12 and Week 48, was detected in 8/13 (62%) subjects post-intervention, reflecting an increase in endogenous adrenal steroidogenesis. While combined treatment with rituximab and depot tetracosactide did not restore normal adrenal function, this study shows that adrenocortical plasticity can be exploited post-diagnosis to improve endogenous steroid secretion. Future considerations should include exploring the utility of an alternative immunotherapeutic regimen, alongside newer regenerative medicine approaches, with the aim of improving patient outcomes for those with AAD.

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OC5.3

11βHSD1 mediates therapeutic glucocorticoid-induced muscle atrophy in chronic inflammatory disease

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Objective
Therapeutic glucocorticoids (GCs) are commonly used in the treatment of chronic inflammatory disease. Unfortunately, their long-term administration is associated with deleterious systemic side effects including muscle atrophy. 11 beta-hydroxysteroid dehydrogenase type 1 (11βHSD1) activates glucocorticoids within muscle, is increased with inflammation, and has previously been shown to mediate GC induced muscle wasting. We examined the role of 11 beta-hydroxysteroid dehydrogenase type 1 in mediating muscle wasting in a mouse model of inflammatory myopathy receiving therapeutic GCs.
Methods
Wild type (WT) and mice with a global deletion of 11β-HSD1 were crossed onto the TNF-tg murine model of chronic inflammation that develops inflammatory myopathy. Animals received either vehicle or the GC corticosterone (100 ug/ml) in drinking water, over 3 weeks at therapeutic doses. Tibialis anterior (TA) and quadriceps muscle weights were examined at 7 weeks. Anabolic, catabolic and inflammatory gene expression was examined by RT-PCR.
Results
Significant GC activation by 11β-HSD1 was identified in WT and TNF-tg animals at 7 weeks ($0.06+0.001$ and $0.072+0.002$ pmol/mg/hr), whilst activity was completely abolished in 11β-HSD1 KO and TNF-tg/11βHSD1-KO animals. TNF-tg and TNF-tg/11βHSD1-KO developed significant muscle atrophy characterised by reduced TA and Quadriceps weights and increased expression of pro-inflammatory cytokines (IL-6 and TNFα). In addition, muscle catabolism related gene expression (MYOST, FOXO-1, TRIM63) was increased in TNF-tg muscle. In response to cort, muscle atrophy exacerbated in TNF-TG but not TNF/11βKO mice, despite an equal or larger increase in CORT-induced catabolic gene expression in TNF/11βKO compared to TNF-Tg mice. Moreover, CORT suppressed inflammatory gene expression in TNF but not TNF/11βKO muscle.
Conclusions
These data suggest that GCs and inflammation additively induce muscle wasting during chronic inflammation and that 11β-HSD1 is involved in mediating local anti-inflammatory and catabolic effects of corticosterone.

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OC5.4

Glucocorticoid receptor-mediated signalling inhibits mesenchymal cell proliferation via repression of the V1 isoform of versican during mouse lung development

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Glucocorticoid (GC) signalling via the glucocorticoid receptor (GR) is essential for normal lung development. Previous work using conditional mouse knockouts of the GR gene established that GR activity in the mesenchymal compartment of the lung is critical for normal respiratory development. Screens for GC-target genes with conditional mesenchymal GR deficient mouse lung (GRmeskO) identified Versican (Vcan), an important extracellular matrix (ECM) component and cell proliferation regulator, as a potential GR-regulated gene target. Alternative exon splicing of the Vcan gene generates up to 5 isoforms termed V0, V1, V2 V3 and V4 that vary in structure, tissue-specific expression and function. We hypothesised that the severe mesenchymal cell hyperplasia observed in the GRmesKO fetal mouse lung is in part due to the lack of normal GR-mediated repression of Vcan levels. We show that of the five Vcan isoforms, the V1 isoform is the predominate isoform in the fetal mouse lung. Both V1 mRNA and protein levels were strongly over-expressed in the GRmesKO lung at E18.5 compared to wildtype controls. To further characterise the proliferative role of Vcan we performed siRNA-mediated knockdown of Vcan expression in primary rat lung fibroblasts that showed a modest reduction in cell proliferation.

Finally, we showed that ADAMTS12, a protease that has been proposed to degrade Vcan is also markedly reduced in the GRmesKO mouse lung and was strongly induced by both cortisol and betamethasone in cultures of primary fetal rat lung fibroblasts. In summary, GC steroids regulate repression of the ECM protein Vcan and induction of the protease ADAMTS12 to contribute to coordinated normal respiratory development in mammals.

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OC5.5

Androgen modulation of mouse uterus: a tissue-based bioassay for testing endogenous and synthetic androgen receptor modulators (SARMs)

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The uterus is an androgen-responsive tissue and AR is expressed in cells within the endometrium and myometrium. We have demonstrated that treatment of ovariectomised mice with the potent androgen dihydrosterone (DHT) induces a uterotrophic response with changes in expression of genes involved in cell-cycle progression, Wnt signalling and an expansion of the glandular epithelium. Selective androgen receptors modulators (SARMs) are AR ligands in development as potential therapeutic agents for conditions associated with muscle wasting but their tissue-specific effects on the uterus are unknown. In this study we used a uterine bioassay to compare the impacts of SARMs (GTx-007, GTx-024) with Danazol and DHT. Adult female mice (C57BL/6J) were ovariectomised and treated with either (a) vehicle solution [0.4% methycellulose/5% ethanol], (b) DHT, (c) GTx-024 (Ostarine), (d) GTx-007 (Andarine) or (e) Danazol by daily subcutaneous injections for 7 days [$n=10$–14/treatment group]. Uteri were collected and analysed by RT-qPCR, immunohistochemistry and uterine morphometric analyses. Treatment with DHT, GTx-024 or Danazol significantly increased uterine weight and size; GTx-007 was not uterotrophic. Immunostaining of AR increased in the myometrium, stroma and glandular epithelium following treatment with GTx-024 and DHT, while Danazol increased AR expression only in the endometrial stromal compartment. Endometrial and myometrial cell proliferation was differentially affected by treatments. Expression of candidate AR-regulated genes (*Igf1, Wnt4, Wnt7a, Cdh1, Foxa2, Rb1, Mki67, Fgf7*) was altered in a treatment-specific manner, with DHT, GTx-024 and Danazol inducing similar expression patterns. Both DHT and GTx-024 stimulated formation of endometrial glands. In summary, while GTx-024 appears to exhibit identical uterine effects to those of DHT, Danazol only partially reflects these changes and GTx-007 appears to have no uterotrophic effects. These results have implications for the use of SARMs in women.

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OC5.6

Therapeutic glucocorticoids prevent local and systemic bone loss in the TNF-tg model of chronic inflammatory disease

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Both therapeutic glucocorticoids (GCs) and chronic inflammation are powerful inducers of systemic bone loss, resulting in osteoporosis and increased morbidity. Whilst GCs suppress inflammation, it is unclear how these factors interact to determine net bone metabolism. We investigated the balance between osteo-protective and osteo-destructive properties of GCs in the TNF-tg model of chronic inflammatory disease. Wild-type (WT) and TNF-tg mice were treated with corticosterone (100 mg/ml) for three weeks. Tibias were assessed by micro-CT and RT-PCR. Markers of bone metabolism were measured by serum ELISA. Corticosterone potently suppressed markers of inflammation and synovitis in TNF-tg mice. Whilst inflammation in the TNF-tg mouse resulted in a significant decrease in trabecular bone relative to WT animals, TNF-tg mice receiving corticosterone possessed a marked protection from inflammatory bone loss, with significantly greater BV/TV and Tb.N relative to untreated controls (BV/TV: TNF-tg 2.19% $\pm$0.2 vs TNF-tg CORT 4.25% $\pm$0.2, $P\leq0.001$; Tb.N: TNF-tg 0.0004 1/μm $\pm$0.00009 vs TNF-tg CORT 0.0008 1/μm $\pm$0.00003, $P\leq0.001$). Serum markers of bone resorption did not change across groups, however a significant reduction in juxta-articular osteoclasts was observed in TNF-tg mice receiving corticosterone relative to untreated controls. Although WT and TNF-tg mice receiving corticosterone did not develop a significant level of bone loss by micro-CT, we observed a significant reduction in mature osteoblast markers OSC and ALP and the serum marker of bone formation 'P1NP' in both WT and TNF-tg animals receiving corticosterone relative to untreated controls, (WT 494.2 ng/ml $\pm$ 61.1 vs WT CORT 31.4 ng/ml $\pm$7.4, $P\leq0.001$; TNF 269.7 ng/ml $\pm$38.4 vs TNF-tg CORT 32.3 ng/ml $\pm$4.2, $P\leq0.001$). These data indicate that whilst therapeutic GCs suppress bone formation, they ultimately protect bone from inflammatory osteoporosis by suppressing osteoclast mediated bone resorption *in vivo*.

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Neuroendocrinology and Reproduction

OC6.1

A controlled cross-sectional study of bone microarchitecture in transgender individuals

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Sex steroids have complex effects: testosterone predominantly regulates trabecular and estradiol, cortical bone[1]. Studies in transgender individuals use insensitive technology and report conflicting effects[2]. We hypothesized estradiol therapy will increase cortical volumetric bone mineral density (vBMD) in male-to-female (MtF) individuals and testosterone therapy will increase trabecular vBMD in female-to-male (FtM) individuals.

Aims

To vBMD in transgender individuals receiving cross-sex hormones. HRPQCT was performed in a cross-sectional study MtF and FtM individuals. Unpaired students t-test was used to compare transgender individuals with healthy age and birth-assigned sex matched controls.

Results

Tibial trabecular vBMD ($P=0.011$) was decreased in MtF compared to control males and cortical vBMD was decreased. Conversely, compared to female controls, FtM individuals receiving testosterone therapy had increased distal tibial trabecular vBMD ($P<0.001$), with increased trabecular number ($P<0.001$) and decreased trabecular separation ($P=0.008$) but no difference in cortical vBMD. Similar findings were seen at the radius.

Conclusion

The findings in FtM (increased trabecular vBMD) and MtF individuals (decreased vBMD) support a role for testosterone in building trabecular bone. This study did not confirm a role for estradiol in building cortical bone.

	MTF ($n=39$)	Control male			Control female	
Distal tibia	Mean $\pm$ s.d.	($n=57$)	*P*	FTM ($n=45$)	($n=79$)	*P*
Cortical vBMD	**841.7 $\pm$ 39.4**	**861.5 $\pm$ 40.3**	**0.019**	898.6 $\pm$ 34.4	892.5 $\pm$ 41.3	0.398
Trabeculae						
vBMD	**189.7 $\pm$ 29.6**	**206.5 $\pm$ 32.2**	**0.011**	**202.3 $\pm$ 29.6**	**180.5 $\pm$ 35.2**	**<0.001**
Thickness	0.088 $\pm$ 0.011	0.089 $\pm$ 0.015	0.615	**0.093 $\pm$ 0.014**	**0.086 $\pm$ 0.017**	**0.038**
Number	**1.82 $\pm$ 0.29**	**1.96 $\pm$ 0.32**	**0.029**	1.84 $\pm$ 0.25	1.78 $\pm$ 0.37	0.369
Separation	**0.477 $\pm$ 0.088**	**0.436 $\pm$ 0.081**	**0.019**	**0.462 $\pm$ 0.068**	**0.500 $\pm$ 0.114**	**0.044**
Total						
Average vBMD	**297.9 $\pm$ 49.0**	**326.3 $\pm$ 42.0**	**0.003**	**343.4 $\pm$ 50.6**	**308.7 $\pm$ 48.5**	**<0.001**

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OC6.2

Towards an understanding of the function of the mineralocorticoid receptor in zebrafish: the stress response, behaviour and osmoregulation

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The mineralocorticoid receptor (MR) is primarily involved in osmoregulation in mammals, with additional roles of brain-behaviour implicated. However, the

understanding of this role is limited, partly due to the mortality of MR-knockout mice due to impaired Na^+ reabsorption. Many steroidogenesis pathways and hormone receptors are highly conserved in zebrafish, providing a great potential to become a high-throughput model for translational endocrine research. My project is to characterise the role of the MR in zebrafish and evaluate whether zebrafish are an appropriate non-mammalian model of mineralocorticoid-resistance. I have created a viable zebrafish mutant line carrying a constitutive loss-of-function mutation in *mr* using CRISPR-Cas9 technology. Behavourial assays show an abnormal behavioural phenotype, with a significant increase in locomotion activity in the dark periods of standard dark/light interval assays; a potential output for high-throughput in vivo drug screening. Wholemount *in situ* hybridisation on 5 day-old zebrafish larvae showed a reduced expression of a transcriptional regulator of neurogenesis, *neurod1,* in *mr* homozygous mutants compared to wildtype sibling controls. In wildtype zebrafish, we showed differential expression of *mr*, the glucocorticoid receptor (*gr)* and *11hsdb2* during zebrafish development and between adult organs using qRT-PCR. The wildtype zebrafish brain exhibited a higher *mr* expression than osmoregulatory organs such as the gills and kidney. In the adult zebrafish brain, *mr* expression was localised at the periventricular gray zone of optic tectum, area with high proliferative cells that contribute to neuronal and glial lineages. Whilst in mammals the MR is primarily involved in the RAAS pathway to regulate electrolyte balance and blood volume, in zebrafish it appears to have an important role in the brain, affecting both behaviour and neuronal development. This zebrafish model of mineralocorticoid-resistance may provide further insights into the MR's role in the brain and behaviour, the stress response and osmoregulation.

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OC6.3

Gamma knife radiosurgery for the primary management of acromegaly

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Introduction
Trans-sphenoidal Surgery (TSS) remains the primary treatment for acromegaly in most patients, but no previous data exist on outcomes for patients treated with gamma knife radiosurgery (STRS) as a primary treatment.
Methods
20 patients with acromegaly underwent primary STRS at the National Centre for Radiosurgery, Sheffield, UK between 1985 and 2015. Data collection: note review, database, laboratory results, patient questionnaire, and death certification. Guideline-based Biochemical control was defined as normal age-sex-adjusted IGF1 levels *and* either GH <0.3 μg/l (OGTT) *or* random GH <1 μg/l or mean Growth Hormone Day Curve (GHDC) <1 μg/l. Pragmatic remission was defined as any one of the above criteria.
Results
Of 12 patients taking acromegaly-specific medication all had 'guideline-based' control at 20 years ($n=9$; 3 deaths), with median time to control being 3 years. Median time to guideline-based control off medication was 7.4 years, with 75% achieving this at 20 years (3/4; 3 deaths; 5 censored). Using 'pragmatic remission', all patients achieved biochemical control on acromegaly-specific medication at a median of 3 years ($n=19$; 1 death). 72% achieved control off medication ($n=7$), with 25% achieving this by 3 years. Median marginal radiation dose was 27.5 Gy and median follow-up was 166.5 months. Seven patients died at a median age of 65 years. There were no STRS-related deaths. 53% of patients developed new hypopituitarism at a median follow-up of 146 months, with first onset of hypopituitarism as late as 20 years after treatment. No other complications were noted. 3 patients underwent subsequent TSS due to poor biochemical control.
Conclusion
This is the first report to selectively analyse patients who have undergone primary STRS for acromegaly, and shows low morbidity, but significant latency to biochemical control and new onset hypopituitarism mandating very long-term follow-up for all patients who have undergone gamma knife treatment for acromegaly.

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OC6.4

Kisspeptin receptor activity in human granulosa lutein cells

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Background
Kisspeptin stimulates gonadotropin secretion indirectly by stimulation of hypothalamic GnRH neurons. Kisspeptin and kisspeptin receptor, a G-protein coupled receptor (GPCR), are also expressed in the human ovary, but their direct actions on ovary, if any, are unclear.
Objectives
To examine the direct actions of kisspeptin on granulosa lutein cells (GL cells) and the role of kisspeptin in steroidogenesis.
Materials and methods
GL cells were isolated from follicular fluid collected at oocyte retrieval for IVF. Cells were treated *in vitro* with kisspeptin-10, hCG or a combination of both and then lysed for extraction of RNA, protein, or for measurement of IP1, a marker of phospholipase C activation. Western immunoblotting was used to detect phospho-ERK and phospho-AKT, and an IP1 accumulation assay was carried out, all of which are indicators of activation of receptor Gq activation and signalling.
Results
Treatment *in vitro* with kisspeptin-10 50 nM for 15 min increased phospho-ERK (2-fold increase, $n=9$, $P<0.05$) in GL cells. There was a non-significant increase in phospho-AKT (2-fold, $n=7$, $P=0.1$). Kisspeptin treatment for one hour resulted accumulation of IP1 (2.5 fold increase, $n=8$, $P<0.05$). Interestingly we detected activation of these Gq signalling pathways in samples from 70% of women, suggesting that kisspeptin receptor is active in the ovaries of some but not all women.
Conclusion
This is the first study examining direct effects of kisspeptin in human granulosa lutein cells. In vitro treatment with kisspeptin activates intracellular signalling, suggesting that it may play a direct role in regulation of ovarian function.

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OC6.5

Is the metabolic phenotype altered in decidualised stromal cells from women with endometriosis?

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Endometriosis is a chronic incurable hormone dependent condition characterized by growth of endometrial tissue in sites outside the uterus: 30–40% of women with endometriosis have sub/infertility however the underlying cause is unknown. We have previously demonstrated that steroid-induced differentiation of endometrial stromal cells (hESC) (decidualisation) is associated with increased expression of metabolic genes that are thought to be essential to support the implanting blastocyst. Disordered glucose metabolism by hESC has been implicated as a cause of subfertility. The aim of this study was to compare the metabolic phenotype of hESC from women with and without endometriosis so as to inform our understanding of the mechanisms underpinning infertility in this patient group. Primary hESC from the proliferative phase of the cycle were isolated from endometrial biopsies collected from women with endometriosis ($n=8$) and women with no evidence of endometriosis ($n=6$). Decidualisation was induced *in vitro* (progesterone and cAMP) and metabolic analysis performed on days 1, 2, 4 and 8 using the Seahorse bioanalyser. RNA was isolated from cells to examine expression of genes involved in metabolism by qRT-PCR: secretion of decidualisation-associated proteins (e.g. IGFBP1) were measured in media by Elisa. Seahorse analysis revealed a significant shift towards increased glycolysis in decidualised hESC compared to undecidualised cells (as determined by extracellular acidification rate, ECAR) with a corresponding drop in glycolytic reserve. Cellular oxygen consumption rate (OCAR) revealed a significant decrease in ATP production and a significant decrease in coupling efficiency in primary hESC from women with endometriosis compared with controls. Decidualisation was associated with a significant increase in IGFBP and PPARGC1A (coordinates gene expression regulating mitochondrial biogenesis) and a decrease in PCK2 (implicated in metabolic reprogramming). The results demonstrate a shift towards a 'Warburg' like phenotype in hESC during decidualisation that appears altered in women with endometriosis.

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OC6.6

An epigenetic modifier reduces proliferation in pituitary cells and suppresses calcium-sensing receptor signalling

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JQ1 is a bromodomain inhibitor that specifically targets the BET protein family (comprising Brd2, Brd3, Brd4 and BrdT), which promote the transcription of genes by binding acetylated histone residues and recruiting transcriptional machinery. JQ1 has been shown to have efficacy in the treatment of neuroendocrine tumours, however the genes regulated by the BET family in endocrine tissues, particularly in the pituitary, have not been elucidated. We therefore performed RNA-Seq analysis on the mouse corticotrophinoma pituitary cell-line AtT20 following treatment with JQ1, or the JQ1 negative stereoisomer JQ1-. This identified the calcium-sensing receptor (CaSR) gene, *Casr*, and six genes within its signalling pathway, as significantly downregulated, which we confirmed by quantitative PCR. CaSR is a G-protein-coupled receptor that detects extracellular calcium (Ca^{2+}_e) and elicits calcitropic (calcium homeostasis) and non-calcitropic effects through multiple G-protein pathways. Within normal pituitary cells, CaSR helps regulate anterior pituitary hormone secretion. However, in AtT20 cells CaSR activates a tumour-specific cAMP pathway that promotes ACTH and PTHrP secretion. Based on these results we hypothesised that the *Casr* promoter must harbour binding sites for BET proteins, and that JQ1 treatment should suppress CaSR signalling. Using chromatin Immunoprecipitation (ChIP)-sequencing we demonstrated that the BET protein Brd3 binds to the promoter of 5 of the genes identified as downregulated by RNA-sDefault (*CaSR*, *Plch1*, *Plce1*, *Prkcg* and *Creb3l2*). To determine if JQ1 treatment altered CaSR-mediated signalling we measured Ca^{2+}_e-induced intracellular calcium (Ca^{2+}_i) mobilisation using a fluo-4 calcium assay, and cAMP signalling using a CRE luciferase reporter assay. We demonstrate that JQ1 treatment significantly decreased both Ca^{2+}_i and cAMP signalling, compared to DMSO or JQ1- treated cells. Thus, aberrant CaSR signalling in pituitary tumour cells can be regulated by epigenetic modifiers, and the CaSR pathway represents a novel target in pituitary tumorigenesis.

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Poster Presentations

Adrenal and Steroids

P001

Glucocorticoids promote DNA repair to reduce efficacy of radiotherapy in Glioblastoma

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Glioblastoma (GBM) is a highly aggressive form of brain cancer with a median survival time of 12–15 months from diagnosis. Standard therapies utilise a combination of radiotherapy, chemotherapy, and surgery. Patients also receive high doses of the potent anti-inflammatory glucocorticoid (Gc), Dexamethasone (Dex).Recent studies show that patients receiving the highest dose of Dex also have reduced survival time. Defining pathways under Gc control relevant to GBM is necessary to understand how Gc may affect the efficacy of standard cancer therapies. We have used genome-wide transcriptional profiling (RNA-seq) of GBM cells treated with a vehicle control, two doses of hydrocortisone (HC, corresponding to minimum and maximum endogenous levels), or an equivalent therapeutic dose of Dex. We identify Gc dependent regulation of 307 genes (>1.5 fold change, FDR <0.05). Of these, 37 genes are regulated by all three treatments, 72 genes are regulated by high HC and Dex, and 140 genes are regulated by Dex alone. Gene ontology analysis across all Gc-regulated transcripts predicts changes in the activity of IL-6, NFkB and AP-1 pathways, consistent with anti-inflammatory effects. Gc were also predicted to affect cell cycle and DNA repair pathways, largely through control of p53 effector proteins. This is particularly relevant in the context of GBM treatment, as radiotherapy and chemotherapy both rely on the induction of DNA damage to induce GBM cell death. We demonstrate that Gc treatment reduces levels of DNA damage (COMET assay), thereby increasing survival (MTT assay) of GBM cells following irradiation. This Gc induced radioresistance occurs in cells which lack functional DNA-PK, suggesting a DNA-PK independent mechanism. Our study now reveals novel Gc actions which affect genome stability and treatment efficacy in GBM.

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P002

11β-HSD type 1 inhibitor ameliorates metabolic disorders associated with hypercortisolemia: A clinical trial to assess its safety and efficacy in Japanese patients with refractory Cushing's syndrome and subclinical Cushing's syndrome

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Cushing's syndrome (CS) and subclinical Cushing's syndrome (SCS) show poor prognosis due to hypercortisolemia, which causes metabolic disorders, such as diabetes mellitus, hypertension, dyslipidemia, and osteoporosis. Aiming to improve prognosis and develop a novel treatment for these refractory diseases, we have been constructing a patient registry of CS and SCS founded on a multicenter database at Kyushu University hospital and related facilities since 2001. CS included Cushing's disease, adrenal CS, and ectopic ACTH syndrome. The proposed diagnostic criteria for adrenal SCS has been described (Akehi, *et al.* Endocr J. 2013, 60: 903–12). First, we performed a prognostic survey using the registry comprising 112 patients (40% CS and 60% SCS). The prevalence of complications of glucose impairment, hypertension, and dyslipidemia was 75, 48, and 23% in CS and 72, 49, and 31% in SCS, respectively. Despite surgery, 70% of CS patients were not cured. In addition, 59% of SCS patients have not undergone surgery. Consequently, a considerable number of patients still need treatment for hypercortisolemia. Second, we performed an investigator-initiated phase I/IIa clinical trial to assess the safety and efficacy of a 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor in patients with refractory CS and SCS between 2016 and 2018 (Registration ID: UMIN000024482). Although 11β-HSD1 bidirectionally interconverts the inactive glucocorticoid cortisone and the active cortisol, it predominantly generates cortisol. Hypercortisolemia activates 11β-HSD1, which promotes the development of hypercortisolemia-related metabolic disorders. In the present study, 16 patients with refractory CS and SCS with impaired glucose tolerance were enrolled. Administration of 11β-HSD1 inhibitor for 24 weeks showed its safety and efficacy with reduction of urine 11α- and 11β-tetrahydrocortisol/11β-tetrahydrocortisone ratio by one-tenth. Inhibition of 11β-HSD1 activity is expected to be a new therapeutic approach for the patients with refractory CS and SCS.

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P003

Mass spectrometry-based assessment of childhood androgen excess in 487 consecutive patients

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Background
Androgen excess in childhood is a common clinical presentation with potentially serious underlying pathology.
Objectives and Design
We have examined the diagnostic utility of simultaneous measurement of serum dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), and testosterone (T) to delineate the biochemical signatures of conditions underlying paediatric hyperandrogenism in a large tertiary care referral centre (2013–2017). Serum A4 and T were measured by tandem mass spectrometry, DHEAS by immunoassay; results were interpreted using Tanner-stage defined cut-offs. Patients with ≥ 1 increased androgen were clinically phenotyped.
Results
1525 children underwent serum androgen measurements; in 487 children, DHEAS, A4, and T were measured simultaneously, with ≥ 1 increased androgen in 41% ($n=199$). Premature adrenarche (PA) was the most common diagnosis (42%), followed by polycystic ovary syndrome (PCOS) in 12.6% and congenital adrenal hyperplasia (CAH) in 7.0%. In 13% of children, the underlying cause could not be established. There was one case of adrenocortical carcinoma (ACC), identified by isolated DHEAS excess (28-fold above upper limit of normal). PA was characterised by raised DHEAS levels in 85% of cases. A4 was raised in 26% of PA children, T in only 9%. CAH was characterised by A4 excess in 86% of patients, whereas T was raised in 35% and DHEAS in only 21%. In adolescent PCOS, the distribution of androgen excess levels was similar for DHEAS, A4 and T (50, 42 and 42%, respectively).
Conclusions
PA was the commonest condition and characterised by DHEAS excess in the majority of cases. CAH most frequently presented with A4 excess and normal DHEAS. In adolescent PCOS, DHEAS, A4 and T excess are evenly distributed. ACC is extremely rare in childhood and isolated DHEAS excess should prompt urgent investigation. To our knowledge, this is the first systematic evaluation of androgen levels in a large cohort of children presenting with hyperandrogenism.

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P004

Feasibility of immunological markers and osteocalcin as a barometer of glucocorticoid replacement

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Objective
To investigate a selection of novel bone or immunomarkers which may act as indicators for steroid replacement in Adrenal Insufficiency (AI).
Introduction
AI is a condition where individuals are not able to produce sufficient steroids for their body's requirement. Although mortality rates have improved since the introduction of exogenous steroid replacement, this condition is still associated with increased mortality and morbidity. This could be attributed to either over- or under-replacing patients with exogenous steroids. The absence of an objective

marker makes steroid replacement a challenge. It has been shown that excess glucocorticoids lead to increased bone loss as well as immune suppression.
Methods
This is a pilot cross-sectional study looking at 22 participants who were split into four groups based on the dose of exogenous steroid administered (high-dose steroids, replacement dose hydrocortisone, replacement dose prednisolone and healthy controls). Blood samples and anthropometric data were collected from participants. Carboxylated-Osteocalcin (Gla-OC) and bone-related immunological cytokines were investigated.
Results
The high-dose steroid group had a significantly higher Gla-OC vs control (9.78 ng/ml vs 4.70 ng/ml, $P=0.034$) and vs the prednisolone group (9.78 ng/ml vs 3.78 ng/ml, $P=0.032$). IL-4 was significantly higher between the high-dose steroid and hydrocortisone group (22.6 ng/ml vs 3.52 ng/ml, $P=0.033$) and between the control and hydrocortisone group (21.0 ng/ml vs 3.52 ng/ml, $P=0.032$).
Conclusion
This study has demonstrated that Gla-OC and IL-4 show significant detectable changes between healthy controls, steroid replacement regimens and anti-inflammatory steroid regimens. They display potential to be long-term markers of steroid replacement and a larger prospective study to evaluate these markers further, is warranted.

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P005

A model to predict Hypothalamic-Pituitary-Adrenal (HPA) axis recovery at 6 weeks post trans sphenoidal adenomectomy: a single-centre retrospective analysis

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Background
Hypopituitarism can occur post trans-sphenoidal adenomectomy(TSA). Accurate prediction of HPA axis recovery would inform hydrocortisone replacement strategies but there are limited studies on this. In our centre, HPA axis is assessed with pre-operative short synacthen test (SST), day-8 post TSA 9am cortisol and 6-week post-TSA SST. Patients are commenced on hydrocortisone post TSA until 6 weeks review.
Methods
We performed a single-centre, longitudinal, retrospective analysis of 118 consecutive patients undergoing TSA between January 2016-March 2018. Multiple regression models were used to identify variables contributing to 6-week post-TSA HPA axis recovery. Patients with apoplexy, corticotroph adenomas, radiotherapy or incomplete data sets (pre- and post-op SST plus day 8 cortisol) were excluded.
Results
Multiple regression analysis was conducted on 64 patients. 36 were excluded due to incomplete data points, 10 as corticotrophs, 4 as apoplexy, 4 received radiotherapy. Post-op day 8 cortisol above 210 nmol/l (AUC ROC = 0.78) and pre-op SST 30-minute cortisol levels above 465 nmol/l (AUC ROC = 0.85) best predicted adrenal recovery: 79.3% of patients with day 8 cortisol >210 nmol/l (RR = 0.189) and 71.9% of patients with pre-op 30-minute cortisol >465 nmol/l (RR = 0.417) recovered HPA-axis function at 6 weeks. Combining these two measures significantly increased the ability to predict recovery (AUC ROC = 0.894): 87.8% of patients with pre-op SST 30-minute and day 8 cortisol levels above the cut-offs eventually recovered at 6-weeks while none of the patients below both cut-off values recovered HPA-axis function ($\chi^2=24.128$, $P<0.01$).
Conclusions
There is potential to use pre-op SST 30-minute cortisol and post-op day 8 cortisol alone, or in combination to predict 6-week HPA recovery in patients undergoing TSA. This may aid clinicians to decide on treatment strategy post TSA, and inform patients regarding likelihood of restoration of HPA axis function.

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P006

Increased urinary glucocorticoids in obese pregnancy suggest a potential mechanism underlying macrosomia

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Background
Both excess and insufficient glucocorticoid exposure in utero is associated with adverse fetal outcomes. Characterising the maternal hypothalamic-pituitary-adrenal (HPA) axis is challenging with large intra-individual variations in plasma and saliva. We hypothesised that 24-hour total urinary glucocorticoid (TUG) is a marker of maternal HPA axis during pregnancy. We tested associations of TUG with maternal BMI and birthweight.
Methods
TUG was measured by GC-MS/MS in 24-hour urine samples collected at mean 17.3 (s.d. = 2.4) weeks' gestation from 153 women aged 30.3 (s.d. = 5.1) years, body mass index (BMI) 27.9 (s.d. = 7.5) kg/m^2, participating in a longitudinal cohort pregnancy study. Birth outcomes were available for 145 infants with mean birthweight 3470 (s.d. = 495) grams, gestational age 39.4 (s.d. = 1.5) weeks. Differences in TUG according to maternal BMI were tested. Regression analysis tested associations between TUG and birthweight adjusting for confounding factors.
Results
TUG was higher in women with higher BMI ($r=0.413$, $P<0.001$). In adjusted models, increased TUG was associated with increased birthweight. This was most marked in obese women (BMI ≥ 30 kg/m^2) (Table 1).

Table 1 Linear regression model for TUG compared to birthweight.

	Univariate	Multivariate Model 1	Multivariate Model 2
All participants	β = 0.148 *P*-value = 0.074	β = 0.187 *P*-value = 0.007	β = 0.161, *P*-value = 0.041
BMI < 30	β = 0.130 *P*-value = 0.190	β = 0.150 *P*-value = 0.077	β = 0.022 *P*-value = 0.813
BMI > 30	β = 0.254 *P*-value = 0.105	β = 0.233 *P*-value = 0.051	β = 0.423 *P*-value = 0.002

Model 1: TUG, gestational age
Model 2: TUG, gestational age, infant sex, ethnicity, maternal age, smoking status, gestational hypertension, pre-eclampsia, diabetes, maternal BMI, TUG gestation
Conclusions
Obese pregnancy is associated with raised second trimester TUG. This increased peripheral clearance of maternal cortisol likely contributes to the low plasma cortisol levels in obese compared to lean pregnant women. The positive association of increased TUG with increased birthweight in obese women suggests a mechanism whereby increased peripheral clearance reduces fetal glucocorticoid exposure, contributing to macrosomia in infants of mothers with high BMI.

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P007

Salivary cortisol determination using the Roche generation II assay

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The Endocrine Society guidelines recommend initial testing for Cushing's syndrome (CS) can be based on non-invasive late-night salivary cortisol measurement (NSC). In the BHSCT NSC (11pm), measured using the IBL ELISA kit has been found to be highly discriminative in identifying patients with CS. However it is a labour intensive test and the need for analysing samples in

batches delays turnaround time, limiting its use in the routine work-up for CS. Roche provide an automated competitive electrochemiluminescence immunoassay for salivary cortisol standardised against IRMM/IFCC-451panel using ID-GCMS. The aim of this project was to evaluate Roche's automated assay for NSC. NSC samples were obtained from 52 patients (8 CS+, 44 CS−). Cortisol was measured in each sample using the ELISA and Roche assays and results correlated. An optimal cut-off for the Roche assay was determined. Between batch imprecision of the Roche assay was 8.7% at 11.5 nmol/l and 5% at 29.2 nmol/l and within batch was <1.95% at 8.0 and 26.7 nmol/l. The assay was shown to be linear to approximately 2 nmol/l. Measurement Uncertainty (MU) was determined at a level of 11.46 nmol/l to be 1.99 nmol/l (9.48–13.45 nmol/l) and for a level of 29.17 nmol/l the MU was 2.97 nmol/l (26.21–32.14 nmol/l). Correlation between test kits was demonstrated with $r^2 = 0.933$ and $y = 0.5835x + 0.8152$. ROC curve analysis (Roche) showed area under curve 0.956 ($P < 0.001$) with an optimal cut-off 7 nmol/l to identify CS (sensitivity 100%, specificity 93.2%). This correlates well with the cut-off provided by Roche of <7.56 nmol/l and <11.3 nmol/l, 95th and 97.5th percentiles respectively. In conclusion the Roche automated assay meets performance requirements and will be introduced into clinical practice. Further evaluation of the diagnostic usefulness of the assay as a routine test is planned. Genomic thyroid hormone action is mediated via receptor subtypes (TRα, TRβ) with differing tissue distributions. Resistance to Thyroid Hormone, due to mutations in thyroid hormone receptor α (RTHα), is characterised by features of hypothyroidism in specific tissues, but near-normal thyroid function tests. Our identification of potentially pathogenic TRα variants in genome databases suggests that RTHα is more common but underdiagnosed. TRα mutants inhibit wild type receptor function via a dominant negative mechanism, involving constitutive inhibition of target gene expression by a mutant receptor-transcriptional corepressor (TR-CoR) complex. Beneficial patient response to thyroxine therapy correlates with mutant TRα whose dysfunction is T3-reversible. Thyroid hormone analogues, which promote dissociation of the TR-CoR complex, may have therapeutic utility in RTHα associated with severe, T3-refractory, receptor defects.

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P008

Post-operative haemodynamic instability after adrenalectomy for phaeochromocytoma: is routine intensive care admission necessary?

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Introduction
UK guidelines state that all patients undergoing adrenalectomy for phaeochromocytoma must be admitted to intensive care post-operatively due to the risk of haemodynamic instability (HDI). Intensive care beds are a scarce resource and it is important to regularly evaluate the need for admission, preventing unnecessary admission.
Methods
The study population included all patients who underwent adrenalectomy for phaeochromocytoma at a UK tertiary centre between 2007 and 2017 ($n = 39$). Based on the parameters quoted in the literature post-operative HDI was defined as: systolic blood pressure >200 mmHg or <90 mmHg and heart rate >120 bpm or <50 bpm (all within the first 24 hours post-operatively). Additionally, the need for vasopressors within the first 24 hours post-operatively was recorded. A number of pre-operative variables were analysed including: tumour characteristics, pre-operative blood pressure, plasma metanephrines, alpha and beta blockade and the presence of genetic syndromes. Intra-operative variables were also recorded. Data was retrospectively analysed from pre-operative assessment charts, anaesthetic charts, ITU charts, clinic letters, lab results and observations in Clinical Portal/PICS. Univariate analysis was performed using Fisher's exact test and Kruskall Wallis to identify risk factors for post-operative HDI and post-operative vasopressor use.
Results
19/39 patients (49%) experienced HDI with 11 of these patients requiring vasopressors within the first 24 hours post-operatively. Patients who underwent open surgery were significantly more likely to experience HDI than with laparoscopic surgery (76% vs 17%; $P < 0.001$). Additionally, patients who had epidural anaesthesia were significantly more likely to experience HDI than patients who did not have epidural anaesthesia (69% vs. 32%; $P = 0.05$). For tumours <4 cm ($n = 14$) there was no HDI following laparoscopic surgery (laparoscopic 0% vs open surgery 50%; $P = 0.08$).
Conclusion
Patients undergoing laparoscopic adrenalectomy with tumours <4 cm in diameter are less likely to experience post-operative haemodynamic instability and may not need routine intensive care admission.

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P009

Discordance between imaging and adrenal vein sampling in primary aldosteronism

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Background
Subtyping of primary aldosteronism (PA) using imaging and adrenal vein sampling (AVS) can yield discordant results. Varying interpretation criteria in determining AVS lateralization may affect discordance rates.
Methods
We identified 337 consecutive patients with PA who underwent AVS at a quaternary care centre between August 2006 and February 2018. Patient demographics, laboratory results, diagnostic imaging, AVS results, and pathology were retrieved. Adrenal cross-sectional imaging was compared with AVS findings. Imaging was considered abnormal if any discrete nodule, bulkiness, or hyperplasia was reported. The presence of lateralization was defined using varying thresholds for the lateralization index (LI) from >4:1 to >2:1. Discordance was defined by a unilateral lesion on imaging with contralateral lateralization or bilateral disease on AVS.
Results
A total of 334 patients had adrenal imaging and 325 had technically successful AVS. The median age was 52 years, 58.8% were male, and hypokalemia was present in 67.5%. A total of 194 (58.1%) had unilateral lesions, 44 (13.2%) had bilateral lesions, and 96 (28.7%) had normal imaging. When present, unilateral lesions were more common on the left (67.0%) than the right (33.0%). Discordance between imaging and AVS was correlated with LI threshold stringency. Using the most 'strict' threshold of >4:1, the discordance rate was highest at 26.4%. Using 'lenient' thresholds of >3:1 and >2:1, the discordance rates were 23.7% and 22.0%, respectively. Lateralization, when present, was balanced between left and right irrespective of LI thresholds (44.0:56.0% for >4:1; 46.1:53.9% for >3:1, and 46.0:54.0% for >2:1).
Discussion
Discordance between imaging and AVS was common, and differences were greatest with 'stricter' AVS interpretation criteria. The preponderance of left-sided lesions seen on imaging, but not on AVS, is likely due to difficulties visualizing right-sided lesions on imaging rather than from biological differences.

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P010

Exploring the utility of renin measurements in the routine management of salt-wasting congenital adrenal hyperplasia

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The importance of measuring renin or plasma renin activity (PRA) and aldosterone in establishing mineralocorticoid deficiency is not in doubt. Once mineralocorticoid replacement therapy is initiated, guidance suggests that optimization of mineralocorticoid dose should be based upon measurements of blood pressure, renin (or PRA), and electrolytes. The aim of this study was to explore the relationship between renin and clinically important variables to determine whether measurement of renin can help guide appropriate mineralocorticoid dose titration. We performed an observational, longitudinal, retrospective analysis of data from 55 patients with congenital adrenal hyperplasia (CAH) including 23 patients with salt-wasting (SW) CAH. Multiple regression modelling was used to identify variables contributing to mean arterial blood pressure (MAP), electrolytes and renin. High renin levels were associated with lower sodium concentrations ($P = 0.01$) and sodium and potassium were inversely related ($P = 0.03$). However, there were no relationships between renin and mineralocorticoid dose ($P = 0.23$) or potassium levels ($P = 0.07$). Reflecting the complexities of blood pressure control, multiple regression modelling

demonstrated that renin was a weak predictor of MAP ($P<0.01$) with a low coefficient of relation ($B=-0.008$) suggesting that a 100-fold variation in renin was associated with a 1 mmHg change in MAP. Glucocorticoid (but not mineralocorticoid) dose ($P=0.01$) and body mass index ($P=0.02$) predicted MAP. Renin levels were predicted by MAP ($P<0.01$), BMI ($P=0.02$) and glucocorticoid dose ($P<0.01$), but not by mineralocorticoid dose ($P=0.20$). Longitudinal analysis (mean follow-up $=644\pm389$ days) demonstrated no relationship between changes in mineralocorticoid dose and renin over time. In our small cohort of patients with SW-CAH, the lack of a clinically significant relationship of renin with MAP, or any relationship with mineralocorticoid dose or serum electrolytes calls into question its utility in the optimization of mineralocorticoid replacement. Additional larger studies are now warranted to identify the best strategies and clinical tools to optimize mineralocorticoid replacement.

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P011

Androgen deprivation therapy causes selective loss of levator ani and leg muscle volumes

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Background
Androgen deprivation therapy (ADT) for prostate cancer (PCa) leads to a global loss of lean mass. ADT leads to sexual dysfunction and a selective loss of leg muscle function, however individual muscle volumes have never been evaluated. We aimed to assess in men undergoing ADT, the muscle volumes of levator ani, which in mice is androgen-responsive, and of lower-limb muscles.
Methods
We conducted a prospective case-control study involving 34 men newly commencing ADT and 29 age-matched PCa controls. Levator ani and leg muscle volumes (litres) of primary muscles involved in walking (iliopsoas, quadriceps, gluteus maximus, gluteus medius, calf) were measured using MRI and quantitated using Slice-O-Matic software at 0, 6 and 12 months. Generalised linear models determined the mean adjusted difference (MAD) (95% confidence interval) between groups over time.
Results
Compared with controls over 12 months, men receiving ADT had a mean reduction in total testosterone level from 14.1 to 0.4 nmol/l and demonstrated greater decreases in levator ani (MAD -0.005 litres (-0.007, -0.002), $P=0.002$, -16% of initial median value), gluteus maximus (MAD -0.032 litres (-0.063, -0.002), $P=0.017$, -5%), iliopsoas (MAD -0.005 litres (-0.001, 0.000), $P=0.013$, -5%) and quadriceps (MAD -0.050 litres (-0.088, -0.012), $P=0.031$, -3%). No significant differences were observed in gluteus medius and calf muscles.
Conclusion
Testosterone deprivation causes marked decreases in levator ani muscle, demonstrating that it's androgen responsiveness is evolutionarily conserved across men and mice. Further studies are required to investigate whether loss of levator ani muscle mass contributes to the profound sexual dysfunction seen in men on ADT. Consistent with previously reported functional deficits, ADT selectively decreases volume of muscles that support body weight. Future interventional studies aimed at reducing ADT-related sarcopenia and sexual dysfunction should evaluate the role of targeting these muscle groups, including the pelvic floor.

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P012

Newly diagnosed adrenal patients are poorly prepared to manage adrenal crisis

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Steroid-dependence is a life-long condition with a risk of premature mortality from undertreated adrenal crisis or omission of steroids. Previous studies identified rates of adrenal crisis around 8.3/100 patient years (Hahner 2015). We invited members of Addison's Disease Self-Help Group to complete an online questionnaire about any experiences of adrenal crisis. Respondents($N=628$) were asked to provide demographic information and details of their most recent adrenal emergency. 74 people (12%) reported diagnosis <12 months previously. Concerningly, 34% of this cohort had already experienced 1 – 3 episodes of post-diagnosis adrenal crisis. Only 35% reported vomiting as a trigger factor; 35% also reported flu-like illness with fever as a cause. 26% reported anxiety, bereavement or severe emotional stress as a trigger; 22% reported dehydration, sunstroke or overexertion. The most common time of day for the newly-diagnosed to realise they needed emergency treatment was 18:00 – 24:00 (35%), followed by 06:00 – 12:00 (30%). 63% had an injection kit in their possession at the time of their most recent adrenal crisis ($N=23$), but only 19% were able to self-inject or receive IM hydrocortisone from a partner. 27% were treated by ambulance crew, 27% by A & E staff, 18% by a GP, nurse or other hospital doctor. 9% recovered by taking extra oral hydrocortisone. Over half of this cohort were taken to hospital by ambulance; over 40% were admitted for 1+ days. Only 22% said they had received 1-1 training in injection method from an endocrine nurse. A further 26% receiving 1-1 training from a GP, practice nurse or other hospital specialist. These findings emphasize that adrenal patients should be adequately trained in self-management for adrenal crisis prevention at the time of diagnosis, to preserve life. Adrenal patient education should not be postponed until later followup appointments in outpatient clinics.

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P013

Adrenalectomy for removal of adrenal incidentalomas: are we being too cautious? A Retrospective Database Analysis

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Objective
Incidentally discovered adrenal masses ('incidentalomas') are found in 2% of the population. Adrenalectomy is necessary only in a small proportion of such subjects as outlined by the relevant ESE/ENSAT guideline[1]. However, uncertainty exists over the need for removal of lesions between 4 and 6 cm and those with low lipid content on CT scanning (found in 20% of benign adenomas). Our centre tends to offer surgery for all adenomas >4 cm.
Method
We scrutinised our adrenal surgical database for all patients who had undergone adrenalectomy due to size $>$ 4 cm, imaging characteristics not typical of benignity (low lipid content) or growth velocity $>20\%$ over 12 months[1]. We then examined subsequent adrenal histology with original indication for surgery.
Results
Ninety-seven patients with incidentalomas $>$ 1 cm were identified between 2009 and 2017. Patients with malignant disease and/or hormone excess ($n=48$) were excluded. The remaining 49 patients underwent adrenalectomy for criteria outlined above. The majority of excised lesions were benign cortical adenomas (38; 78%). Of the eight malignant adenomas, five were adrenocortical carcinoma, as well as a sarcoma, hepatocellular carcinoma and the other 'unclear'. Three tumours were histologically classified as phaeochromocytoma despite being biochemically silent. If the size threshold had been increased to >6 cm, removal of benign lesions is reduced by 39%.

Table 1 Characteristics of lesions

	Benign ($n=38$)	Malignant ($n=8$)	Functional ($n=3$)
Size >4 cm	26	6	2
Size >6 cm	11	5	2
Atypical radiology	10	2	1
Growth velocity	5	0	0

Discussion
In our series of 49 subjects who underwent adrenalectomy, only 8 (16%) were found to be malignant. Increasing the size threshold for surgery to 6 cm reduced

the number of 'unnecessary' operations without missing malignancy. These data support a more conservative approach towards adrenal incidentalomas in whom size >4 cm would be the sole indication for surgery.

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P014

Characteristics of patients with normal adrenal imaging in primary aldosteronism

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Background
Negative imaging in the work-up for unilateral (surgical) primary aldosteronism (PA) presents a diagnostic dilemma. Clinicians may assume bilateral disease and treat medically or may proceed to adrenal vein sampling (AVS) to try to localize a unilateral source of aldosterone secretion. However, AVS is not without cost, risk, and limited access. We describe AVS results among imaging-negative PA patients.
Methods
We identified 96 patients with PA and normal adrenal imaging who underwent AVS at a quaternary care centre from February 2008 to February 2018. Patient demographics, laboratory results, diagnostic imaging, and AVS results were retrieved. AVS lateralization was defined by an aldosterone-cortisol ratio of >3:1 from the dominant to non-dominant side. Clinical characteristics were compared for those with AVS findings of unilateral vs. bilateral disease.
Results
AVS was technically successful in 95 individuals with normal adrenal imaging (99.0%). The median age was 50 (interquartile range, 41–58) years and 53.1% were male. Hypokalemia was present in 52.6% and the mean estimated glomerular filtration rate (eGFR) was 83.5 (standard deviation, 21.1) ml/min per 1.73 m^2. The median aldosterone-renin ratio (ARR) was 344.1% (interquartile range, 217.0–665.9) above the assay-dependent upper limit of normal. One-third had evidence of lateralization (left in 12.6% and right in 21.1%). Subjects with unilateral PA, compared to those with bilateral disease, were more likely to be ≥40 years of age (90.9% vs 69.8%; $P=0.02$). Sex, ARR, eGFR, and serum potassium levels were not significantly different between groups.
Discussion
One-third of patients with normal adrenal imaging lateralized with AVS. AVS lateralization was more common in individuals aged ≥40 years. Sex, renal function, and hypokalemia were not predictive of lateralization. Older patients with normal imaging should still be considered for AVS. Future research should explore possible etiopathologies that may cause PA in young patients lacking adrenal adenomas.

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P015

Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess; a systematic review and meta-analysis

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Background
Adrenal incidentalomas are mostly non-functioning adrenal tumours (NFAT) or adenomas with mild autonomous cortisol excess (MACE), of which the natural history is unclear. We conducted a systematic review and meta-analysis focussing on NFAT and MACE to determine the: (i) proportion and degree of tumour growth, (ii) incident change in hormone function, and (iii) proportion of malignant transformation.
Methods
We searched MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, and CENTRAL (January 1990 to February 2018). We included studies of adults with NFAT or MACE (as defined by authors), with ≥20 patients undergoing conservative management, and reported outcomes of interest at baseline and after ≥12 months follow-up.
Results
We included 32 studies (17 retrospective, 15 prospective) reporting 2690 patients with incidental NFAT and MACE; 61.9% females, mean age 60.1 years, and mean follow-up 49 months. Studies used heterogeneous definitions for MACE and for studied outcomes. Overall, the data quality was medium-high. Development of overt Cushing's syndrome and phaeochromocytoma in NFAT and MACE was very rare, 0.4% of 2482 patients and 0.4% of 2690 patients, respectively. None of 2690 NFAT and MACE patients developed primary hyperaldosteronism. Of 2088 NFAT patients, only 5.2% developed MACE, while pre-existing MACE resolved in 1.5% of 780 patients during follow-up. Mean tumour growth in NFAT and MACE was 1.4 mm (CI95% 0.46–2.3) over mean follow-up 41.6 months. While 10.5% of NFAT and MACE patients demonstrated tumour enlargement, growth of ≥1 cm occurred in only 4.7% of patients. None of 2690 NFAT and MACE patients developed adrenal malignancy.
Conclusions
New diagnosis of overt Cushing's syndrome, primary hyperaldosteronism, or phaeochromocytoma is rare. Only 5.2% of NFAT developed MACE, while only 1.5% of MACE became non-functional, possibly suggestive of initially false-positive results. Tumour growth ≥1 cm occurred in 4.7% of patients. None of NFAT and MACE patients developed adrenal malignancy during follow-up.

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P016

Can morning salivary cortisol or cortisone predict short synacthen test outcome?

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Aim
If '0'minute salivary cortisol (SALCORT_0) or cortisone (SALCONE_0) can predict normal post-synacthen cortisol response.
Method
Baseline salivary sample was collected for 110 patients who had short synacthen test (SST) between 09:00 and 10:00 after hydrocortisone withdrawal for at least 24-hour. SST was labelled 'pass' if 30-minute serum cortisol was >450 nmol/l. Serum cortisol was measured by immunoassay whereas salivary cortisol and cortisone were measured by liquid-chromatography tandem mass-spectrometry.
Results
SALCORT_0 and SALCONE_0 were undetectable in 13 and 2% respectively. SALCORT_0:SALCONE_0 ratio was 5.1±3.4 nmol/l (1.2–20.6) in patients not on steroid (PNS; $n=72$, 8 'fail' SSTs) and 4.4±2.2 nmol/l (0.09–9.83) in patients on hydrocortisone (POH; $n=38$, 8 'pass' SSTs). Ratio <1.2 hinted saliva contamination by hydrocortisone, and both patients had 'failed' SST. In POH, SALCORT_0 and SALCONE_0 as high as 25.4 and 35.2 nmol/l were in 'failed' synacthen. As they were with CORT_0 of >300 nmol/l and flat SST, they are likely result of non-compliance with instruction to omit hydrocortisone before test. That a reason why they are not useful to predict 'pass' in SST. Lowest values of SALCORT_0 and SALCONE_0 amongst 'pass' SSTs in POH were 2.91 and 17.3 nmol/l respectively; and 13 of 38 patients had both values below these. In PNS; highest values of SALCORT_0 and SALCONE_0 in 'failed' synacthen were 4.07 nnol/l and 25.8 nmol/l respectively; and would preclude any predicting ability as no patient had both values above this.
Conclusion
SALCORT_0 and SALCONE_0 under cut-off could predict 'failed' SST in POH and it could be delayed till either value cross the cut-off and the ratio >1.2. 9am salivary sample collection at home would significantly alleviate logistic and financial implications of repeated SSTs in those with low pre-test probability of 'pass' and could have avoided 39% SSTs in our cohort.

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P017

Addressing adrenal incidentalomas (AIs): a snapshot of the investigation of AIs in a tertiary endocrine centre and the effect of implementing a local management pathway

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Introduction
Adrenal incidentalomas (AIs) are found in ~3% abdominal scans, rising to 10% in the elderly. In 2016, the European Society of Endocrinology (ESE) published new guidance on their management.
Aims & objectives
To (1) compare how AIs have been managed at the University Hospital of Wales (UHW) against ESE guidelines, and (2) provide an early evaluation of the impact of service changes implemented based on initial findings.
Methods
Reports of radiological scans performed at UHW (2011–2013) including terms related to an adrenal mass/lesion were retrieved. Electronic patient records were accessed to determine the characteristics reported in the initial radiological scan, the type of hormonal investigations requested and if any follow-up investigations were undertaken.
Results
Four hundred and sixty five patients with adrenal masses were identified. 79 (17%) were investigated by Endocrinology. *Radiological characterisation*: Lesion size was recorded in 96%, character in 63% and Hounsfield Units (HU) in only 9%. *Hormonal evaluation:* Metanephrines were measured in 94%, 86% had an overnight dexamethasone suppression test and 82% at least one urinary free cortisol. Patient records of 100 consecutive search results were also analysed to investigate the low referral rate: a total of 35 met the criteria for further investigation, but only 12 were referred to Endocrinology.
Conclusions
(1) Only a small fraction of AIs were referred to Endocrinology for further assessment; (2) There is significant variation in radiological reporting; (3) Whilst most patients undergo appropriate initial hormonal evaluation, many tests were unnecessary.
Outcomes
(1) A local management pathway was proposed to aid appropriate evaluation and timely discharge (2) We will present the first 10 months of data from this new Nurse-led clinic which was started in December 2017, with an average of 6 patients now seen per month.

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P018

The role of plasma metanephrines and plasma catecholamines in the biochemical testing for Pheochromocytoma

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First line screening for pheochromocytoma, as recommend by Endocrine Society guidelines, is to determine plasma free or urinary fractionated metanephrines. We routinely offer the latter. Although negative results rule out pheochromocytoma, it is not uncommon to see borderline results which require further investigation. In this situation we have historically relied on the measurement of plasma catecholamines in the clonidine suppression test (CST). Plasma metanephrines, however, offer a simpler and cheaper alternative. We compared results for CST with plasma metanephrine results. To date 26 patients have been investigated with urinary metanephrines, supine plasma metanephrines and CST. Results demonstrate concordance between CST and supine plasma metanephrine results when both were normal ($n=17$). Nine had abnormal supine plasma metanephrine results, seven of which also had abnormal CST confirming the biochemical diagnosis of pheochromocytoma. In the remaining two patients with abnormal supine plasma metanephrines one had equivocal CST (although the patient was on Imipramine, adrenal imaging was negative, and there was a low suspicion of pheochromocytoma) and the other had a normal CST, negative imaging, and pheochromocytoma was excluded. These preliminary results from 26 patients demonstrate that in the diagnosis of pheochromocytoma plasma metanephrines are an appropriate test in patients with elevated urinary metanephrines. If plasma metanephrine is normal then a CST is not required and pheochromocytoma can be excluded. For cases where supine plasma metanephrines are abnormal and diagnostic uncertainty remains then CST can be used.

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P019

Utility of Adrenal vein sampling (AVS) in the investigation of functional bilateral adrenal adenomas

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Adrenal vein sampling (AVS) is the gold standard for detecting aldosterone production in bilateral adrenal hyperplasia and for distinguishing the lateralization of aldosterone secretion. Successful AVS is determined by calculating the selectivity index (SI). The cut off value for the SI is ≥ 2.0 under un-stimulated conditions. The aldosterone level (AL) is corrected for cortisol level (CL) and adjusted values are then compared to determine the lateralizing index (LI). Most centres use LI between 2.0 and 4.0. LI ≥ 4 is compatible with a unilateral source of aldosterone. Contralateral gland suppression can also confirm the diagnosis. There is also an increase in the detection of synchronous excretion of aldosterone and cortisol from adrenal masses. AVS is not routinely used in the diagnostic workup of adrenal hypercortisolism. AV: IVC cortisol ratio and the gradient can be used to differentiate unilateral from bilateral cortisol overproduction. Young *et al*. suggested the cortisol gradient of AV to PV or IVC greater than 6.5. Predominant cortisol secretion was considered if the cortisol lateralization ratio was ≥ 2.3. We present a series of 10 cases with biochemically functional bilateral adenomas. Seven patients had successful cannulation and two had difficulty in cannulating right side, one result was equivocal. Five had hyperaldosteronism. Two had hypercortisolemia. One of these patients had synchronous excretion of aldosterone and cortisol. 8 patients had adrenalectomy. The histology showed discrete adenoma in five cases and hyperplasia in 3. 1 case with difficult cannulation of right adrenal vein had adrenalectomy, with removal of adrenal gland that had larger adenoma. All patients have been cured. Our analysis show AVS is a useful tool in expert hands to accurately diagnose and lateralise the hyperaldosteronism, hypercortisolemia and synchronous excretion of aldosterone and cortisol accompanied by bilateral adrenal masses. It can help to provide guidance to the treatment.

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P020

Addison's at high altitude – developing an evidence based patient information resource for Addison's patients who travel to high altitude

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Patients with Addison's or adrenal insufficiency require regular steroid replacement usually in the form of oral hydrocortisone. Standard advice is given on how to deal with intercurrent illness and special situations such as surgery. Organisations such as the Addison's disease self-help group provide authoritative guidelines for patients. Several of our patients with adrenal insufficiency have asked how their steroid replacement treatment should be adjusted for expeditions that take them up high mountains or to altitudes above 1500 m. We did not identify any pre-existing patient information resources about this situation and so we developed one.
Method
We reviewed the published literature on glucocorticoid and mineralocorticoid replacement at high altitude. We adapted the principles learned from this to make a simple and practical patient information guide. We used this to advise our patients on how to handle their steroid replacement while at altitude. We also asked them to provide us with feedback about their own experiences so that the resource can be improved by an iterative method.
Results
The key principles of steroid replacement at altitude are these

1. On the day of travel to altitude (>1500 m) switch to a double dose of hydrocortisone.
2. Remain on the higher dose for 48 hours to acclimatize and then go back to your normal dose.
3. If, during your travels, there is further significant (>400 m) increase in altitude then we recommend you go back to the double dose of hydrocortisone for another 48 hours.
4. The requirements for fludrocortisone do not increase at altitude.

The patient information resource on steroid replacement at altitude is currently being tested and improved by our patients, allowing them to minimise the risk of Addisonian crisis whilst they seek adventure at altitude.

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P021

Does a 60 minute sample in addition to a 30 minute sample for cortisol in the Short Synacthen Test alter patient management?

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Aim
The short Synacthen test (SST) is an established test used to assess the hypothalamic-pituitary-adrenal axis. There remains debate whether a 30 minute or 60 minute cortisol sample has diagnostic superiority. Currently at the Queen Elizabeth University Hospital, Glasgow all tests arranged by endocrinology are performed by endocrine nurse specialists who utilise a 0 and 30 minute cortisol protocol. Performing a further 60 minute sample requires more nursing time and space resulting in increased cost implications and so our aim was to assess whether performing an additional 60 minute cortisol sample would be worthwhile and alter clinical management.
Method
Patients attending for an SST in May 2018 by the endocrine nurse specialists had samples obtained at 0, 30 and 60 minutes. All patients had a standard protocol for the SST using intravenous Synacthen (250 μg). The current local cut-off value for cortisol at 30 minutes is 430 nmol/l.
Results
53 SST were performed during May 2018. 8 (15.1%) patients had an inadequate response to Synacthen based on their 30 minute sample. 3 (5.6% of overall group) of these patients had a further rise in their cortisol measurement which gave them an adequate response at 60 minutes ($>$ 430 nmol/l). Of those who had an inadequate response at 30 minutes, 2 were already on hydrocortisone replacement and 1 was undergoing pituitary surveillance; in no case did the 60 minute cortisol sample alter clinical management. No patient with a baseline cortisol $<$100 nmol/l had an adequate response to synacthen in this audit group.
Conclusions
Assessment of 30 and 60 minute cortisol after Synacthen resulted in discrepant results in only 3/51 cases and did not alter management. We conclude that 60 minute cortisol sampling results in additional resource burdens with no clinical gain.

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P022

A review of short synacthen test results: what is the cut-off?

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Background/aims
The short synacthen test (SST) is a dynamic function test used to assess the hypothalamic pituitary adrenal axis. Interpretation requires consideration of sample timing and cortisol method. Currently the 30 minutes post-synacthen cortisol (CORT30) at NHS Greater Glasgow and Clyde (NHS GGC) is $>$450 nmol/l measured on the Abbott Architect. A large reference range study published a cut-off of $>$430 nmol/l for this method. This audit aims to document clinical outcomes of patients with results in the range 430–450 nmol/l.
Method
SST requests were identified from laboratory databases at NHS GGC for six months beginning 01/05/2017. Requests with CORT30 430–450 nmol/l were selected for further analysis to include reason for request, steroid status prior to test and outcome/clinical management of the patient post test.
Results
Tests with CORT30 430–450 nmol/l accounted for 3.4% requests (53/1573). Request reasons were varied and included: steroids for another condition (26%), pituitary tumour/lesion (11%), blood pressure (11%), adrenalectomy (9%), hypoglycaemia (9%) and lethargy (6%). Outcomes for patients prescribed oral steroids initially ($n=18$) were: steroids continued 29%; reduced dose 17%; steroid cover for illness 17%; steroids stopped 17%; relapse of primary condition requiring steroids 22%. Outcomes for patients not initially prescribed steroids ($n=35$) were: no steroids 71%; steroids started 8%; steroids for illness 8%; steroids for illness but since started 6%; steroids started but stopped soon afterwards 6%. Repeat SST was performed in 13 patients within 6 months of borderline test, 62% were normal. A further 4 patients had a repeat SST planned but not yet performed.
Conclusion
SSTs with results 430–450 nmol/l account for 3.4% of all requests. Repeat testing was performed or planned in 32% of these cases. Findings were reviewed by the endocrinology team and the 430 nmol/l cut-off has been implemented.

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P023

Analysis of diagnosis and growth dynamics of adrenal incidentalomas in a large general hospital

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Introduction
Adrenal incidentalomas are masses discovered incidentally on imaging studies performed for possible pathologies other than suspected adrenal disease.
Aim
To characterise a cohort of adrenal incidentalomas found on CT.
Methods
This was a retrospective analysis, taking into account all the adrenal incidentalomas discovered on CT between July and December 2014 at the main hospital in Malta. The adrenal lesions were then classified according to these radiological features. CT scans done prior to and after the study period were also reviewed to establish any change in size of the lesions.
Results
Adrenal incidentalomas were identified in 296 patients, out of 9100 CT scans reviewed. Mean age was 66.9 years ($\pm$12.2s.d.). 97 (33%) adrenal lesions could not be classified. Of the remaining 199 incidentalomas, 156 (78%) were confirmed adenomas (Hounsfield units $<$10, relative or absolute washout values of $>$40% or 60% respectively), 28 (14%) were metastasis, 12 (6%) myelolipomas, 3 (2%) ganglioneuromas. In the adenoma group, 49.4% were males whereas in the metastasis group 71.4% were males. In the adenoma group, 57% had a left-sided lesion, 34% a right-sided lesion and 9% had bilateral lesions. In the metastasis group 61% had left sided lesions, 21% right sided and 18% bilateral lesions. Largest mean diameter was 20.0 mm ($\pm$7.4s.d.) in the adenoma group and 31.1 mm ($\pm$18.7s.d.) in the metastasis group ($P=0.033$). Median follow up in the adenoma group was 46.3 months (ICR 4.9–96.5) whereas in the metastasis group it was 28 months (ICR 0–28.5). Mean change in size was 0.3 mm (s.d. $\pm$2.0) in the adenoma as compared to 20.8 mm (s.d. $\pm$19.7) in the metastasis group ($P=0.0001$).
Conclusion
This study continues to confirm that adrenal adenomas are the commonest adrenal lesion encountered in clinical practice and the majority, remain stable in size over time.

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P024

Current management of adrenal incidentalomas- a United Kingdom single centre experience

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Background
Adrenal incidentalomas (AI) are asymptomatic adrenal lesions found on imaging not primarily performed to detect adrenal disease. We conducted a retrospective audit of management of AI following European Society of Endocrinology recommendation (2016).
Methods
This was a retrospective review of incidentaloma referrals over 9 months (June 2017–March 2018). Cases were identified using criterion search of the referral console. Additional data collected from clinic letters and investigation results.
Results
Sixty-three cases were identified. Fourteen were excluded (12 pending, 1 not incidentaloma, and 1 declined follow-up). From 49 remaining cases, 25 (51%) were females, with mean age of 63 years (range 33–90). The mean lesion size was 2.5 cm (range 0.8–6 cm) and 30 (61%) were characterised as adenoma on imaging. For Cushing's workup, 39 (80%) had overnight dexamethasone suppression testing (ODST), 5 (10%) 24 h urinary free cortisol, 1 (2%) low dose dexamethasone suppression testing (LDDST), 4 (8%) missing (1 lung metastasis, 1 deemed low risk, 2 unknown). 16 (33%) failed ODST (2 were deemed to be non-functional and remaining 14 underwent LDDST). LDDST revealed 3 (6%) normal, 4 (8%) adrenal Cushing's and 7 (14%) probable autonomous cortisol secretion. For Phaeochromocytoma workup, 44 (90%) had urine/plasma metanepharine levels checked, 5 (10%) missing (1 deemed low risk, 4 requested, but not carried out). 3 (6%) cases of Pheochromocytoma were

identified. For Conn's workup, 44 (90%) had plasma renin and aldosterone checked, 5 (10%) missing (3 deemed low risk, 1 sample lost, 1 lung metastasis). 1 (2%) case of Conn's adenoma identified. 8 (16%) have been referred for surgery (4 Cushing's, 3 Phaeochromocytoma and 1 metastatic disease).
Conclusion
The use of pre-clinic investigation protocol facilitated our adherence to the guideline. Incidence of functional tumours was similar to the literature justifying investigational approach. ODST demonstrated reasonable specificity of 69% minimising need for LDDST.

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P025

Secondary diabetes mellitus in patients with endogenous cushing's syndrome

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Introduction
Endogenous Cushing's syndrome (CS) is a rare disease associated with severe morbidity and increased mortality if untreated. Glucose metabolism is significantly altered in hypercortisolism.
Objective
To retrospectively analyse the clinical presentation of a cohort of patients with endogenous CS and study the frequency of glucose metabolism abnormalities as opposed to other clinical signs and symptoms.
Material and methods
We retrospectively analysed the clinical presentation of 68 cases diagnosed with endogenous Cushing's syndrome followed-up in our institution.
Results
There were 57 women, 11 men aged 18–74 years-old of which 38 had Cushing's disease (CD) and 30 had adrenal CS. Patients with CD were significantly younger (40.42 vs 52.1 years, P 0.000). The most frequent initial signs/symptoms were central obesity (55 cases, 80.88%), purple striae (28 cases, 41.1%), hirsutism in 23/55 women (41.81%), secondary arterial hypertension (27 cases, 39.7%), secondary diabetes mellitus (24 cases, 35.29%). Four cases (5.8%) had impaired glucose tolerance (IGT, defined as per current guidelines). 33% of cases had symptoms of hypogonadism and 25% complained of proximal myopathy. Despite the fact that hypercortisolism was equally severe in CS and CD patients, proximal myopathy, secondary hypertension and glycemic abnormalities were more frequent in cases with adrenal CS compared to those with CD. ($P=0.011$, 0.006 and 0.024, respectively).
Conclusions
Secondary diabetes mellitus is present in a significant percentage of CS patients at the time of diagnosis. Although it is not recommended to screen all patients with DM for hypercortisolism, the coexistence of other clinical symptoms and signs (both nonspecific (central obesity, edema, arterial hypertension) and more suggestive of the disease (purple striae, proximal myopathy)) in a patient with recent-onset diabetes mellitus should prompt a thorough investigation for CS (whose warly diagnosis will lead to significant decrease in morbidity and mortality).

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P026

Evaluation of glucocorticoid secretion in an adrenal incidentaloma cohort

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Background
Adrenal incidentalomas (AI) are being seen frequently in endocrine clinics due to increased cross-sectional imaging with a prevalence of 4% (7% in patients >70 years) of abdominal CT scans. The majority of these tumours are benign and non-functional, but identifying malignancy and functionality is important. Excess cortisol production is the commonest endocrinopathy associated with AI, with a reported prevalence of $\sim$10%. The overnight 1 mg dexamethasone suppression test (ONDST) is one of the recommended tests for assessing glucocorticoid.
Aim
To evaluate the prevalence of excess cortisol production in a cohort of AI patients referred to our hospital.
Methods
Patients referred to our endocrine clinic from July 2016 till May 2018. All patients underwent ONDST with cortisol suppression to <50 nmol/l considered normal. We also measured the diurnal serum and salivary cortisol/cortisone levels and serum dexamethasone levels, as a surrogate for dexamethasone absorption.
Results
Twenty-five patients, 16 women (64%), with a median age of 55.48 ± 7.99 years. 7 (28%) had hypertension, 7 (28%) had type 2 diabetes mellitus and 4 (16%) had both. A total of 16 (64%), failed to suppress to ONDST (cortisol ≥ 50). 15 (60%) had values of 51–130 nmol/l and 1 (4%) had a value >130 nmol/l. 4 (16%) patients had midnight salivary cortisol concentrations of ≥ 2.8 nmol/l. We are currently analysing the dexamethasone data and correlating them with the post dexamethasone cortisol data.
Conclusion
The prevalence of excess cortisol, based on the ONDST, is higher than previously reported. There is discordance between the results of the ONDST and the diurnal rhythm evaluation. The value of measuring dexamethasone levels in ONDST needs further evaluation.

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P027

Prevalence rate, characteristics and predictive factors of primary aldosteronism among hypertensive patients who had aldosterone-renin ratio screening in Southern Thailand: A retrospective, cross-sectional study

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Introduction
After the introduction of the Endocrine Society Guideline 2008, the disease recognition rate in Southern Thailand becomes dramatically noticeable. However, the prevalence rate of primary aldosteronism (PA) in this region is still unknown and aldosterone-renin ratio screening (ARR) is not widely available.
Objective
i) to identify the prevalence rate of PA among patients who had ARR screening, ii) to identify predictive factors for the PA diagnosis
Materials and methods
All patients who underwent the aldosterone-renin ratio (ARR) test, during January 2011 to December 2016 were selected from the electronic database. Eligible cases were including the patients aged over 15 years old who had both of plasma aldosterone concentration and plasma renin activity.
Results
Total 420 cases were enrolled. The overall prevalence rate is 16.7%. The predictive factors are age <60 years old (OR 4.77, 95% CI: 2.12–10.75), BMI <25 kg/m^2 (OR 1.97, 95% CI: 1.03–3.77), DM (OR 0.25, 95% CI: 0.09–0.74), anti-hypertensive agents >3 (OR 5.21, 95%CI: 2.56–10.62), serum sodium ≥ 141 mmol/l (OR 3.55, 95%CI: 1.68–7.50), and serum potassium <3.5 mmol/l (OR 9.15, 95%CI: 4.75–17.61). The predictive scoring system is generated by their coefficients which the AUC of the ROC curve is 0.865. A total score of >4 has the most acceptable negative predictive value (sensitivity, 0.971; specificity, 0.483; NPV, 0.988; PPV, 0.273, test prevalence 59.29%).
Conclusion
The prevalence rate of PA in the clinical practice was established. The predicting factors for PA were identified and the total score of less than 4 from the predictive scoring system indicated that ARR screening was not required.

Item	Points
Age 30–60 years	+3
BMI <25 kg/m^2	+1
DM	−2
Anti-HTN ≥ 3	+3
$Na^+ \geq 141$ mmol/L	+2
$K^+ < 3.5$ mmol/L	+4

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P028

How useful is 24 hour Urinary Free Cortisol as a screening tool for Cushing's syndrome?

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Introduction
Cushing's syndrome (CS) is a rare disease that can be difficult to diagnose. 24 hour urinary free cortisol (UFC) is one of the reliable screening tests to diagnose CS. The Endocrine Society recommends against widespread screening for CS. It advises to screen those patients presenting with multiple and progressive features (easy bruising, facial plethora, proximal myopathy and striae) of CS, in addition to patients who experience unusual features for their age (osteoporosis, hypertension).
Methods
A retrospective audit was done to assess our practice of requesting 24 hour UFC in patients attending Diabetes, Endocrine and Weight management clinics in Mid-Yorkshire Hospital over 3 years. 356 patients were eligible for final analysis.
Results
66.6% of the patients were females and 33.4% were men. The mean age in our cohort was 44.9 years and the mean BMI was 35.8 Kg/m^2. 61% of the patients had hypertension and 21.6% had diabetes. The reason for requesting 24 h UFC is as follows: 41% for secondary hypertension, 21% for obesity, 14% for adrenal incidentaloma, 5% for clinical suspicion of Cushing's, 19% for other reasons (hirsutism, uncontrolled diabetes, flushing). Thirty one patients (8.7%) had clinical features of Cushing's syndrome. Among those with Cushingoid features, seven patients (22.5%) had raised 24 hour UFC and four patients (12.9%) were finally diagnosed with CS. 325 patients had 24 h UFC test requested despite lacking clinical features of Cushing's. Twenty nine patients (8.9%) had initial positive 24 h UFC. Only two patients (0.6%) were finally diagnosed with CS. These two patients had the test because of adrenal incidentaloma.
Conclusion
We did not find any benefit of requesting 24 h UFC in those who did not have classic Cushingoid features. This audit confirms that it we need to adhere to the Endocrine society guidelines on investigations for CS.

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P029

Management outcome of phaeochromocytoma over 10 years (2008–2018) in a Tertiary Centre, UK

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Introduction
Pheochromocytomas (adrenal and extra- adrenal/Paragangliomas) are rare catecholamine producing tumors and required complex dedicated MDTintervention. We preliminarily reported our service in a tertiary referral centre over 10 years (2008–2018).
Method
A retrospectively review of confirmed phaeochromocytoma were carried out by reviewing clinical correspondences and ICE investigation-result system (laboratory, radiology and histology.)
Results
Phaeochromocytoma was confirmed in 51 cases (30 female −59%) with mean age 54.5 years(range 20–85), 4(7.8%) metastasis, 4(7.8%) extra-adrenal phaeochromocytoma. At presentation, 21(41%) had hypertension, 20(39%) had paroxysmal symptoms. 34 (67%) presented as incidentaloma in which only 14 (41%) were truly asymptomatic but 9(26%) hypertension, 7(21%) paroxysmal symptoms, 4(12%) both symptoms and 4(12%) had phenotype of phaeochromocytoma syndromes. In term of treatment, 94% received alpha-blocker, remainder 6% where diagnosis was made histologically at post-op period (4% non-secretary at pre-op assessment). 46(90%) underwent surgery, 1(2%) move away before surgery, 4(8%) were unfit for surgery and managed conservatively. There was no mortality at immediate post op for those who underwent surgery. 43 (84%) is currently cured (normal urine/plasma metanephrine on last measurement), 2 (4%) patients awaiting follow up. 4 (8%) patients have died at the time of review (1 died from unrelated condition, 2 was treated conservatively and 1 had rapid progressive metastasis post surgery.)
Discussion
Number of Phaeochromocytoma referral to our centre has increased recently due to increased referral from other endocrine centres and increasing incident of adrenal incidentaloma. In the later cases, being major presenting feature in our series, most symptoms were missed, and diagnosis was delayed until their presentation as incidentaloma. It highlights the diagnosis challenges. No peri-operative mortality suggested our cohort have received optimal pre, during and post-op cares. Further review is underway for detail of morbidity, histology and genetic testing.

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P030

Analysing management and follow up of adrenal incidentalomas

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Objective
Based on recommendations from the Clinical Practice Guidelines committee group on management of adrenal incidentalomas our project aims to review whether patients found to have adrenal incidentalomas were managed as per recommendations of the committee as follows: If they had a 1 mg overnight dexamethasone suppression test,were they tested for phaeochromocytoma, whether the investigations were used judiciously keeping in view patients co-morbid state, were any of the endocrine tests repeated (as guidelines suggest against repeating) and what was the outcome. We also looked if patients had repeat imaging when guidelines recommend against further imaging for follow-up when adrenal mass is less than four cm with clear benign features on imaging.
Design
Retrospective analysis of patient's electronic notes found to have adrenal incidentalomas in 2014–2015. ($n=24$). Standards included measurement of biochemical parameters (potassium, renin/aldosterone ratio, 24 hour urinary catecholamines, ONDST) assessment of radiological features and whether interval scanning took place.
Results
Total of 24 eletronic notes and imaging reports were reviewed. One patient declined further investigations and three patients were not referred to endocrine clinic. Biochemical measurements were performed as follows:
Overnight dexamethasone suppression test: 25%
24 hour Urinary cortisol: 12.50%
Renin/aldosterone ratio: 70.80%
Urinary catecholamines: 58.33%
66.67 percent of cases had follow up interval scanning (16/24). Out of the 16 who had repeated scanning 13 had size less than 4 cm.Of the 24 cases, one phaeochromocytoma and two possible conns were identified.
Conclusions
This highlights need to develop a pathway for appropriate initial investigation in patients diagnosed with adrenal incidentaloma and ensure investigations are justified. Also need to reduce request for repeat scans in patients found to have incidentalomas that are under 4 cm in diameter and are radiologically benign. There is room to improve the comprehensive investigation of such cases in our practice.

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P031

Audit of Short synacthen test at East Sussex Healthcare NHS trust since introducing new Roche cortisol assay: Diabetes and Endocrinology dept., Biochemistry dept., East Sussex Healthcare NHS trust

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Back ground
Our Cortisol assay was changed from older generation assay to new second-generation Roche cortisol assay for the Short synacthen tests. There is ~ 20–25% difference in cortisol values between these assays. There are debates about the cut off values for normal response (cortisol of 420 or 440 nmols), compared to 550 nmols/l with older assay. And to assess the use of 30 and 60 min cortisol response.

Methods
Short synacthen tests data were collected from hospital database. 114 short synacthen tests were performed in our hospital between August 2016 to July 2017.
Results
Out of the 114 patients, 63(55%) were females and 51(45%) were males. Age range varied from 1 to 89 years. If 440 nmols/l is used as normal response, 19/114 patients failed to reach this level at 30 min sample, but 3/19 reached the 440 nmols at 60 mins. 16/114 patient's results were in the inadequate response range. Three patients who, did not reach the target at 30 min but reached target at 60min, were on some form of steroid treatment. (2 were on long term steroids, and one patient has had depo steroid injection). If 420 nmols/l is used as normal response, 17/114 failed to reach this level at 30 min, 2/17 of these patients reached 420 nmol level at 60 min. one patient was on long term steroids, another had steroid injection. One patients who has been confirmed to have Addison's disease with positive adrenal antibody, would have been missed if the 420 nmol/l is used as the normal response.
Discussion and conclusion
We recommend using 440 nmols/l as normal response for SST. Also changed protocol to use only 30 min response. We are hoping to increase the capacity to do more tests, by reducing the cost of these tests by 33% and reducing the Endocrine nurses time by 50%.

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P032

Glucocorticoid activation by 11β-HSD1 is increased in M1, but not M2 polarised macrophages, where it determines pro-inflammatory cytokine expression

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In chronic inflammatory disease, an increased proportion of M1 polarised macrophages have been shown to contribute to inflammation and tissue damage through the production of pro-inflammatory cytokines such as TNFα. Previously, we have identified expression of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts inactive glucocorticoids (GCs) to their active counterparts, in M1 polarised macrophages in vivo. We hypothesised that 11β-HSD1 plays an important role in regulating M1 macrophage polarisation and function. Primary human monocytes were isolated from blood using CD14 positive-selection, and their purity assessed by FACS. Monocytes were differentiated into M1- or M2-polarised macrophages using GM-CSF or M-CSF respectively (both 50 ng/ml) before being stimulated with IFNγ (50 ng/ml) and LPS (10 ng/ml) for activated M1 or IL-4 (20 ng/ml) for activated M2. Macrophage polarisation and inflammatory gene expression were assessed by RT-PCR and steroid metabolism determined by thin layer scanning chromatography. TNFα secretion was assessed using ELISA. The macrophage marker CD68 was highly expressed in all macrophage cultures, whilst the M1 marker FcγRIB was greatly increased in M1 polarised macrophages following stimulation with IFNγ and LPS. Significant levels of GC activation by 11β-HSD1 were detected in M1 polarised cultures but were significantly lower in M2 counterparts (M1 polarised: 5.73 ± 2.6 pmol/mg per hr vs M2 polarised: 1.35 ± 0.75 pmol/mg per hr, $P \leq 0.01$). Pro-inflammatory gene expression of IL-6 and TNFα were greatly increased in M1 polarised macrophages, where they were potently suppressed following incubation with the endogenous glucocorticoid cortisol (100 nmol/l). Similar suppression of TNFα was observed using ELISA in M1 macrophages (M1 stimulated; 337.6 ± 190.5 pg/ml vs M1 stimulated/cortisol; 88.6 ± 123.01 pg/ml, $P \leq 0.01$). These findings emphasise differences in 11β-HSD1 expression between different macrophage subtypes and highlight a possible role for this enzyme in regulating inflammatory macrophage polarisation and function in chronic inflammatory disease.

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P033

Prolonged exposur to methylprednisolone disrupt the rat adrenal gland steroidogenic pathway and affect intra-adrenal inflammatory mediators

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Pharmacological treatment with synthetic glucocorticoids, which are widely prescribed for the treatment of numerous inflammatory and autoimmune diseases, can also affect the way the adrenal gland produces cortisol. Indeed, patients undergoing synthetic glucocorticoid treatment can develop adrenal insufficiency. This condition is characterised by reduced responsiveness of the adrenal to ACTH stimulation, and adrenal crisis/shock can occur in response to acute physiological stress (e.g. surgical or inflammatory stress). Here we have investigated the effects of prolonged treatment with the synthetic glucocorticoid methylprednisolone on HPA axis dynamics and on the adrenal steroidogenic pathway. We have found that 5 days of treatment with methylprednisolone not only suppresses basal ACTH and corticosterone secretion, as well as corticosterone secretion in response to a high dose of ACTH, but also down-regulates key genes in the adrenal steroidogenic pathway, including StAR, MRAP, CYP11A1 and CYP11B1. Importantly, 5 days after withdrawal of the treatment, ACTH levels are restored, yet basal levels of corticosterone, as well as some key steroidogenic genes, including StAR and HSL, remain down regulated. In addition to affecting the steroidogenic pathway, prolonged exposure with methylprednisolone also increases the expression of pro-inflammatory cytokines and their receptors. Our data suggest that the steroidogenic pathway is directly affected by synthetic glucocorticoid treatment in the long-term, presumably via a mechanism involving activation of the glucocorticoid receptor. Our data also suggest that prolonged treatment with syntetic glucocorticids increases adrenal responsiveness to inflammatory stress.

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P034

Cigarette smoke extract and cotinine, but not nicotine, alter the steroidogenic capacity of adrenocortical cells

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Introduction
The highly active human fetal adrenal gland plays a critical role in long term health. Maternal cigarette smoking alters post-natal health of the fetus and the mechanisms involved may include the fetal adrenal. However, understanding of human fetal adrenal development is limited.
Aim
To examine the effects of nicotine, its metabolite cotinine, and cigarette smoke extract on H295R adrenocortical cell line steroidogenic capacity.
Methods
H295R cells were cultured for 5 days in the presence of cotinine, nicotine, or cigarette smoke extract, and stimulated with forskolin. Steroids and mRNA transcript levels were measured by ELISA, LC/MS and qPCR.
Results
Cell proliferation was not affected by cotinine or nicotine exposure but was reduced by cigarette smoke extract exposure in a dose dependent manner ($P < 0.01$). Levels of *CYP11A1*, *CYP17A1*, *CYP21A2*, *HSD3B*, *PGR* and *ESR2* transcripts were all significantly reduced in cigarette smoke extract exposed cells. The effects of cigarette smoke extract exposure on steroid production was variable. Dehydroepiandrosterone sulphate (DHEAS), 11-deoxycortisol and cortisol were all significantly reduced in cells exposed to cigarette smoke extract, whereas 17α-hydroxyprogesterone was significantly higher on day 3 and lower on day 5 of culture, compared to controls. Nicotine alone was not associated with any differences in steroid production or enzyme expression but its metabolite, cotinine, significantly increased levels of *CYP11A1* ($P < 0.01$), *CYP17A1* ($P < 0.01$), *SULT2A1* ($P < 0.01$), and *ESR2* ($P = 0.03$) at concentrations equivalent to those found in human breastmilk. Cortisol levels, in contrast, were significantly reduced in cells exposed to the same concentration of cotinine.
Conclusions
Cell proliferation, transcript expression, and steroid production are altered in a fetal adrenocortical cell model by exposure to cigarette smoke. Nicotine alone however has a lesser effect on these cells than its major, bioactive, metabolite cotinine. These results suggest that maternal cigarette smoking may directly affect human fetal adrenal development.

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P035

Peripheral glucocorticoid metabolism selectively modulates innate immune receptor RIG-I

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Retinoic-acid-inducible gene I (RIG-I) is a cytosolic receptor that sense RNA viruses, such as influenza, producing proinflammatory cytokines and type 1 interferons. In severe influenza infection, inappropriate immune response can allow influenza virus to proliferate, triggering hypercytokinemia that leads to tissue damage and potentially death of the host. Glucocorticoid hormones (GC) are clinically used to suppress hypercytokinemia. However, the use of GC is controversial during influenza infection and peripheral GC metabolism remains largely unknown. In peripheral tissues, GC action is controlled by pre-receptor GC metabolizing enzyme 11beta-hydroxysteroid dehydrogenase (11b-HSD). 11b-HSD1 predominantly converts inactive GC to active form within cells. Recent work has shown that 11b-HSD1 modulates immune and inflammatory response. Therefore, the aim of this study was to evaluate how peripheral GC metabolism affects RIG-I signaling during influenza infection.

Methods

5'-Triphosphate modified RNA (3pRNA), the ligand for RIG-I, was transfected by lipofection in human lung A549 and HELF cells. Cells were cultured for 24 h in the presence or absence of 1 μM glucocorticoids (cortisone/cortisol) following 3pRNA treatment. The glucocorticoid receptor (GR) antagonist, RU486 added 30 min before GC. siRNA was transfected 48 h before 3pRNA treatment. Genes were measured by RT-qPCR.

Results

3pRNA increased RIG-I downstream genes IFNb and IL6 mRNA levels, which were decreased by cortisol treatment. 11b-HSD1 was also increased by 3pRNA treatment and further increased by cortisol treatment. Accordingly, cortisone decreased IFNb and IL6 mRNA levels, although GILZ was not induced by cortisone treatment. 11b-HSD1 siRNA cancelled cortisone effects. Glucocorticoid receptor (GR) antagonist RU486 abolished GC reduction of IFNb and IL6 mRNA levels. Interestingly RU486 itself increased IFNb mRNA, indicating that GR can affect RIG-I signaling without exogenous GC.

Conclusion

Peripheral GC metabolism could selectively modulate RIG-I signaling during influenza infection. Further studies may address the mechanism of hypercytokinemia due to influenza infection.

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P036

Modelling glucocorticoid-induced HPA axis suppression in mice

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Background

Glucocorticoids are prescribed for >3 months to 1% of the UK population, principally to control inflammation. In 10–30% of patients, chronic glucocorticoid treatment suppresses HPA axis activity, causing atrophy of the adrenals and a failure to mount an adequate response during stress (potentially fatal) and following treatment withdrawal. Understanding the mechanisms resulting in HPA axis failure may allow us to predict those at risk, inform treatment strategies and reduce the potential risks of adrenal insufficiency. To explore these mechanisms, we have developed a mouse model of GC-induced HPA axis dysfunction.

Methods

36 C57Bl6 12-week-old male mice were randomly assigned to receive Dexamethasone (DEX) (10 μg/day) or vehicle (CTL) via drinking water for four weeks. At 4 weeks (time 0) both groups received only water. Tissues were harvested at 0, 1 and 4 weeks following withdrawal of treatment. Serum 11-Deoxycorticosterone and Corticosterone were measured by LCMS/MS. Hypothalamus, pituitary and adrenal gene expression was assessed by qPCR.

Results

Dexamethasone treatment inhibited growth (weight at week 0, CTL:27.7 ± 0.8 g DEX:23.0 ± 0.9 g $P<0.001$) and resulted in adrenal atrophy at 4 weeks (CTL:5.8 ± 0.5 DEX:4.6 ± 0.1 mg). DEX treatment suppressed serum 11-Deoxycorticosterone (CTL:1.1 ± 0.2 nM DEX:0.1 ± 0.01 nM $P<0.001$) and Corticosterone (CTL: 58.6 ± 21.5 nM 2.9 ± 1.8 nM $P<0.001$) at week 0, which recovered by week 1. DEX treatment had no effect on *Pomc, Nr3c1 or Crhr1* expression in whole pituitary, or on *Avp* or *Crh* expression in hypothalamus. In the adrenal, at time 0, *Hsd3b2* and *Cyp11a1* expression was reduced and *Nr3c1* was increased; these returned to control level by 4 weeks.

Conclusion

Four weeks dexamethasone treatment in mice results in HPA axis dysfunction and adrenal atrophy which recovers 1 week following treatment withdrawal. Dysregulation occurs mainly at the level of the adrenal glands.

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P037

Time-dependent cortisol turnover in tissues using stable isotope tracers and MALDI Mass Spectrometry (MS) sampling

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Excess action of glucocorticoid hormones is implicated in metabolic disease and cognitive decline, 11β-hydroxysteroid dehydrogenase 1 (11βHSD1) catalysing generation of active glucocorticoid hormones in tissues. The penetration rates and tissue-specific contribution of 11βHSD1 to glucocorticoid turnover were assessed using tracer kinetics. 9,11,12,12-d4-Cortisol (d4F) was infused (1.75 mg/day, 7 days) into C57Bl6/J male mice and mice lacking 11βHSD1 ($n=3$/group). Regeneration of d3F by 11βHSD1-mediated reduction was assessed in plasma by LC-MS/MS and in tissues using matrix assisted laser desorption ionisation (MALDI) MS. Mean ± SEM. Circulating concentrations of d4F were 936 ± 45 nM at 24 h, reducing to 566 ± 63 nM at 48 h, and remaining steady until 7days, suggesting an initial stimulation of clearance (or changes in infusion rate). This pattern was mirrored in liver; d4F was detected at 6 h, increasing to 24 h and then plateaued at a lower level (~75% of 24 h) by 48 h. d4F was detectable in brain by 6 h, reaching steady state by 24 h, 3.5 fold lower than liver. Tracer was not detected in adipose until 24 h, remaining steady (4 fold lower than liver) until 7 days. D3F was detected in plasma, liver and brain at 6 h, but only after 48 h in adipose. Again in plasma and liver the amounts of d3F peaked at 24 h and declined to steady state at 48 h. D3F abundance in adipose and brain did not change from 24 h to 7days. Regeneration of d3F was abolished in mice lacking 11βHSD1, without changing circulating or tissue levels of d4F. Glucocorticoid regeneration of d3F is mediated solely by 11βHSD1 and circulating levels largely mirror hepatic production. Less glucocorticoid is regenerated in brain and adipose and levels are less dependent of the circulating pool, demonstrating the important contribution of the local enzyme and the importance of targeting therapies to specific tissues, such as brain.

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P038

QRT-PCR analysis of the effect of in utero exposure to sewage sludge on steroidogenic gene expression in ovine foetal adrenal gland

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Endocrine disruptors are chemicals which in low concentrations can disturb gene expression in a range of endocrine glands and organs including the fetal and adult adrenal glands, potentially resulting in altered steroidogenic flux. With exposure to endocrine disruptors affecting both animals and humans, it is important to assess both the mechanisms and consequences of disruption in steroidogenic pathways, particularly as foetal development may be especially sensitive to endocrine disruption. Indeed, disruption of foetal development could affect key foetal functions such as organ maturation and the onset of parturition. Sewage sludge, a biosolid by-product of soil water purification, is commonly used as a fertiliser on livestock pasture and has been shown to have endocrine disrupting effects in multiple organs, including the foetal adrenal gland. However, it is not yet known exactly where in the steroidogenic pathway disruption might occur. The purpose of the present study was to compare the effects on fetal steroidogenic gene expression in experimental groups of sheep maintained before and after fetal conception on pasture exposed to sewage sludge or to an organic fertiliser. Expression of candidate 'rate determining' steroidogenic genes selected following review of the literature was determined in sewage sludge-exposed E110 ovine fetal adrenal glands by QRT-PCR and compared to organic fertiliser

controls. This suggests that flux through the glucocorticoid synthetic pathway may be enhanced during late fetal development, while interconversion of active cortisol and in active cortisone may be suppressed.

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Bone and Calcium

P039

Management of hypoparathyroidism against European guidelines: Experience of a large teaching hospital

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Background
Hypoparathyroidism is a rare endocrine disorder characterised by low serum calcium with inappropriately low parathyroid hormone (PTH) levels. Calcium and vitamin D analogues have traditionally been the mainstay of treatment. However, these treatments may cause complications and may not fully address the well-being of this patient group. This study evaluates the current management of hypoparathyroidism in a large UK teaching hospital compared against current European guidelines.
Methods
We identified 164 patients with hypoparathyroidism seen in our Trust between 2012 and 2017. A standardised data proforma was produced, and information gathered to compare management against European Society of Endocrinology guidelines (2015).
Results
The majority of patients had post-surgical hypoparathyroidism. Only 54% had documentation of symptoms at their most recent clinic visit, of these half remained symptomatic. Only 54% of patients had a recent adjusted serum calcium within the recommended range of 2.1–2.3 mmol/l. 81% had a normal serum phosphate. Calcium-phosphate product had not been formally calculated in any patients. 27% of patients had serum magnesium checked within the last 12 months, of which 69% were normal. 145 patients were taking vitamin D analogues, 17% of these were on calcitriol, 83% patients were on alfacalcidol. 11% of patients were on thiazide diuretics and 23% patients were taking phosphate binders. 31% of the cohort had 24 hr urine calcium measurements in the last 24 months, of which 25% showed elevated levels. 16% of patients had an ophthalmic examination. 49% had a renal ultrasound scan performed, of these 24% showed renal calculi or nephrocalcinosis.
Conclusion
In this large cohort of patients adherence to European guidelines for the management of hypoparathyroidism was poor, with evidence of inadequate metabolic control and monitoring. The recent implementation of local guidelines and specialised parathyroid clinics should improve future outcomes for these patients.

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P040

Symptom documentation in patients with primary hyperparathyroidism before and after the introduction of a symptom scoring questionnaire

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Background
Symptoms consistent with hypercalcaemia are an indication for surgery in patients with primary hyperparathyroidism (PHPT). However, symptoms can be subtle and may not be documented systematically. We analysed the documentation of symptoms in a large series of patients with PHPT, and the subsequent impact of introducing a symptom scoring questionnaire.
Methods
A standardised proforma was used to retrospectively analyse symptom documentation by clinicians for 339 new patients with PHPT between 2012 and 2017. We then prospectively collected self-rated symptom data for patients with PHPT using the validated Pasieka symptom questionnaire.
Results
Of 339 patients, 46% were documented as symptomatic at their initial visit. 35% had documentation about all symptom groups, but 17% had no documentation of any symptoms. In terms of symptoms by individual group, the following table demonstrates documentation pre-surgery:

Symptom Group	%Symptomatic	%Asymptomatic	%Undocumented
Gastrointestinal	24	46	30
Genitourinary	26	42	32
Musculoskeletal	27	37	36
Neurocognitive	13	35	52
Fatigue	33	32	35

For patients referred for surgery solely based on symptoms, 19% had documentation of all symptom groups, 81% had partial documentation. Post-surgery only 27% of 131 patients had documentation about all symptom groups. The Pasieka questionnaire has a threshold value of 200 (out of 1600) for a patient to be considered 'symptomatic'. After introduction of this patient self-rated tool ($n=68$) we found a mean pre-surgery symptom score of 529 (range 0–1165), with 77% of patients scoring over the 'symptomatic' threshold.
Conclusion
This single-centre analysis in a large cohort of patients with PHPT, confirms poor symptom documentation by clinicians, particularly for neurocognitive symptoms, both pre and post-surgery. The use of a specific, symptom self-rating questionnaire captures a greater proportion of symptomatic patients than by clinician documentation alone. This suggests widespread implementation of such questionnaires may help to identify more patients who would benefit from surgery.

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P041

Management of osteogenesis imperfecta in adulthood – a single centre experience

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Introduction
Osteogenesis imperfecta (OI) is a genetic, heterogeneous, connective tissue disorder most commonly caused by mutations in type I collagen genes. A hallmark of disease is frequent fractures that are precipitated by minimal trauma. There are limited data on the impact of OI on non-skeletal outcomes across the lifecourse. We present cross-sectional data of one of the largest single centre patient cohorts of OI in adulthood ($n=186$).The aim of this study was to review the current clinical practice for management and outcomes of OI in adults to inform development of prospective registries and specialist services.
Methods
Patients were identified by a health informatics search and data were collected retrospectively by reviewing patient electronic health records.
Results
One hundred and eighty-six patients with OI (56% female and 44% male) were seen in metabolic bone clinic. Median follow up was 4.7 years. OI was classified as type 1 ($n=63$), type 3 ($n=20$), type 4 ($n=11$), type 5 ($n=1$) and overlap ($n=15$). 76 cases were unclassified. 40 patients had genetic confirmation of diagnosis. The majority of fractures involved long bones. Amongst the treatment options, bisphosphonates were the first line treatment used. 57 (31%) patients had diagnosis of dentinogenesis imperfecta. The phenotype in 29 patients overlapped other connective tissue diseases (Marfan's, Ehler-Danlos and hypermobility) and further molecular testing may help to resolve diagnostic uncertainties. 49 patients had documented evidence of hearing impairment.125 (67%) were functionally independent. There were 7 reported cardio-respiratory diagnoses (valvular and ischaemic heart disease). There were 6 deaths in the cohort.
Conclusions
OI is associated with a number of non-skeletal co-morbidities. We are using this analysis to further develop our collaborative multi-disciplinary service. Prospective evaluation is vital to determine frequency and severity of these conditions, impact on patient quality of life and to inform best practice with regards to surveillance and management.

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P042

Vitamin D status is associated with physical function, frailty and mortality in older patients admitted with acute illness

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Introduction
Vitamin D deficiency has been implicated in adverse health outcomes related to immunity, metabolism and physical function. Comprehensive assessments are required to characterise vitamin D status and relationships with physical function and frailty markers in the acutely unwell.
Aims
To assess vitamin D and related parameters for patients admitted acutely to hospital who have been tested and to assess the relationship with muscle function and general health outcomes. This analysis will inform development of a prospective study of the impact of vitamin D status on outcomes in acute illness relating to clinical course and rehabilitation.
Methods
1332 patients aged over 65 admitted to acute medicine between 1/6/2017-1/6/2018 were identified by health informatics. Data were collected on physical function and frailty markers in addition to clinical diagnosis, management and outcomes. A sub-study was formed of 766 patients where vitamin D status was assessed.
Results
739 were female and 539 male. Median serum 25OH-vitamin D was 31 nmol/L (IQR:14-58). Patients in the lowest quartile for vitamin D had significantly longer length of stay compared to those in the highest quartile (median 34 days, IQR 21–56 vs. 10 days, IQR 4–18, $P<0.05$), lower abbreviated mental test scores (AMT10) (5/10, IQR 3–6 vs 8/10, IQR 5–9 $P<0.05$), higher Waterlow scores (19, IQR 14–22 vs. 13, IQR 13–17) and a trend towards higher falls scores (2, IQR 1–3 vs 1, IQR 0–3) and lower Manchester mobility scores (5, IQR 2–6 vs 6, IQR 5–6). 32% of patients died in the lowest vitamin D quartile vs. 14% in the highest quartile.
Conclusions
Vitamin D status is closely associated with measures of physical function and frailty in acutely unwell older patients. Prospective supplementation studies in this patient group are required to establish causality, investigate mechanisms assess impact on rehabilitation potential and clinical outcomes

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P043

Conventional treatment of chronic hypoparathyroidism results in suboptimal calcium homeostasis

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Background
Conventional treatment for chronic hypoparathyroidism (CHP) is Vitamin-D analogues and calcium supplementation, not replacement of lacking hormone, as done in other hormone-deficiency states.
Objectives
Retrospective evaluation of CHP management in line with European Society of Endocrinology Guideline was undertaken, to assess adequacy of calcium-homeostasis and morbidity.
Methodology
Retrospective case-note and electronic-record review of 93 consecutive CHP cases (Post-surgical-56, Genetic-15, Autoimmune-6, Unknown-16), minimum 12 months follow-up between 1989 and 2017, was undertaken; audit No 9217.
Results
$n=93$ (67-females, 26-males), mean age 53 years (17-94yrs), mean duration of follow-up 13.5 years (1.2-29 years). 94%(87/93) treated with Vitamin-D analogues (86% alfacalcidiol, 8% calcitriol) with or without calcium-salts and 6%(6/93) calcium salts only. At follow-up, target range achieved: serum adjusted calcium 58% (54/93) (2.10 – 2.40 mmol/L); 24-hr urinary calcium 63% (17/27 performed) (2.5–7.5 mmol/L); serum phosphate 81% (75/93) (0.8–1.5 mmol/L); magnesium 92% (54/59 performed) (0.7–1 mmol/L) and vitamin-D 54% (43/79 performed) (>50 nmol/L). Regular monitoring was not undertaken in 71% (66/93) for 24-hr urinary calcium, 37% (34/93) for magnesium and 15% (14/93) for vitamin-D. 365 hypocalcaemia episodes (Ca $<$ 2.0 mmol/L) in 62%(58/93); 56 hypercalcaemia episodes (Ca $>$2.60 mmol/L) in 18% (17/93) patients; 37% (34/93) required hospital admissions related to calcium-dysregulation resulting in 253 total inpatient days over 8 years (2010–2017). There was progression to CKD3 17% (16/93) and CKD4 2% (2/93); Renal stones 3; Nephrocalcinosis 1; Cataracts 4; unrelated death 5.
Discussion
1. Conventional CHP management resulted in suboptimal calcium homeostasis in half of patients; 1/3rd required hospital admissions for calcium regulation.
2. Suboptimal monitoring of 24-hr urine-calcium and magnesium was noted.
3. Regular biochemical monitoring and dose adjustments may improve outcomes.
4. Evidence seems to be growing for recombinant human parathyroid hormone (1-84) for challenging cases.

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P044

Prevalence and risk factors of low vitamin D in Kano, Northwestern Nigeria

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Introduction
The role of Vitamin D in bone formation and cardiovascular health could not be overemphasized. Sunlight is one of the principal sources of this vitamin/hormone. However, it's deficiency has been observed in sunlight affluent areas. The objective of the study was to determine the prevalence and risk factors of low vitamin D among adults in the tropics (Kano).
Methods
The study was a community-based cross-sectional descriptive study. The study population was adults 18 years and above that have consented. Five hundred participants were obtained using multistage sampling. A questionnaire was employed for data collection. The anthropometric measurements were determined. Vitamin D was assayed using ELISA technique.
Results
Females comprised 59.4% of the participants and 44.9 ± 12.7 years was the average age of the study subjects. Among the participants, 10.6% have Vitamin D insufficiency and deficiency occurred in 31.3%. The proportion of those with adequate vitamin D was 58.1%. The factors that were significantly associated with Hypovitaminosis D include female gender, Body mass index $\geq$25 kg/m2, increased waist circumference and high parity among females ($P<0.05$). On multiple logistic regression, female gender $P=0.01$ (95% C.I 0.337–0.884) was a determinant of Hypovitaminosis D.
Discussion
The findings show that low vitamin D levels are prevalent in the tropics where sunlight is adequate. Research has shown that staying in sunlight comfortable places does not prevent low vitamin D levels; other factors also play a role in determining the adequacy of the vitamin. These include age, skin pigmentation, diet, time and level of sun exposure e.t.c. Women in Kano tend to be at risk of low vitamin D levels because of cultural reasons which prevent them from staying outdoors or covering their body when outside.
Conclusion
The inhabitants of the tropics are at increased risk of low vitamin D in spite of the abundant sunshine.

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P045

Evaluation of effect of primary hyperparathyroidism and parathyroidectomy on blood pressure

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Primary hyperparathyroidism (PHPT) is one of the common endocrine conditions and is frequently associated with hypertension and increased cardiovascular mortality but this association is not well recognised. The purpose of this study was to evaluate the effect of parathyroidectomy on blood pressure. The data of 112 patients who attended our out patients clinic over the period of 12 months, with the confirmed diagnosis of primary hyperparathyroidism was evaluated. Average age was 69 years (range 30 to 89) with 88 female and 22 male patients. Out of 112 patients 66 (59%) had a diagnosis of essential hypertension and were treated with one or more anti hypertensive medications. Out of 66 patients with hypertension, 30 underwent parathyroidectomy, 17 are being monitored, 14 awaiting surgery, 2 not fit for surgery, 2 passed away and 1 declined. Out of 30 patients who underwent parathyroidectomy, mean systolic blood pressure of 20 patients improved from 154 to 132.5 mmHG (range 2 to 39) and mean diastolic blood pressure of 18 patients improved from 83 to 74 mmHg (range 1 to 23) after the surgery. Although it is a retrospective evaluation with a small study population and a randomised controlled study with a large study sample is required, definitive association of primary hyperparathyroidism with hypertension and a reduction in blood pressure following parathyroidectomy is demonstrated. So we recommend hypertension to be considered as one of the criteria to consider surgery for patients with primary hyperparathyroidism.

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P046

Role of Ultrasound Neck (US), sestamibi Scintigraphy and Multidisciplinary team (MDT) discussion prior to intervention in the localization of parathyroid lesion

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Background
Primary hyperparathyroidism is an endocrine disorder characterized by autonomous production of parathyroid hormone (PTH) results in the derangement of calcium metabolism. Imaging modalities used to localize includes technetium-99m sestamibi, sestamibi-single photon emission computed tomography (SPECT), SPECT-CT fusion, ultrasound Neck and Four dimensional computed tomography (4D-CT). Sestamibi scintigraphy combined with sestamibi single photon emission computed tomography (SPECT) has the highest positive predictive value among available imaging techniques. In our trust we do ultrasound scan (USS) neck prior to sestamibi scintigraphy as it is highly sensitive in experienced hands, inexpensive, non-invasive and reproducible in operating room. In addition to two imaging modalities there is dedicated parathyroid MDT prior to intervention.
Aims
This study aims to determine the role of Ultrasound Neck, sestamibi scintigraphy and Multidisciplinary team discussion in localization of parathyroid lesion.
Methods
A retrospective, quantitative study of patients that had been diagnosed with primary hyperparathyroidism was performed. All patients who had been diagnosed from April 2014 - April 2017 were evaluated; these patients were identified using the institutes' clinical coding. Data collected included patient demographics, diagnosis, types of imaging, histological diagnosis, post-operative calcium and parathyroid hormone levels, and whether recurrence occurred in any of these patients.
Results
A total of 71 patients met the inclusion criteria for the study. Analysis of results showed that 95.8% (68/71) patients received an ultrasound scan of the neck and 93% (66/71) received a SPECT-CT. Out of the 68 patients, 76% (54/71) were correctly diagnosed as having a parathyroid adenoma by USS and 80% (57/71) by SPECT-CT. All these patients were discussed in dedicated parathyroid multidisciplinary team meeting prior to intervention. Only 2 (3%) of the patients had a recurrence, although follow-up was still awaited for multiple patients.
Conclusion
US neck is non-invasive subjective dependent highly sensitive imaging modality with comparable results with Sestamibi Scintigraphy.

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P047

Clinical efficacy of cinacalcet in primary hyperparathyroidism in reducing calcium and admission avoidance

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Aim
Cinacalcet is a useful treatment option in primary hyperparathyroidism (PHPT) who are managed conservatively; however there are licensing issues and challenges for prescribing in primary care. The aim of our study was to assess the efficacy of cinacalcet treatment in PHPT and benefit of admission avoidance.
Methods
Data on patients treated with cinacalcet for PHPT were analysed. PTH, adjusted calcium and vitamin D at initiation, calcium at 6 and 12 months (if completed) and latest calcium were collected. Number of hospital admission for treatment of hypercalcaemia prior to (since 2012) and since cinacalcet initiation was collected.
Results
Of the 14 patients included in the study, 2 were men; Baseline parameters were (range in brackets): age 81.6 years (59–93), initial calcium 3.1 mmol/L (2.92–3.2), PTH 21.1 pmol/L (7.7–58.1), vitamin D 74 nmol/L (21.4–152.9, two patients were vitamin D deficient). Mean duration of treatment was 22 months (2–69). Latest calcium results were significantly better at 2.61 mmol/L (2.23–2.92, $P<0.0001$) with all patients showing an improvement from the initial calcium. Among patients who completed 6 months of treatment ($n=12$), calcium improved from 3.05 to 2.63 ($P<0.0001$), which was sustained at 12 months ($n=8$) with calcium improving from 3.02 to 2.52 $P<0.005$). Total number of hospital admissions for symptomatic hypercalcaemia (IV fluids or pamidronate infusion) reduced from 15 patient episodes (10 patients, mean 1.1 admission/patient, range 0–3) to 2 episodes (2 patients, mean 0.2 admission/patient, range 0–1), $P=0.001$. One patient developed biochemical hypocalcaemia during follow-up requiring dose alteration.
Conclusion
Our study demonstrates the immediate and sustained clinical efficacy of cinacalcet in PHPT. Cinacalcet can reduce the need for hospital/endocrine day case admissions for fluids and bisphosphonate infusions therefore providing a cost effective and safe treatment option for inoperable PHPT. Guidelines are required for continuation of this treatment in primary care.

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P048

Postoperative hypocalcaemia after thyroidectomy and parathyroidectomy: A streamlined cost effective treatment pathway

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Background
Transient hypocalcaemia post parathyroid or thyroidectomy is common. Locally, post operative follow up was Ad-hoc with weekly visits where one of the Endocrine team would reduce Adcal D3© or 1α-Hydroxycholecalciferol doses to maintain eucalcaemia. This was frustrating for staff and patients who spent weeks and sometimes months having weekly blood tests. In an effort to improve the experience we piloted a pathway based on fixed dose replacement and day 1 parathyroid hormone (PTH) and corrected calcium results.
Method
Day 1: PTH and corrected Calcium was checked and everyone was discharged on 1 × Adcal D3© bd and 1α-Hydroxycholecalciferol 0.25 mcg tds. Day 7: review day 1 results. Reference range results; thyroidectomy patients stop supplements and parathyroidectomy patients reduced to 1 × Adcal D3© bd and 1α-Hydroxycholecalciferol 0.25 mcg bd. Low PTH or corrected calcium; thyroidectomy patients reduced to 1 × Adcal D3© bd and 1α-Hydroxycholecalciferol 0.25 mcg bd while Parathyroidectomy stayed on day 1 dose. Post operative week 8 and month 6: Check PTH and calcium and if within reference range stop treatment and if below reference range continue.

Results
Ten patients (9 thyroidectomy and 1 parathyroidectomy) were seen. Five thyroidectomy patients had normal Day 1 results and stopped treatment after 7 days. The remaining four had reference range results at week 8 and stopped treatment then. The Parathyroidectomy patient reduced their dose week one, had reference range results week 8 and stopped treatment. No patient has developed hypocalcaemia after stopping treatment.
Conclusion
The pathway is simple to follow. All patients stopped supplements by week 8 and visits reduced from over eight to just two. Our next step is to use same day PTH results. This will remove the need for day seven review and further streamline the process and further reduce the burden to patents and staff.

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P049

Primary Hyperparathyroidism (PHPT) audit

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Introduction
This audit was undertaken to determine whether Primary Hyperparathyroidism (PHPT) management in the clinical setting is compliant with the nine standards set of the existing PHPT pathway in the City Hospital Sunderland Foundation Trust (CHSFT). PHPT pathway was developed in (CHSFT) to allow effective management and surgical referral for this common condition in line with available national and international guidelines.
Methods
Data was retrospectively collected for 34 patients diagnosed with PHPT last year. A questionnaire based on these pathway nine standards was designed
Audit results
The study showed 100% compliance with the first three standards. 88% compliance with standard four. 93% compliance with standard five. In 82% of cases, MIBI scan was done first and end organ damage was excluded. In 79% of cases, ultrasound scan of the neck was performed, based on the MIBI scan results. 26% patients had concordant images and referred to the ENT, another 26% with non-concordant images underwent CT scan following discussion in the MDT. Overall, 46% patients underwent parathyroid surgery successfully, 35% were commenced on Cinacalcet due to surgical non-suitability and 18% were on regular monitoring as per patient choice and suitability.
Discussion
Compliance with our PHPT pathway was extremely good.This illustrated the great value of following the pathway and indicated the good compliance with the guidelines.The study showed the importance of MDT approach and the liaison with the surgical team in order to achieve the desired outcome. Since developing the pathway, our approach to management of Primary hyperparathyroidism has been streamlined. Surgical colleagues appreciate the uniformity in approach by the Endocrine team.This has resulted in fewer unnecessary scans and a more cost-effective approach,without compromising on quality. Although patient cohort audited was small, no benign familial hypocalciuric hypercalcaemia cases were detected in this audit. This will be re-audited to ensure maintenance of the standards.

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P050

Prevalence of metabolic bone disorders in patients with bony stress injuries - implications for endocrine services

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Background
Bone stress injuries are typically overuse injuries associated with repetitive loading of bone and inadequate recovery. A continuum of bone stress injury from periosteal reaction to cortical fracture exists. Intrinsic and extrinsic recognised risk factors have been encapsulated within broader working consensus statements e.g. Relative Energy Deficiency in Sport (RED-S). There is uncertainty as to the appropriate metabolic work-up for such patients.
Objectives
To ascertain the prevalence of metabolic disorders and assess current management of patients with bony stress injuries referred to a secondary/tertiary care sports exercise medicine (SEM) service.
Methods
Retrospective analysis of patient records ($n=41$) attending between February 2016-December 2017. Patients with a working diagnosis stress injury and subsequent MRI confirmation were identified. Data analysis was performed in-line with the RED-S consensus paper.
Results
70.7% were female. The commonest associated sport was running (61%). Stress injuries were located in the tibia (51%), metatarsal (22%), femoral neck (10%) and pelvis (5%). Vitamin D results were normal in 37%. Concentrations ranged from <30 (22%) to >75 mmol/L (29.3%). One abnormal calcium concentration (high) and three abnormal TFTs were identified (subclinical hypothyroidism). 88% had blood tests, and 10% were referred for DXA scanning. 7% were referred to endocrinology.
Discussion
Most patients had no evidence of an underlying metabolic condition. We would advocate that patients are referred to SEM for initial assessment. Patients with endocrine abnormalities can then be discussed/referred to endocrinology.
Conclusion
Through collaboration between SEM and endocrinology we have utilised the analysis to develop a trust-wide clinical pathway. This demonstrates the utility of SEM within the NHS whilst ensuring that endocrine services referrals are used where there is a true clinical benefit. Implementation of this will enable prospective data collection across specialties to ensure compliance with best evidence - thus improving healthcare resource utilisation and morbidity.

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P051

***Chromolaena odorata* and *Tithonia diversifolia* synergistically stimulate kidney erythropoietin and repress cyclin-dependent kinase inhibitors in the bone marrow of Wistar rats**

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Aim
Chromolaena odorata and *Tithonia diversifolia* have been combined as folkloric treatment for pediatric anemia. However, the underlying molecular mechanism of this pharmacology has not been established. This study sought to establish the effects of these plants on erythropoietin (kidney), and erythropoietin receptor (bone marrow) expression and to monitor cyclin-dependent kinase inhibitors, and FasL/FAS signaling mechanism therefrom.
Materials and methods
Cold-water extracts of fresh leaves of *Chromolaena odorata* and *Tithonia diversifolia* were administered individually and in combination on young Wistar rats for 72 hr followed by RT-PCR analysis of erythropoietin (Epo), erythropoietin receptor (Epo-R), kip1.p27 (p27/cdkn1b), p21Waf1, Kip2-p57 and FAS/FASL. Western blot was used to investigate JAK2 phosphorylation *in vitro* in bone marrow primary culture.
Results
In the kidney, *C. odorata* and *T. diversifolia* act synergistically to up-regulate erythropoietin. Similarly, bone marrow erythropoietin receptor was upregulated synergistic. p21Waf1, Kip2-p57 were downregulated in treatment groups. It was also observed that *T. diversifolia* alone is sufficient to up-regulate Epo-R in the bone marrow. The combination of *C. odorata* and *T. diversifolia* failed to evoke JAK2 phosphorylation *in vitro* in bone marrow,
Conclusion
The combination of *C. odorata* and *T. diversifolia* indeed stimulate erythropoietin expression but not via erythropoietin receptor agonism.
Chromolaena odorata; *Tithonia diversifolia*; erythropoiesis; cyclin-depedent kinase inhibitor.

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P052

Utility of Whole Genome Sequencing in diagnosing complex disorders: lesson from renal tubular disorders

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Bartter's syndrome (BS) and Gitelman's syndrome (GS) are renal tubular disorders affecting reabsorption of sodium, potassium and chloride. Common clinical features include muscle cramps and weakness, hypokalaemia, hypochloraemic metabolic alkalosis and elevated plasma aldosterone concentrations. Urinary calcium excretion and plasma magnesium concentrations may be differentiating features, such that hypomagnesaemia and hypocalciuria are typical of GS, and hypercalciuria is typical for BS. GS is due to *SLC12A3* mutations, whereas BS may be due to mutations involving one of six genes (*SLC12A1, KCNJ1, CLCNKA, CLCNKB, BSND* and *CASR*). Here, we report the utility of DNA sequence analysis using whole genome sequencing (WGS), for establishing the correct diagnosis in a patient who had features of BS and GS. The patient presented aged 10-years in 1959 with periodic tetany precipitated by vomiting or diarrhoea. Trousseau's and Chvosteks' signs were present. Serum biochemistry revealed her to have a hypokalaemia with a hypochloraemic metabolic alkalosis, in association with hyponatraemia, hypercalcaemia, and normomagnesaemia. However, she was subsequently found to have hypocalciuria and hypomagnesaemia. A renal biopsy did not reveal evidence for juxta-glomerular hyperplasia. Plasma renin and aldosterone concentrations were not elevated, and in 2003 she developed chronic kidney failure. In 2014 ocular schlerochoroidal calcification was identified which has previously been associated with both BS and GS. The clinical features in this patient overlapped with those of GS and BS, and to enable a parallel assessment of all of the 7 known causative genes, we undertook WGS, instead of Sanger DNA sequencing, after obtaining informed consent. This identified a homozygous c.226C>T variant in *CLCNKB* resulting in a nonsense mutation pArg76Ter, which has previously been reported in BS type-3 (Nozu *et al.* 2010 *JCEM*). Thus, our results, which demonstrate the importance of WGS in diagnosing disorders with overlapping phenotypes, reveal the patient has BS type-3.

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P053

Identification of a frame-shifting c.348dupC GNAS mutation in a family with Pseudohypoparathyroidism type 1a (PHP1a) by Whole Genome Sequencing

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Pseudohypoparathyroidism (PHP) is due to parathyroid hormone (PTH) resistance that results in hypocalcaemia, hyperphosphataemia and elevated plasma PTH concentrations. Some PHP patients also have Albright's hereditary dystrophy (AHO), which is characterised by short stature, round faces, dental hypoplasia, brachydactyly, subcutaneous ossifications and reduced mental acuity. The 3 major types of PHP referred to as PHP type 1a (PHP1a), PHP1b and pseudopseudohypoparathyroidism (PPHP) may be inherited as autosomal dominant disorders. PHP1a and PPHP are due to mutations of the *GNAS1* gene that involve parental imprinting, and PHP1b is due to abnormalities upstream of *GNAS1*. PHP1a patients have plasma biochemical abnormalities in association with AHO; PHP1b patients have plasma abnormalities only; and PPHP patients have AHO only. Here, we report a *GNAS1* mutation (c.348dupC), which is predicted to cause a frame-shift and a premature stop codon p.Val117fs*23, that occurred in a Scottish kindred with 4 siblings affected with PHP1a. Informed consent was obtained using guidelines approved by the local ethical committee. The mutation was not detected by Sanger sequence DNA analysis, but instead was identified by whole genome sequencing (WGS). Other examples of variants identified by WGS, but not traditional sequencing approaches, include patients with Dravet syndrome, hereditary motor and sensory neuropathy type 2 and Charcot-Marie-Tooth type 2C (Landouré *et al*. 2012 *Neurology*; Klein *et al*. 2014 *J Neurol Neurosurg Psychiatry*; Djemie *et al*. 2016 *Mol Genet & Genome Med*). Mutations may not be detected by Sanger DNA sequencing due to technical problems, which include: the mutated peak being too low either due to insufficient dideoxy-chain termination or somatic mosaicism; the mutation being located in a homopolymer stretch; or the design of PCR primers spanning common polymorphisms, thereby leading to mono-allelic amplification. Thus, our results demonstrate that WGS can identify mutations in known causative genes previously not detected by Sanger sequencing.

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P054

Risk of bone fracture is not increased in women with TS compared to women with ovarian failure

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Women with Turners Syndrome (TS) have been shown to have reduced bone mineral density (BMD) but there is uncertainty about how this relates to fracture risk. The little data that does exist is conflicting, with one case series finding no difference compared to controls and one survey suggesting an increased risk of fracture particularly of the forearm. Proposed mechanisms for reduced BMD include short stature, oestrogen deficiency and bone dysplasia. In addition, fracture risk might be related to hearing impairment and propensity to falls. Here we investigate fracture risk factors in women with TS.

Methods

Self reported fracture history was collected from 265 women with TS. To control for oestrogen deficiency we selected a control group of women with early onset Premature Ovarian Insufficiency (POI) ($n=42$). Fracture risk variables included; age, height, hip and spine BMD, BMI, age of first oestrogen exposure and hearing aid use. We also compared fracture rates of the spine, arm, wrist, femur and foot.

Results

Women with TS were older (31.3 vs 37.5years), diagnosed earlier (17.4 vs 9.6 years) and shorter (1.66 vs 1.50 m). Spine BMD was lower in POI (t-score -1.4 vs -0.90, $P<0.05$) but not different for the hip (t-score -0.96 vs -0.77). There was no significant difference in fracture rate 87/265(32.8%) vs 14/42(33.3%); $P=0.9$ or fracture site between groups. Within the TS group, there was no difference in fracture risk variables in those with a facture history compared to those without.

Conclusions

When compared to a similar oestrogen deficient group, women with TS appear not to have an increased rate of fracture. The results suggest that fracture risk in TS can be accounted for by oestrogen deficiency, rather than propensity to falls or bone dysplasia. BMD scans may not be a good surrogate marker of fracture risk in TS.

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P055

Resistant hypocalcemia post parathyroidectomy attributed to imatinib

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Background

Hypocalcaemia post parathyroidectomy and thyroidectomy is common and usually transient. A variety of drugs including tyrosine kinase inhibitors can cause hypocalcaemia. We present a case where a patient with primary hyperparathyroidism on imatinib with pre-op calcium 2.86 mmol/l, post-operatively developed resistant hypocalcaemia necessitating prolong hospitalisation and multiple calcium infusions which was not solely attributable to hungry bone syndrome.

Case description

54 years old female on imatinib for Gastro intestinal stromal tumor (GIST) developed primary hyperparathyroidism. Sestamibi scan confirmed two parathyroid adenomas and thyroid nodules. FNA graded the thyroid nodules as Thy 3, therefore, a total thyroidectomy with removal of two parathyroid adenomas was performed. Two weeks post operatively she developed tetany with calcium 1.26 mmol/l. despite correction of mild hypomagnaesemia (0.6 mmol/l),repeated intravenous calcium, 1 alfa calcidol and oral calcium supplimentations she failed to achieve normocalcaemia. This was only acheived by withholding imatinib after discussion with oncology. She subsequently was able to restart imatinib with no further hypocalcaemic episodes.

Conclusion
Hyopcalcaemia due to tyrosine kinase inhibitors is recognised but rare (1) and possibly due to bone remodelling (2). We believe the combination of hungry bone syndrome and concurrent imatinib use caused prolong hypocalcaemia in this patient. We therefore would suggest tyrosine kinase inhibitors are withheld immediately before and for a few weeks post parathyroidectomy to reduce the risk of severe hypocalcemia.
References
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Clinical Biochemistry

P056

Interference of Asfotase Alfa in immunoassays using ALP detection systems
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Asfotase alfa (AA, STRENSIQ, Alexion Pharmaceuticals, Inc.) is the first FDA-Approved treatment for patients with hypophosphatasia, the result of a mutation in the tissue-nonspecific alkaline phosphatase (*ALPL*) gene. Because it contains the ALP active site, AA is able to catalyse the substrate as the antibody-conjugated ALP would within an assay. Therefore, AA present in a patient's sample may generate a false positive or a false negative result. We investigated whether the presence of AA within a sample induces interference in measurements of LH, TSH, FSH and fT4 in large automated analysers (Siemens Immulite and ADVIA Centaur, Roche Diagnostics COBAS 6000 and Abbott Architect) using ALP as detection system or an alternate detection system. AA was added to samples at concentrations from 0.08–5 μg/ml. All experiments were repeated a minimum of 3 times. The presence of AA was demonstrated in ALP chemistry assay (COBAS and Centaur) by measuring the activity of the enzyme. ALP showed a significant (ANOVA, $P<0.0001$) linear increase in concentration with increasing asfotase alfa concentrations. We showed no effect of AA in assays using ruthenium (COBAS and Centaur fT4, COBAS TSH), acridium ester (Centaur and Architect LH, Centaur TSH and Architect FSH), nor ALP (Immulite LH and FHS). Although we were not able to show an effect of AA on the assay we tested, demonstrating the high specificity of the detection antibodies in this instance, an interference cannot be ruled out for all assays that uses ALP. The likelihood of misdiagnosis remains low but cannot be excluded and consultants should ensure laboratories are aware of the presence of AA in the sample sent for analysis. The presence of AA must be taken into consideration when analysing blood samples using certain assay technology to avoid any risk of misinterpretation of false positive/negative results.
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P057

Genetic susceptibility to type 1 diabetes: genomic variants in the vitamin D pathway
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Type 1 diabetes mellitus (T1D) is an autoimmune disease that results from the destruction of insulin producing β cells, in genetic susceptible individuals. Vitamin D (Vit D) is mostly known for its role in bone and calcium metabolism, however it is also involved in the modulation of the immune response. Serum levels of vitamin D partly depend on diet and sunlight exposure. However, genetic factors are also involved. Patients with T1D have been reported to have a higher prevalence of Vit D deficiency. In addition, the vit D supplementation decreases the risk of developing T1D in humans and prevents the disease in animal models. Single Nucleotide Polymorphisms (SNP's) located within or near genes that encode crucial enzymes for synthesis (*DHCR7*-rs12785878), metabolism (*CYP2R1*-rs2060793) and degradation (*CYP24A1*-rs6013897) of Vit D have been associated with serum levels of Vit D and with the risk for T1D. However, the results are not consistent for all populations. The aim of this study was to determine the association between these SNP's, in the Vit D pathway and the genetic susceptibility to T1D in the Portuguese population. We conducted a case-control study to analyse the prevalence of these SNP's in 320 T1D patients and 486 controls, using PCR-RFLP techniques. Allele and genotype frequencies were compared between patients and controls, as well as diverse clinical parameters. Single locus analysis showed an overrepresentation of the rare allele of the SNP in *CYP2R1* gene in patients when compared to controls (OR = 1.26; 95%CI: 1.02–1.59; $P=0.03$). No association was found concerning the other two polymorphisms. Our findings suggest that *CYP2R1* polymorphisms may be associated with an increased risk to develop T1D and may contribute to a better understanding of the pathogenesis of T1D and of the role of Vit D in autoimmunity.
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P058

A cross-sectional study of sensitivity and specificity of late-night salivary cortisol in a single-centre heterogenous population
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Endogenous Cushing's syndrome poses considerable diagnostic challenges. It is recommended to use two screening tests to confirm hypercortisolaemia. While late-night salivary cortisol assessment (LNSC) is reported to have good specificity and sensitivity and deemed to be cost-effective, it is the least widely biochemical tool used both nationally and in Europe. We aim to compare the specificity and sensitivity of LNSC against and in combination with other diagnostic tests, within a heterogenous cohort who were referred with symptoms of hypercortisolaemia to a single tertiary centre. Sixty-nine patients screened for hypercortisolaemia were retrospectively reviewed. All patients had been asked to perform a midnight salivary cortisol test at home. 66 valid samples were returned. Further tests for hypercortisolaemia had also been performed, chosen based on patient and clinician preference: overnight dexamethasone suppression test (ODST) ($n=33$), low-dose 48-hour dexamethasone suppression test (LDDST) ($n=20$) and urinary free cortisol (UFC) ($n=17$). The patients were then categorised as follows; true hypercortisolaemia ($n=22$) defined by response to treatment and/or diagnostic histology, or no hypercortisolaemia ($n=25$). The specificity and sensitivity for these tests were calculated. Overall, 47 patients had both a LNSC and a second biochemical test for hypercortisolaemia. Median BMI across the cohort measured 35 (IQR 25–40) kg/m^2. Specificity and sensitivity were as follows: LNSC specificity 92%, sensitivity 86%. ODST specificity 71%, sensitivity 100%. LDDST specificity 73%, sensitivity 100%. UFC specificity 67%, sensitivity 55%. A combination of LNSC and LDDST or ODST suggests specificity of 98% and sensitivity of 86%. A combination of LDDST and ODST suggests specificity of 92% and sensitivity of 100%. These preliminary data have demonstrated LNSC to have superior specificity for determining hypercortisolaemia. Furthermore, our data suggests that the combination of LNSC/ODST is preferable to LDDST/ODST, thus reducing length of hospital admission required for diagnosis.
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P059

A novel metaoblic index as a predictor of mortality in intensive care patients
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Introduction
Failure to recognise critically ill patients delays escalation to intensive care units (ICU) and results in increased mortality. Objectively identifying the sickest patients on admission remains challenging for healthcare professionals. This study proposes a novel Metabolic Index as a marker of metabolic disturbance based on a patient's sodium, potassium and bicarbonate. The Metabolic Index is proposed as a predictor of outcome in patients presenting to A&E. A Metabolic

Index of 0.8–1.2 was defined as normal. This study aims to investigate the association between Metabolic Index value on hospital admission and transfer to ICU and subsequent mortality.
Methods
17,346 patients were included who had received an arterial or venous blood gas test in the Accident and Emergency (A&E) departments of St Mary's and Charing Cross hospitals between March 2017 and March 2018. Patients were assessed for subsequent transfer to ICU. 516 patients admitted to ICU were followed up to primary end-point; discharge or death.
Results
Patients transferred to ICU were significantly more likely to have had a low Metabolic Index value than a normal value on admission (OR 3.01, 95% CI 2.36–3.85, $P = < 0.001$). Patients who died in ICU were significantly more likely to have had a low Metabolic Index value than a normal value on admission (OR 2.03, 95% CI 1.22–3.46, $P = 0.0075$).
Discussion
This novel Metabolic Index could easily be incorporated into clinical practice and has been demonstrated to be associated with increase transfer to ICU and mortality in ICU. Further work is needed, including prospective studies to control for confounders and to assess whether serial Metabolic Index calculations are stronger predictors of outcome.
Conclusion
This study demonstrates the potential use of a novel Metabolic Index to assess metabolic disturbances and objectively predict outcome in patients on presentation to A&E.

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P060

Low plasma glucose results from primary care are not associated with morbidity, mortality or underlying endogenous hypolgyaemic disorders

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Background
Low glucose is a relatively common primary care referral to specialist endocrine services. However the prevalence of endocrine disease causing endogenous hypoglycaemia is extremely rare.
Methods
We obtained all plasma glucose results <4 mM originating from primary care within NHS Lothian, in non-diabetic individuals (20 145 people (77.6% female)) aged 18–40 years, between 2002 and 2017. These data were linked to national admission, mortality, cancer and diabetes registers to assess associations with mortality and morbidity.
Results
Median follow-up was 4.8 years (IQR 2.6–7.8). Glucose was marginally higher in women 3.6 mM vs 3.5 mM, $P<0.0001$. Glucose concentration was <2.2 mM in 0.63% (A), 2.2–<3.0 mM in 8.7% (B), 3.0–<3.5 mM in 28.0% (C) and ≥ 3.5 mM in 62.6% (D). A history of eating disorder was present in 2.4% (A), 1.1% (B), 0.4% (C) and 0.3% (D), $P<0.0001$. Increasing age (HR 1.03, $P<0.001$) and male gender (HR 4.20, $P<0.001$), but not glucose <3 mM (HR 0.89, $P=0.79$), were associated with mortality. The risk of a subsequent new diagnosis of cancer or hospital admission with incident cardiovascular, renal, liver or infectious disease was not related to glucose category. Incident diabetes was observed in 0.2% of those with glucose <3 mM and in 0.6% of those with glucose ≥ 3 mM (OR 3.0, $P=0.009$). No cases of insulinoma were detected based on the results of these tests.
Conclusion
Low plasma glucose results from primary care are almost never indicative of an endogenous hyperinsulinaemic disorder and are not associated with adverse outcomes in adults up to 40 years of age. Underlying eating disorder should be considered in this context. Assessment by an endocrinologist should be limited to cases where Whipple's triad is present.

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P061

An analysis of hypocalcaemia post thyroidectomy: diagnosis and predictors

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Background
Post-thyroidectomy hypocalcaemia is a common complication with significant short and long term complications. The aim of this study was to determine the incidence and predictors of post-thyroidectomy hypocalcaemia (corrected calcium <2.1mmol/l).
Method
A total of 183patients who underwent total thyroidectomybetween 2012 and 2015 in a national general hospital were included in this retrospective study. Clinical and biochemical data were obtained from electronic and hard copy medical records.
Results
Out of atotalof 183 patients, 142 (77.6%) were female, while 41 were males (22.4%). Ages ranged from 15 to 84 years, with a mean of 50.6 years (SD 15.84 years). There was variation in the incidence of hypocalcemia dependent on the timing of measurement of calcium on post-op day 1 (POD1) and the measuring of calcium on subsequent days. The incidence of post-operative hypocalcaemia on day 1 was 17.5% ($n=32$). The indications for surgery included Graves' disease (62 patients, 33.88%), multi-nodular goitre (50 patients, 27.32%), malignancy (28 patients, 16.39%), the presence of a thyroid nodule (22 patients, 12.02%), hyperparathyroidism (18 patients, 9.83%) and in 3 patients (1.63%)the indication was unclear. A lower preoperative uncorrected calciumwas associated with post-thyroidectomy hypocalcaemia ($P=0.048$). However it was found that the incidence of post-thyroidectomy hypocalcaemia was underestimated by 55.5% if only POD1measurement was used.
Discussion
Measuring calcium on POD1may miss patients who would subsequently develop hypocalcaemia. Other possible contributing factors for post-op hypocalcaemia, including age, gender, histology and indication for surgery were not found to be statistically significant, and could not be used to predict who will develop hypocalcaemia. This emphasises the need for stringent guidelines for assessing and managing patients undergoing total thyroidectomy and possible associated hypocalcaemia.
Keywords: Hypocalcaemia, Post total-thyroidectomy
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P062

Urine steroid profiles: what can they do for me?

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A recent audit of the urine steroid profile (USP) service at Glasgow Royal Infirmary (GRI) revealed that up to 25% of requests are made inappropriately, or without any clinical information. In contrast to the majority of biochemical testing, USP analysis is very labour intensive, and interpretation of results requires both quantitative and qualitative assessment of the profile. Adequate clinical information is essential to generate a complete report, as a number of steroids found in specific conditions must be identified manually. For example, 5-alpha reductase deficiency can only be identified by USP over the age of 3 months. Clinical indications for USP analysis are limited, but include ambiguous genitalia, salt-losing states, virilisation, hypertension, and adrenal tumours. The test is primarily used in the investigation of congenital adrenal hyperplasia. However USPs can also identify conditions such as 5α-reductase deficiency, hypo-/pseudohypoaldosteronism, Cushing's and Conn's syndromes, and adreno-cortical carcinoma. Over the last two years, the service has confirmed cases of classical and non-classical 21-hydroxylase deficiency, non-classical 11-beta hydroxylase deficiency, adrenocortical carcinoma, and has provided additional evidence in the investigation of cases of hyperaldosteronism, and Cushing's syndrome. In 2017 the service moved to a highly specific tandem mass spectrometric method, which is UKAS accredited, and the improvement in analytical specificity has enabled investigation of steroid ratios for identification of specific abnormalities. Herein we present data from a recent audit of the USP service, review clinical indications for USPs, and outline identification of different conditions. In 2014 GRI introduced a serum androgen profile, which has enhanced our ability to investigate steroid disorders, and compliments the USP service. In summary, with the right clinical information, USPs are a powerful and potentially diagnostic test for investigating disorders of adrenal steroid metabolism.

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P063

Hypernatraemia in acute unselected general medical inpatients: clinically relevant associations

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Introduction
Disorders of plasma sodium are one of the commonest electrolyte abnormalities affecting acutely unwell patients. The North Middlesex is a busy district general hospital with a diverse population. We reviewed our hypernatraemic population to identify possible trends in age, demographics and outcomes.
Methods
Through the biochemistry laboratory, we identified all patients with sodium level above 145 mmol/L who were acute inpatients or attended the Emergency Department in May or October 2017. Using the hospital records system, we matched patients to their demographic details, place of residence on admission and discharge, sodium level on admission, peak sodium during admission and final outcome including mortality in-hospital and within 30 days of discharge. We performed simple descriptive statistics by applying correlation coefficient calculation and t-test analysis.
Results
The hospital pathology system returned serum sodium results above 145 mmol/L for 589 patients, of which 84 were analysed in detail. Patients with peak sodium above 165mmol/L represented 1% of all results. Mean age increased with severity of hypernatraemia. There was a moderately positive relationship between degree of hypernatraemia at point of discharge and mortality ($r=0.49$). There was a statistically significant difference between sodium on admission and on discharge ($P<0.05$). There was no significant difference between the sodium values on admission for nursing home versus non-nursing home residents ($P=0.18$). All patients with peak sodium >165 mmol/L had an unplanned re-admission to hospital within 3 months.
Discussion/Conclusion
Hypernatraemia is associated with increased mortality and is more common with advancing age. There was no difference between nursing home versus non-nursing home residents but this could be specific to our patient demographic and associated cultural backgrounds. Our data suggests that hypernatraemia is a potentially correctable medical problem but the patients are nonetheless at increased risk of future acute hospital admissions.

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P064

Gitelman Syndrome (GS) is a rare, salt-losing tubulopathy. Prevalence 1 in 40,000 higher in Asia. GS is an autosomal recessively inherited disease with a wide clinical spectrum, usually seen in adolescents and adults. It is reported that function loss develops in the sodium chloride cotransporter system in the distal renal tubule as the result of SLC12A3 gene mutation

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GS, Patients have hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria together with normal blood pressure. Most of the patients are clinically asymptomatic, but some patients experience seizures, muscle weakness, cramps, episodic tetany, and paresthesia. The diagnosis is usually made based on clinical features and laboratory blood test. In this study we present a young patient with persistent hypokalaemia. She feels well in herself. She denies any symptoms of hypokalaemia such as muscle weakness and has no medical history other than childhood asthma and chronic tonsillitis for which she had a tonsillectomy. She is not on any regular medications and denies any history of laxative use nor is she on any diuretics. She also denies any history of diarrhoea or vomiting, drinks very occasional alcohol and smokes 6–7 cigarettes a day. No family history of any endocrine disorders. BP in clinic was 108/60. Blood test: K 2.7–3.3 over the last persisting few months. The K of 3.3 was after a two week course of sando-K given by GP. We suspected a rare renal tubular abnormality causing her persistant hypokalaemia. To investigate for renal tubular abnormality such as Gitelman's syndrome we did further Blood test and 2×24 hr urine collections for electrolytes and calcium. Further blood test: Na 142, K 2.9, Urea 6.7, Creatinine 55, Mg 0.71, PO4 1.24, Adj ca 2.39, TSH 1.04, glucose 4.8. Renin 255.2 mu/L (High) and aldosterone 176 pmol/L, ARR 0.7 pmol/miu$^2\times24$ hr urine collection for electrolytes and calcium: urea 361(n), creatinine 12.3(n), urine Na 262 high, ca 0.3 low, K 84(N). Our finding's of normal BP, hypokalemia, Metabolic alkalosis, loss of Nacl in urine and hypocalciuria confirmed our diagnosis of Gitelman's syndrome. Timely diagnosis helped us to initiate early treat with long term K replacement and K sparing diuretics and follow up.

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P065

An oestrogen profiling mass spectrometry method using N-Methyl Pyridine-3-sulfonyl chloride derivatisation

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Objectives
Oestrogen analysis using liquid chromatography mass spectrometry is problematic, as oestrogens do not readily ionise. This coupled with low concentrations in men, pre-pubertal and post-menopausal women provides an analytical challenge. We investigated N-Methyl Pyridine-3-sulfonyl chloride (NMPS) derivatisation, as described by Wang *et al.* (Steroids 2015 Apr;96:140-152) to improve sensitivity of 11 oestrogens; oestrone (E1), oestradiol (E2), 2-hydroxy-oestrone, 4-hydroxy-oestrone, 16-hydroxy-oestrone (oestriol-E3), 2-methoxy-oestradiol, 2-hydroxy-oestradiol, 4-hydroxy-oestradiol, 2-methoxy-oestrone, 11β-hydroxy-oestradiol.
Methods
NMPS derivatisation is a two-step process. A pyridine sulfonyl group is first added to hydroxyl groups on the aromatic ring, then treatment with iodomethane adds the N-methyl group, the new molecule termed an oestrogen-NMPS. We used a Waters Xevo-XS with Acquity UPLC, a HSS T3, 1.8 μm, 1.2×50mm column with water and methanol (both with 0.1% formic acid) as elution solvents over five minutes.
Results
Six of the non-derivatised oestrogens were chromatographically separated. Both the 2- and 4-hydroxy metabolites of E1 and E2 co-eluted. LOQ ranged from 0.05 to 0.2ng/mL. Following NMPS derivatisation sensitivity for most analytes at least doubled with LOQ ranging from 0.025 to 0.2 ng/mL. Again, six of the 11 oestrogens chromatographically separated. However, both single and double derivatised products of the 2 and 4-hydroxy oestrogens were observed, adding to the complexity of the method. Excluding these analytes the method was reproducible with repeatability measured as relative standard deviation of less than 10%. Matrix effects were less than $\pm20\%$, process efficiency and absolute recovery were between 30 and 50%. Further optimisation of the derivatisation procedure is required to improve recovery and to produce only the double derivatives.
Conclusions
NMPS derivatisation improves oestrogen sensitivity in mass spectrometry, and could provide the sensitivity required for low concentration oestrogen analysis in numerous conditions.

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Clinical Practice, Governance & Case Reports

P066

Cranial Diabetes Insipidus – A survey of patient safety concerns in secondary care

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Background
Knowledge of Cranial Diabetes Insipidus (CDI) is poor amongst healthcare professionals. Intra-nasal Desmopressin sprays are often mistaken for pulmonary inhalers, and Diabetes Insipidus mistaken for Diabetes Mellitus, leading to incorrect management and harm. Correct Desmopressin administration and fluid management is paramount in inpatients, especially in reduced conscious states.
Aim
To explore Clinicians' concerns regarding safety issues arising from inpatient management of CDI over last 2 years.
Methods
A survey with the following 5 questions was sent electronically to 1195 members of the Society for Endocrinology:

- The clinician's role.
- If they had concerns regarding the management of an inpatient with CDI in the last 2 years.
- Did this result in significant harm or a near miss?
- Details of safety issue.
- If there are initiatives in their Trust to support the safety of patients with CDI.

Results
200 responded: 68% Consultants; 18% Registrars; 12% Nurse Specialists and 2% others. 55% had concerns regarding the management of a patient with CDI within the last 2 years. Of these, 47% of responders reported significant harm or near miss due to omissions of Desmopressin, non-availability, incorrect prescription, incorrect recognition of CDI, suboptimal fluid status assessment, hypo- and hypernatraemia, cerebral oedema and death. The most common reason for a safety issue was related to the prescription and/or administration of Desmopressin. 41% (82/200) reported that their Trust supported safety initiatives for optimal management of CDI.
Discussion
Inpatients with CDI continue to be at risk of significant harm due to the paucity of healthcare professionals' knowledge, and needs addressing imperatively. Crucial messages of Desmopressin as a life-sustaining medication, meticulous fluid management and the need for early Endocrinology input needs to be widely disseminated. Trust-wide safety initiatives, electronic pharmacy alerts and perhaps a change in nomenclature of Diabetes Insipidus may all be useful interventions in reducing risk.

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P067

An audit of electronic consultations for provision of endocrine specialist advice

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Background
Nationally, there has been a concerted drive to utilise technology to support the provision and delivery of specialist services. Within our local area, both secondary care and 95% of GP surgeries utilise the Systm-One electronic health care record. Since October 2016, we have been providing a local Endocrine E-consultation service. A GP requiring advice, rather than referring the patient to the hospital would (after obtaining patient consent), share their record, tasking the specialist with a request for specific advice. The specialist in turn, after perusing the patients record provides appropriate advice and records this within the electronic record. The perceived benefit was that it would facilitate advice in a timely manner and reduce unnecessary referrals to hospital outpatients impacting positively on outpatient capacity. This audit was undertaken to assess workload, response-time and conversion to hospital face-to-face appointments. Information obtained was compared to income/expenditure assessing the cost-effectiveness of the service and other resulting benefits.
Results
During the audit period (Oct 2017-April 2018), 955 e-consultations received for Endocrine Advice. Average 36 per week. The ward-consultant was allocated 3 hours per week for this. Mean response time was 1 day, Average 1.77, Range 1–17. 212 (24%) e-Consultations had subsequent New Face-to-Face Endocrine outpatient appointments. The cost-savings to primary care from saved appointments was £69980 for the period. The trust accrued savings of £1151. Other benefits included:

- Advice provided to GPs/Practice nurse in advance of hospital appointments, saving time and additional follow-up impacting on referral-to-treatment time.
- Allowing patients in secondary care to be discharged with recourse to future e-consultation advice as needed without needing further appointments.
- Avoiding unnecessary tests by GPs.
- GP education with links and documents signposted
- Fully auditable advice provided, embedded in the patient record (good clinical governance).

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P068

Utilization of the internet for health-related information among endocrinology patients

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Background
The internet is widely consulted for health-related information (HRI). Online health information (OHI) seeking behaviors have never been investigated in the field of endocrinology.
Objective
We examined the frequency, how and why the internet is utilized for HRI, the impact of such activity and the future information needs of our patients.
Methods
A cross-sectional mixed-methods study was performed with more quantitative data. Qualitative data underwent thematic analysis. Patients attending a general endocrinology clinic were recruited from two clinical sites. A questionnaire survey was designed to answer our research questions.
Results
312 patients were included; the response rate was 78.4%. OHI seeking was reported by 175 patients (78.1% among those that sought any form of HRI). OHI seekers perceived OHI to be of high quality (135, 77.1%) and demonstrated a good understanding of what constitutes trustworthy information. Notwithstanding, 71 (40.6%) relied on the top search engine options as their main criterion for choosing a website and 104 (59.4%) were unaware of website certification tools. OHI seekers sought general information (90, 51.4%). Among OHI seekers, 63 (36.6%) reported that their behavior changed after seeking OHI e.g. by improved self-care or compliance. Only 45 (25.7%) of OHI seekers discussed the information they gathered with their endocrinologist. 194 (62.2%) of the 312 patients expressed a will to use interactive e-learning modules if available, especially existing OHI seekers ($P<0.0001$) and those expressing a wish for more HRI ($P=0.024$).
Conclusions
OHI seeking is practiced by the majority of endocrine patients before their appointments. Patients have a good awareness of what makes a website trustworthy, but more education and guidance is needed. Many patients are keen to utilize e-learning modules, even those patients that are not current OHI seekers. The concerns regarding an adverse impact on the doctor-patient relationship by OHI seeking seem to be unfounded.

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P069

Patient perception of provision of care for multiple endocrine neoplasia disorders in the UK compared to other EU member states

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We report the results of the first Europe-wide survey of patients with multiple endocrine neoplasia (MEN) disorders by the European MEN Alliance (EMENA). METHOD: An online questionnaire was distributed via patient groups, social media and health professionals. A total of 284 responses were analysed. RESULTS: 35% ($n=99$) UK responses and 65% ($n=185$) from 17 other EU countries: 68% female, 32% male (UK; 75% and 25%). Disorders represented were: MEN1 $n=201$ (UK $n=72$), MEN2A $n=66$ (UK $n=22$), MEN2B $n=16$ (UK $n=5$), MEN4 $n=1$ (UK $n=0$). Overall, MEN patient care was provided mainly by Endocrinologists (UK 82%; other EU 79%) in specialist referral centres (UK 53%; other EU 74%) with access to a specialist multidisciplinary team (UK 71%; other EU 69%). Appointment frequencies were similar; most commonly 6 monthly (UK 38%; other EU 43%) or annually (UK 44%; other EU 37%). Appointment length was perceived to be appropriate by the majority of respondents, although only 32% of patients in other EU countries had access to a specialist nurse compared to 57% in the UK. The typical intervals between surveillance biochemical testing were similar between the UK and rest of the EU, respectively (3 monthly (17%, 18%), 6 monthly (30%, 39%), annually (48%, 37%), over 12 months (1%, 4.5%) and none (4%, 1.5%)) as were those for radiological surveillance (3 monthly (6%, 5%), 6 monthly (14%, 20%), annually (44%, 41%), over 12 months (25%, 23%)). CONCLUSION: Although perceptions regarding the provision of care are generally similar between the UK and rest of Europe, differences in access to specialist referral centres and to specialist endocrine nurses are reported by patients with multiple endocrine neoplasia in the UK compared to other European countries.

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P070

Physiological versus synthetic oestrogen therapy and bone mineral density in premature ovarian insufficiency

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Introduction
Premature ovarian insufficiency (POI) affects approximately 1% of females. In POI, hormone replacement manages symptoms and reduces the risk of bone mineral density (BMD) loss as oestrogen acts to enhance bone deposition in bone remodelling. Oestrogen may be given either as synthetic oestrogen (ethinylestradiol) as in most combined oral contraceptives (COCP), or as physiological oestrogen (oestradiol) as in hormone replacement therapy (HRT preparations) and a select few COCPs. In clinical practice patients are prescribed either the COCP or HRT; it is still unclear which of these provides optimal treatment. There is limited evidence comparing physiological vs synthetic oestrogen use in patients with POI. We investigated the BMD in females with primary and secondary POI who were taking either physiological (HRT & COCPs containing physiological oestrogen) or synthetic oestrogen therapy (COCP).
Methods
30 females (46XX karyotype) received oestradiol ($n=15$) or ethinylestradiol ($n=15$). POI was diagnosed based on clinical amenorrhoea, raised LH and FSH levels and low oestradiol. Spine and hip BMD Z scores were obtained from DEXA scans. Z scores were chosen instead of T scores to control for age differences between groups. Mean duration of therapy was 4.7 years for ethinylestradiol and 4.0 years for oestradiol.
Results
Mean BMD at the lumbar spine was significantly greater with oestradiol (Z score -0.5 ± 0.7) than with ethinylestradiol therapy (Z score -1.5 ± 0.5, $P<0.05$, $P=0.03$). No significant difference was found in the BMD at the hip ($P>0.05$).
Discussion
These findings suggest that physiological oestrogen may have additional beneficial effects for lumbar spine density regardless of its provision in HRT or COCP forms that contain physiological oestrogen, when compared to synthetic oestrogen replacement. This may have implications when advising patients with POI on their hormone replacement.

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P071

Review of the reasons cited by GPs who refuse to prescribe medications recommended by the London gender identity clinic

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Introduction
Transgender medicine is a rapidly expanding field and GPs have historically played a vital role in prescribing hormones therapies for those with gender incongruence. Despite this, some GPs are refusing to prescribe medication recommended by the Gender Identity Clinic (GIC) in London. This problem is persisting despite the GMC guidance that prescribing is the GPs responsibility. The aim of this audit was to establish reasons why GPs are refusing and if there were factors that made refusal more likely.
Method
53 patients whose GPs had refused them prescriptions were identified and information about comorbidities, drug recommendation and reasons for refusal were collected. These were then compared against 53 controls matched for age and gender.
Results
Refusal to prescribe hormones is uncommon ($<0.001\%$). The most common reasons cited by GPs were lack of knowledge or experience (35.5%), they felt it was a specialized area of medicine (26.6%) and that it was flagged as an amber drug by their local CCG (12.7%). Estrogen was significantly less likely to be refused than other drugs (20.6% vs 34.2%, $P=0.007$). People on the autistic spectrum were significantly more likely to be refused prescriptions (11% vs 0% $P=0.012$). On average the time from recommendation by the GIC to GP refusal to reply by the GIC was 86 days. With further correspondence, 87% of patients had been prescribed hormones in primary care.
Discussion
These results show that most GPs will prescribe hormones, often through simple reassurance by the endocrine team and quoting the GMC guidance. This demonstrates that endocrine input is required to support primary care. Delays are exacerbated by community pharmacy advice from CCGs who often unnecessarily classify transgender medications as amber drugs. Moving forward, the NHS must work towards clearer endocrine advice in primary care to ensure timely and effective treatment for transgender patients.

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P072

Patient perception of quality of care for multiple endocrine neoplasia disorders in the UK compared to other EU countries

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We report the results of the first Europe-wide survey of the Quality of Care of patients with multiple endocrine neoplasia (MEN) disorders by the European MEN Alliance (EMENA).
Method
An online questionnaire was distributed via patient groups, social media and health professionals. A total of 284 responses were analysed.
Results
35% ($n=99$) of responses were from UK patients and 65% ($n=185$) from 17 other EU countries: 68% female, 32% male (UK; 75% and 25%). Disorders represented were: MEN1 $n=201$ (UK $n=72$), MEN2A $n=66$ (UK $n=22$), MEN2B $n=16$ (UK $n=5$), MEN4 $n=1$ (UK $n=0$). Patients felt overwhelmingly that their specialist listened to their concerns (UK 82%; other EU 80%), involved them in decision-making (UK 77%; other EU 80%), were knowledgeable about MEN and MEN care and monitoring (UK 82%; other EU 85%), and were trustworthy (UK 82%; other EU 85%). Nevertheless, these positive results were not strongly reflected in the patients' ratings of their overall care for MEN with only 34% and 25% of patients rating their care as excellent in the UK and other EU countries, respectively. There were additional variations in all patient responses when the type of MEN was taken into consideration including more UK MEN2A patients rating their overall care as excellent compared to MEN1 and MEN2B (59%, 26%, 40% respectively).
Conclusion
Despite very positive patient perceptions across many aspects of clinical provision, overall ratings of care are somewhat surprising by comparison. Nevertheless, this comparison shows that patients in the UK and other EU countries consider the quality of their care to be of a good standard.

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P073

Transition in Turner syndrome

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Background
A Turner Syndrome (TS) Transition clinic, Royal Hospital for Children Glasgow(RHCG), with paediatric and adult endocrinology/gynaecology teams was set up in 1998.
Objective
1) To evaluate the success of TS transition
2) To determine what factors influence long-term follow-up in an adult service – good early attendance in an adult clinic and meeting an adult specialist prior to transfer to adult clinic.

Methods
Girls attending the TS Transition clinic at RHCG, 1998–2017, were identified. Attendance data were obtained from patient records and an electronic appointment system. Success of TS Transition was determined by the proportion of girls in established follow-up. Good late attendance and good early attendance was assessed in all girls and was defined as those attending last and penultimate paediatric appointments and both first and second adult appointments respectively. Only girls transferred prior to 2015 were included in analysis of established follow-up, defined as those girls remaining in an adult clinic 3 years after transfer.
Results
46 girls (median age 18.3yrs) were identified. 36/46 girls transferred prior to 2015 and 26/36 (72%) girls were in established follow-up at 3 years. 26/36 girls, transferred prior to 2015, were good early attenders, of them, 21(80.7%) are in established follow-up. 42/46 (91%) girls were good late attenders and 32/46(70%) girls were good early attenders. 27/46 girls had met with an Adult specialist prior to transfer, 20/27(74%) were good early attenders. 19/46 had not met with an adult specialist prior to transfer, 12/19(63%) were good early attenders.

Conclusion
A significant proportion of girls with TS are currently lost to follow-up following transfer to adult clinics. Early attendance at an adult clinic appears to predict established long-term follow-up. Strategies to improve early attendance and long-term follow-up are needed to ensure lifelong health needs are addressed.

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P074

A retrospective analysis of electronic endocrinology advice and guidance via NHS e-referral service at University Hospitals Leicester NHS Trust

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Background
Electronic endocrinology advice and Guidance (e-Endo A&G) via NHS e-Referral Service was introduced at University Hospitals of Leicester NHS Trust (UHL) in March 2017 to address General Practitioners' (GP) non-urgent endocrinology clinical concerns. Primary aims of the service, was to prevent inappropriate outpatient visits, avoid acute admissions and reducing length of time in resolution of queries.
Objectives
To retrospectively evaluate utility of e-Endo A&G for 12-month period, and to estimate whether the service is compliant with National CQUIN of >80% questions answered within 48-hours.
Methodology
Retrospective analysis of all UHL's e-Endo A&G queries ($n=366$) from Leicestershire GPs from April 2017 to March 2018 was undertaken.
Results
$n=366$; 96% answered by Consultants; 4% by Registrars. Referral composition: Thyroid-38%; General Endocrine-18%; Gonads-10%; Bone-9%; Gynae-Endo-8%; Pituitary-6%; Parathyroid-6%; Adrenal-5%. Average response time <48-hours-94% (343/366), against CQUIN target of >80%. <24-hours-83% (303/366). 65% (238/366) queries were resolved preventing an hospital episode. 35% (128/366) resulted in clinic visit, following appropriate workup and/or treatment initiation. Furthermore, at £25 per query, £9,150 income was generated for the Trust.
Discussion
e-Endo A&G is a clinical governance compliant, time-efficient system resulting in reduction in clinic visits/admissions by 65%. It is recommended for trusts to avail following benefits:
1) For patients:
   a) Patients' speciality concerns resolved within 48-hours.
   b) Shorter clinic waiting times if outpatient visits necessary.
   c) Prevents travelling to secondary care centres.
1) For GPs:
 i) Rapid access of Endocrine expertise for non-urgent clinical queries.
 ii) No loss or delay in communication.
 iii) Cost saving measure.
1) For Endocrinology department:
 i) Prevents inappropriate outpatient visits.
 ii) Shorter waiting times.
 iii) Priority patients seen earlier
 iv) Registrar training opportunities.
1) For Trust:
 i) Clinical Governance compliant (audit trail and medico legal)
 ii) Income generation
 iii) Potentially fewer complaints handling.

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P075

Pituitary MRIs in hypogonadotrophic hypogonadism – essential or essentially a waste of time?

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We audited 46 pituitary MRI scans for patients with hypogonadotropic hypogonadism. We were particularly interested to see if adopting The Endocrine Society's (TES) 2010 guidelines for Testosterone Therapy in Men with Androgen Deficiency Syndromes (pituitary MRIs only for those with testosterone level below 5.3 mmol/l, panhypopituitarism, persistent hyperprolactinaemia or if the patient has symptoms consistent with a mass effect such as headaches, a visual field defect or visual impairment) in our department could potentially result in fewer unnecessary MRI scans being performed and therefore saving time, money, resources and, most importantly of all, saving patients from having unnecessary scans. 49 patients were identified who had been booked for MRI scans of their pituitary glands at Queen Alexandra Hospital with the indication 'hypogonadotrophic hypogonadism'. These scans dated from March 2015 to January 2017. Two patients were female and therefore removed from the numbers and one patient had never attended for the scan so was also removed from the numbers. Out of the 46 scanned male patients, 13 (28%) had a structural pituitary abnormality on their MRI – 7 of these abnormalities were small pituitaries or empty or nearly empty sellas. One macroadenoma and two microadenomas were found. Four of the scanned patients had biochemical profiles and documented histories which, according TES guidelines meant they did not require a scan – indeed all of their scans were normal. 19 patients had a documented indication for an MRI according to TES guidelines and 6 of those had abnormalities on their scans. For the remaining 23 patients, the documentation was unclear whether they had indications for their scans and 7 of them had structural abnormalities on their scans. These results support The Endocrine Society's guidelines for pituitary MRIs in hypogonadotropic hypogonadism patients since the patients without the TES indications for MRIs all had normal MRI scans.

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P076

Outcomes of endoscopic surgical intervention for acromegaly – the Wessex experience

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Background
Transsphenoidal surgery is the primary therapy in majority of Acromegaly patients with GH-secreting somatotroph adenomas. Reported outcomes of surgery show an initial remission rate of 40–50% for macroadenomas and >85% for microadenomas. Rates of hypopituitarism following endoscopic pituitary decompression vary between 5 and 25%. Invasion of cavernous sinus indicates the tumour is unlikely to be resectable.
Methods
We audited the results of endoscopic pituitary decompression for patients with biochemically proven Acromegaly between January 2015 and January 2018 at the Wessex Neurological Centre. Biochemical tests were reviewed to establish remission rates and post-operative hypothalamus-pituitary-adrenal (HPA) integrity. Remission rates were analysed using both historical criteria used in literature (defined as a random GH less than 5 μ/l or <2 μ/l during oral glucose tolerance test (OGGT) and normalised IGF-1), as well as latest remission criteria in accordance with Endocrine Society guidelines 2014 (A normal IGF value and random GH < 1 μg/l or GH nadir of < 0.4 5 μ/L during OGGT.). In addition patients were subdivided into 2 groups according to pre-operative MRI findings, namely either intrasellar or extrasellar subgroups.
Results
29 cases with Acromegaly undergoing surgery were analysed. 17 had intrasellar tumours, 12 had extrasellar tumours, 75% of these invaded the cavernous sinus. Remission rates in patients with intrasellar tumours was 82% using historical criteria, 76% using latest criteria and none had impairment of HPA. Of the patients with extrasellar tumours 42% had biochemical cure using old criteria and 17% using latest one, 40% had impaired HPA axis, including one patient who presented with apoplexy. Overall HPA dysfunction is 16% for both groups combined.
Conclusion
The Wessex regional neurosurgical pituitary service has comparable Acromegaly remission rates post pituitary surgery to that in published series, with low postoperative HPA dysfunction rates.

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P077

Management of patients with gynaecomastia in a single centre – a retrospective analysis

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Introduction
Gynaecomastia, a benign enlargement of glandular breast tissue in males, may be associated with anxiety, depression and reduced self-esteem.
Aims
To assess current practice in management and treatment outcomes in the management of gynaecomastia with a view to improving quality of service and rationalising investigations and referral pathway.
Methods
A health informatics search identified 42 patients with documented gynaecomastia reviewed in general endocrinology outpatient clinics between 2013-and 2018. 2 had incomplete data and were excluded from further analysis. A structured proforma was completed for each patient. Data were collected on patient demographics, clinical features on presentation, investigations, diagnosis, treatment and outcomes. Baseline investigations included liver, thyroid and kidney function, serum testosterone, oestradiol, LH, FSH, prolactin and beta-hCG.
Results
Underlying causes of gynaecomastia were divided into 3 categories: idiopathic ($n=18$, 45%), medical ($n=4$, 10%) and endocrine ($n=18$, 45%). Mean age at presentation was 40.4 years, ($+/-18.9$). 50% of patients had a BMI >25. Causes included primary ($n=5$, 12.5%) and secondary hypogonadism ($n=3$, 7.5%), hyperprolactinaemia ($n=2$, 5%), Klinefelter's ($n=6$, 15%), anabolic steroids ($n=1$, 2.5%), alcohol excess ($n=1$, 2.5%) and spironolactone ($n=1$, 2.5%). Management of underlying cause and weight were offered. 7/40 (17.5%) had a documented improvement in symptoms. Of these all had endocrine diagnoses. 38% with endocrine conditions improved symptomatically. 15/18 with idiopathic gynaecomastia were referred for surgical opinion on the NHS and all were discharged without surgical treatment.
Conclusions
In the majority of cases a hormonal cause for gynaecomastia was not identified. Screening for these conditions at referral may help utilise resources more effectively. Symptomatic improvements may be seen in those with endocrine conditions. There remains a large unmet need for effective treatment options for resistant cases.

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P078

An audit of vitamin D supplementation in pregnancy in an ante-natal centre in Birmingham

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Background
Approximately a third of pregnant women in the UK are Vitamin D deficient, which may confer deleterious consequences, including an increased risk of pre-eclampsia, gestational diabetes mellitus, and intrauterine growth restriction. Vitamin D supplementation in pregnancy has shown to be beneficial, including a reduced risk of pre-eclampsia and pre-term birth, compared to placebo. This audit investigated the extent to which women attending an ante-natal centre adhered to the standards set out by The National Institute for Health Care Excellence (NICE) regarding Vitamin D supplementation in pregnancy.
Methods
This was a single-centre cross-sectional audit carried out between September-December 2017. Pregnant women attending ante-natal clinics received a questionnaire regarding their experiences with Vitamin D supplementation during their pregnancy.
Results
Data from 141 pregnant women was collected. 44% ($n=62$) received written and/or verbal advice about Vitamin D supplementation, (NICE standards = 100%). 48% ($n=67$) were eligible for the Healthy Start supplementation; among these 75% ($n=50$) were offered supplementation. 87% ($n=122$) had one or more risk factors for Vitamin D deficiency, of which 67% ($n=40$, NICE standards = 100%) were asked about supplementation. Among those asked, 50% ($n=20$, NICE standards = 100%) received the correct dosage.
Conclusions
Adherence to the NICE guidelines regarding Vitamin D supplementation in these patients was suboptimal. Lack of adherence may be attributed to insufficient training of clinicians on the importance of Vitamin D supplementation, causing them to underestimate the concerns around gestational Vitamin D deficiency. Furthermore, there is no mandatory screening system in place for ante-natal patients that are at risk of Vitamin D deficiency or are eligible for Healthy Start. Various recommendations may therefore be proposed, such as implementing a mandatory ante-natal screening tool and providing more clinician training, in order to ensure that Vitamin D supplementation during pregnancy is standard of care.

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P079

Thyroid shared care – a nurse-led, virtual service for our patients

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Background
A large proportion of patients who attend the Endocrine clinic have thyroid dysfunction, usually thyrotoxicosis. These patients require regular thyroid function tests (TFTs) and advice on medication dose alteration, usually through frequent clinic appointments. At our University Teaching Hospital, we have a nurse-led system whereby TFT monitoring and advice is managed virtually, with patients usually attending clinic annually for review. We call this the Thyroid Shared Care (TSC) scheme.
Aim
To evaluate the number of patients managed under TSC, how many virtual consultations occurred and the advice given regarding thyroid related medication over a 1 year period.
Method
We searched our electronic database for patients having active monitoring under TSC between 01/05/2017 and 30/4/2018. Data were gathered on the number of advice letters sent and the advice given.
Results
1908 patients had thyroid monitoring in this period under the TSC scheme, with 7322 advice letters sent. 1499 reminder letters were also sent. The advice given (doses were specified in patient letters), after reviewing the most recent TFTs, is as follows:

Advice	Number of letters	Percentage
Continue off ATD	3048	41.6%
Continue on ATD	2914	39.8%
Increase ATD	281	3.8%
Decrease ATD	653	8.9%
Start ATD	163	2.2%
Stop ATD	157	2.1%
Other Advice	106	1.4%
Total:	**7322**	**99.8%**

ATD = Anti-Thyroid Drug (Carbimazole or Propylthiouracil)

Advice	Number of letters	Percentage
Continue off levothyroxine	6159	84.1%
Continue on levothyroxine	920	12.6%
Change levothyroxine dose	153	2.1%
Start levothyroxine	45	0.6%
Stop levothyroxine	6	0.1%
Other Advice	39	0.5%
Total:	**7322**	**100%**

Discussion
Providing a virtual thyroid service offers a convenient way for patients to have their thyroid dysfunction monitored and medications adjusted. It saves patients from multiple clinic appointments and allows patients care to be provided efficiently.

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P080

Are we adhering to Simon Broome criteria for referrals for Familial Hypercholesterolaemia genetic mutation at Queen Alexandra hospital and are there any clear differentiators between the 2 outcome groups?

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Patients with Familial Hypercholesterolaemia (FH) have premature Cardiovascular disease and have a standardised mortality ratio nine times greater than normal. FH must therefore be correctly diagnosed and treated aggressively. Referral for FH is based on fulfilling the Simon Broome's (SB) Criteria. We aimed to evaluate practice at Queen Alexandra Hospital with regards to referral for FH genetic mutation. We set out to see whether SB's criteria were being fulfilled when patients were referred over a 2-year period in 2014 and 2015. As a secondary endpoint, we aimed to look for any obvious differentiators between the two outcome groups. In total, 80 patients were identified for the audit. Out of those, 61 tested negative for FH and 19 patients tested positive for FH. Clinical information for audit was available for 59 patients tested negative and for 18 patients tested positive. Overall, we found that 71 patients out of a total of 77 did fulfill the SB's Criteria. 92% did meet the SB criteria for total cholesterol. We found that mostly there was no significant difference between the 2 outcome groups. The biggest differentiator was having a family history of MI in first degree relative below the age of 60. 46% of those tested positive had such a family history compared to 30% in those tested negative. Other criteria used for referral were Xanthelasma and other family history of MI. 19 out of 59 of those tested negative had other family history of CVD not in-keeping with SB, with 4 having this as the only referral criterion alongside high cholesterol. In conclusion, SB criteria were met in 92% of cases. The biggest factor with higher predictive value for a positive genetic test for FH was a family history of MI in first degree relative below the age of 60.

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P081

A re-audit on treatment outcomes of patients with acromegaly in the sussex pituitary multidisciplinary team

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This study aimed to re-audit the surgical and medical treatment of acromegalic patients in the Sussex Pituitary Multidisciplinary Team (MDT). This involved assessing biochemical control and treatment complication rates. The study compared treatment outcomes with previous 2010 audits and national published standards. Fourty patients (25 males, aged between 23 and 79 years at diagnosis) were identified from East Sussex as being treated for acromegaly between 2010 and 2016. Data collection involved accessing patients' notes and hospital electronic information systems; this included diagnosis date, symptoms, Growth Hormone (GH) and Insulin Growth Factor-1 (IGF-1) values, imaging and surgical, medical and radiotherapy outcomes. Data was recorded on the UK Acromegaly Register proforma and analysed using Excel 2016. Macroadenomas were more common than microadenomas (32 vs 7 respectively). Surgery was first-line treatment for 75% of patients and at least 3 months' post-surgery, 48.6% ($n=18$) were biochemically controlled. The surgical success rate for obtaining full biochemical control (both normal GH and IGF-1) for microadenomas, intrasellar and extrasellar macroadenomas were 60, 41.7 and 15% respectively. For medically treated patients, 36.4% ($n=8$) were biochemically controlled with Somatostatin analogues contributing to 50% of this. 60% ($n=6$) of radiotherapy patients were biochemically controlled at some point with 3 patients achieving this without concurrent medication. In conclusion, current clinical practice adheres to 2014 guidelines. There was an improvement in full biochemical surgical success rates from previous 2010 audits by 500% for extrasellar macroadenomas. Medical and radiotherapy outcomes were similar to 2010 audits. Nonetheless improvement areas were identified which includes regular post-op biochemical tests. Results were given to the Sussex Pituitary MDT to improve service provision and the national acromegaly database.

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P082

ICP based approach to DKA management improves performance

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Prompt, effective and safe management of Diabetic Ketoacidosis (DKA) is key to reducing mortality rate and length of stay. An Integrated care pathway (ICP) Pro-forma for DKA management during the first 24 hrs, based on a modified JBDS guideline was introduced in the trust. DKA management based on the pro-forma between Nov 17 to Feb 18 was audited; focussing on fluid management in terms of timing and electrolyte replacement, CBG monitoring, faster senior reviews, HDU admissions and other criteria assessed like checking HbA1c, post treatment insulin counselling and considering Psychological assessment. The audit data was compared to those done in 2007 and 2009–2010, when the pro-forma was not available. A sample size of $N=5$ was included in the audit for that period, with patients who did not fulfil all criteria for DKA being excluded.

Results

Showed all IV fluid administration meeting guidelines compared to 83% in 2010, 70% in 2007. Prescribing of Dextrose to cover potential Hypoglycemia was 100% compared to 90% in 2010 and 50% in 2007. All CBG monitoring met guidelines compared to 86% in 2010, 0% in 2007. No delay in assessments (>1 hour) compared to 20% in 2007 and no HDU admissions compared to 20% in 2010 and 2007. 80% received Insulin counseling, 20% had Psychological assessment considered but none had HbA1c checked during admission.

Conclusion

An overall improvement in meeting all clinical target areas was noted, highlighting the efficacy of introducing the ICP on improving care and safety. Areas needing improvement like HbA1c measurement was also noted. Aim is to re-Audit DKA management on a quarterly basis to sustain improvement.

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P083

Evaluation of quality of care provided to patients with Turner syndrome (TS) cared for by the University Hospitals of Leicester NHS Trust

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Background

TS, resulting from partial or complete loss of an X-chromosome, is a rare diagnosis[1]. In addition to its well-described phenotypic features[2], a number of multi-systemic conditions may develop over the lifespan of a Turner female that require long-term surveillance which is challenging to deliver in today's 'specialised' services NHS.

Aim

To evaluate UHL service provision against the only guidelines for the care of girls and women with TS published recently[3].

Methods

Retrospective analysis of comprehensive data collected from various sources for each patient held within the hospital, from 1991 to December 2017. The information collected includes demographic data, clinical features at presentation, karyotype, specialised care input in the areas of paediatric and adult endocrinology (including growth and puberty), cardiology, fertility and pregnancy, otorhinolaryngology, ophthalmology, dermatology, bone health, and others as recommended in the guidelines[3].

Results

Seventy patients have been identified on initial screening and data analysis is ongoing. Interim analysis shows that care is better when diagnosis is established in early life than in adulthood, when standards of care are variable depending on the speciality a TS woman presents to. Early trends indicate relatively better capture of demographic data, biochemical screening of thyroid disorder, initial cardiac and renal imaging, and management of short stature and puberty compared to deficient care in the remaining aspects of the recommendations.

Discussion

A multidisciplinary team approach is essential for early recognition and appropriate management of systemic disorders to enable each TS woman to achieve good quality of life. With this work we hope to build links with all the specialities to deliver good standard of care to every woman with TS.

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Diabetes & Cardiovascular

P084

Differential regulation of urinary peptides between men and women at early stages of diabetic nephropathy

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Background
There are differences in the development of diabetic nephropathy (DN) between men and women but the underlying molecular mechanisms are unknown. The urinary proteome may contain sex-specific biomarkers and thereby identify differentially regulated pathways to DN in men and women.
Method
Urine samples were obtained from 157 patients with type 2 diabetes (age, 61 (29–71) years; 120 men and 37 women), preserved renal function (eGFR, 88 $\pm$ 17 ml/min) and microalbuminuria (UAER, 85 [34;194] mg/24hrs). Peptidomic analysis was undertaken using capillary electrophoresis coupled to mass spectrometry. We compared individual urinary peptides between men and women.
Results
We detected 4914 individual peptides across all samples. Sex-specific differences were seen in expression of 343 (Chi squared, $P < 0.05$); with 86 and 257 peptides more common in men and women respectively. We then performed quantitative analysis of 196 peptides that were found in at least 25% of male or female subjects. Of these, 165 peptides were significantly (Mann-Whitney U-test, $P < 0.05$) differently expressed in urine; eight of these displayed a 10-fold difference between sexes at significance level of <0.001. Sex was the strongest determinant of abundance after adjustment for age, eGFR and UAER. In men, presence of Peptide 186095 was associated with lower UAER ($P < 0.001$), in women this was the case for Peptide 187114 ($P = 0.024$).
Conclusions
Of 4914 urinary peptides, 196 exhibit sex-specific regulation in a cohort of patients with early DN. Specific peptides are associated with albuminuria in men and women. These are derived from collagen alpha 1; alpha 1 antitrypsin; and membrane associated progesterone receptor component 1. Biological activity and predictive value of these peptides are unknown. Exploration of larger datasets is required to confirm these results and determine whether sex-specific regulation of urinary peptides explains differences in DN progression.

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P085

Canagliflozin attenuates the progression of atherosclerosis and inflammation process in APOE knockout mice

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Sodium glucose co-transporter2 (SGLT2) inhibitors reduce the incidence of cardiovascular events in patients with Type 2 Diabetes Mellitus (T2DM) based on the results of recent cardiovascular outcome studies. Herein, we investigated the effects of long-term treatment with canagliflozin on biochemical and immunohistochemical markers related to atherosclerosis and atherosclerosis development in the aorta of Apolipoprotein E knockout (Apo-$E^{(-/-)}$) mice. After 5 weeks of intervention, animals were sacrificed, and heart and aorta root sections were incubated with primary antibodies against MCP-1, CD68, a-smooth muscle actin, MMP-2, MMP-9, TIMP-1 and TIMP-2. Histomorphometry and immunohistochemistry were carried out while q-PCR experiments were performed to quantify mRNA expression. Canagliflozin-group had lower total-cholesterol, triglycerides and glucose levels ($P<0.01$), while heart rate was significantly lower ($P<0.05$). Histomorphometry revealed that one in seven Cana-group mice versus four in six control mice developed atheromatosis, while aortic root plaque was significantly less, and collagen was 1.6 times more intense in Canagliflozin-group suggesting increased plaque stability. Immunohistochemistry revealed that MCP-1 was significantly less expressed ($P<0.05$) in the aortic root of Canagliflozin-group treated mice while reduced expression of a-actin and CD68 was not reaching significance ($P=0.15$). VCAM-1 and MCP-1 mRNA levels were lower ($P=0.02$ and $P=0.07$, respectively), while TIMP-1/MMP-2 ratio expression was higher in Canagliflozin-group trending towards statistical significance ($P=0.07$). Canagliflozin attenuates the progression of atherosclerosis, reducing i) hyperlipidemia and hyperglycemia, and ii) inflammatory process, by lowering the expression of inflammatory molecules such as MCP-1 and VCAM-1. Moreover, Canagliflozin was found to increase the atherosclerotic plaque stability via increasing TIMP-1/MMP-2 ratio expression.

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P086

The role of dietary protein intake on glycaemic variables in a young healthy south-asian population at risk of type 2 diabetes

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Background
Existing interventional trials show high dietary protein intake can reduce glycaemia in type 2 diabetic (T2DM) individuals. At present, there is limited data on this relationship in a young, healthy population at risk of T2DM. This study investigates the association of animal and plant-based dietary protein intake on fasting blood glucose (FBG) and 2-hour oral glucose tolerance test (OGTT) concentrations in a young South-Asian population at high-risk of type 2 diabetes.
Methods
A post-hoc analysis of a randomised controlled trial of 1250 South-Asian participants aged <18 assigned to intensive (3-monthly, $n=573$) or control (12-monthly, $n=677$) lifestyle modification. Median follow-up was 3 years, with participants annually self-reporting dietary data using a food-frequency questionnaire. Total protein indices and plant-protein ratios were calculated for each participant. Pearson's correlation and multiple linear regression models, including age, gender, change of waist circumference, and change in physical activity assessed relationships between protein intake and i) FBG and ii) 2-hour post-OGTT blood glucose.
Results
Total protein intake was significantly positively correlated to FBG in year 3 ($r=0.059$, $P=0.042$), but significantly negatively correlated with OGTT in year 4 ($r=-0.119$, $P=0.001$). Between baseline and trial completion, total protein (animal and plant-based) was neither significantly related to changes in FBG ($\beta=-0.025$, $P=0.56$) nor changes in OGTT ($\beta=-0.0015$, $P=0.72$). Changes in plant protein ratio were neither significantly related to changes in FBG ($\beta=-0.026$, $P=0.54$) nor changes in OGTT ($\beta=-0.030$, $P=0.48$).
Conclusion
Total protein intake was weakly positively correlated with FBG, contrasting the negative correlation seen with OGTT in years 3 and 4, but overall regression found non-significant relationships. Furthermore, total protein intake in this population was low and despite multiple regression accounting for key confounders, recommendations from these findings are at present limited.

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P087

Electronic inpatient diabetes referrals in a university teaching hospital – A glasgow experience

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Background
People with diabetes account for 15–20% of total inpatients in Scottish hospitals. Provision of specialised diabetes care is integral in minimising length of stay and diabetes-related complications in such patients. Consequently, inpatient diabetes teams have been implemented throughout the UK as recommended by the Joint British Diabetes Societies.
Methods
The amalgamation of several Glasgow hospitals into a single large teaching hospital, the Queen Elizabeth University Hospital, permitted the establishment of a new inpatient diabetes service and the integration of electronic diabetes inpatient referrals. We conducted an analysis of electronic diabetes inpatient referrals made via the Trakcare patient management system in October 2017 ($n=143$), which replaced an email-based system. We assessed patient diabetes subtype, referral reason and location. Lastly, we analysed the total number of referrals made ($n=2034$) in the 1-year period following the introduction of this referral process (May 2017–May 2018).
Results
The majority of referrals were made for people with type 2 diabetes (58.7%), compared to type 1 diabetes (36.8%) and 'steroid induced diabetes' (4.9%). The most common reason for referral was hyperglycaemia (27%), followed by patient education (15%), diabetic ketoacidosis (12%) and hypoglycaemia (11%). Referral issues were resolved within the same day in 59.1% of cases, however, 20.8% of patients were referred more than once per month. 40% of referrals were made from general medical wards, 10% arose from admission units and 7% from critical care. After 1 year the number of referrals per month increased from 105 to 194, compared to ~50 referrals per month observed when emails were utilised.
Conclusion
Engagement with the integrated electronic diabetes inpatient referral system has been excellent. The significant increase in referrals demonstrates the previously unmet need for specialist inpatient diabetes input and care, and highlights the impact of electronic referral systems upon local diabetes service provision.

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P088

Assessment of liver imaging in a diabetic population with an abnormal AST-to-platelet-ratio-index (APRI) or Fibrosis-4-score (FIB4)

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We conducted a retrospective study examining the prevalence of abnormal liver function tests (LFTs) in a diabetic population attending a tertiary referral centre and APRI and FIB4 scores were also calculated where possible. APRI and FIB4 scores can be used to estimate degree of liver fibrosis. APRI score >1 has 76% sensitivity, 72% specificity for predicting cirrhosis. APRI score >0.7 has 77% sensitivity, 72% specificity for predicting significant fibrosis. A FIB4 score >3.25 has 97% specificity and 65% positive predictive value for advanced fibrosis. However these have not been validated in a diabetic population. Of 1777 patients 600 (33.76%) had at least one abnormal LFT. APRI and FIB4 scores could not be calculated in 734 (41.31%). Of the remaining 1043 (58.69%), 31 (2.97%) had an APRI score >0.7, 18 (1.73%) ≥ 1. Of these 31, 22 had recent liver imaging performed. 3 (13.6%) of these were reported normal, 2 (9.1%) as mild fatty change and 17 (77.3%) as fibrotic change or cirrhosis. 265 (25.41%) had a FIB4 ≥ 1.45 and <3.25, and 18 (1.73%) ≥ 3.25. Of these 18 patients, 12 had recent liver imaging. 4 (33%) were reported normal, 1 (8.3%) showed metastases and 7 (58.3%) showed fibrosis or cirrhosis. This study shows that APRI may have a role in screening patients with diabetes for significant fibrosis or cirrhosis. However it does not indicate the aetiology of liver disease and so these results should be interpreted in correlation with a full clinical history and exam. Some studies also suggest that abnormal LFTs are a poor indicator for non-alcoholic steatohepatitis. For the 734 patients where APRI and FIB4 could not be calculated, this was due to a platelet count being unavailable and so a full blood count would be required to be added to routine diabetic bloods to utilise these scores.

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P089

Comparison of the impact of camel milk and cow milk on blood glucose, insulin and GLP1 in healthy individuals

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Background
Interest is rising in the use of traditional food as potential treatments for diabetes. In some arid regions camel milk is believed to have special health promoting properties. Some studies have linked consumption of camel milk to diabetes prevention in addition to describing hypoglycaemic effects in those with diabetes. The potential mechanism is incompletely understood.
Aims
To investigate the impact on glucose metabolism after a mixed meal of a camel milk preload compared to an isocaloric cow's milk preload.
Methods
In a randomised, double-blinded crossover design, eight healthy volunteers were allocated to receive 300 kcal pre-load of cow milk or camel milk ten minutes prior to ingestion of a 500 kcal protein and glucose mixed meal. Samples for glucose, insulin and GLP-1 were taken at intervals over 3 hours.
Results
Peak mean glucose was 6.24 ($\pm$0.28) mmol/l at 25 minutes for camel milk and 6.92 ($\pm$0.47) mmol/l at 20 minutes for cow milk. Peak mean insulin concentration was 577.4 ($\pm$64.6) pmol/l in the camel milk group at 30 minutes and 771.9 ($\pm$124.6) pmol/l at 35 minutes in the cow milk group. The area under the curve (AUC) of the time courses of glucose and insulin did not differ between the groups ($P=0.48$ and $P=0.32$ respectively). GLP-1 activity peaked at 25 minutes in both camel and cow milk (59.06 ($\pm$4.8) pmol/l and 51.07 ($\pm$6.8) pmol/l) with no significant difference in AUC ($P=0.16$).
Conclusions
In this single meal study, although a camel milk preload produced flattening of the post prandial glucose and insulin curve compared to cow milk this was not statistically significant. However, the degree of variability in response to the two milks suggests individual factors may predict a beneficial response to dietary supplementation with camel milk.

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P090

Patients with diabetes are at no greater risk for contrast induced nephropathy than those without diabetes?

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Introduction
Contrast-induced nephropathy (CIN) is an important cause of acute kidney injury (AKI) in inpatients. However, the prevalence and predisposing factors for CIN remain poorly documented. The aim of this study was to investigate the association between CIN, kidney function and diabetic status in inpatients.
Methods
We identified inpatients who received IV contrast prior to a computed tomography (CT) scan between July 2012 to March 2018 at Austin Health, Melbourne. Our study was restricted to patients $>$ 54 years as all patients above this age who have a HbA1c measurement when admitted to our hospital as part of the Diabetes Discovery Initiative. Outpatients, patients $<$54 years, patients who had multiple CT scans with IV contrast and patients with a baseline estimated Glomerular Filtration Rate (eGFR) $<$30 ml/min per 1.73 m^2 were excluded. We obtained creatinine measurements at baseline and 48 hours post contrast administration and defined CIN as an absolute rise in creatinine of $\geq$44 mmol/l. Patients were divided into those with and without a history of diabetes and/or those with renal impairment (defined as an eGFR $<$ or $\geq$60/ml/min per 1.73 m^2). Firth logistic regression model was used for data analysis.

Results
Out of 1280 patients, 28.75% had a history of diabetes and 29.53% had baseline eGFR of <60/ml/min per 1.73 m^2 and 70.47% has baseline eGR of ≥ 60/ml/min per 1.73 m^2. The overall prevalence of CIN was 3.2%. Pre-existing diabetes, degree of glycaemic control (assessed by admission HbA1c) or presence of renal impairment was not associated with an in increased risk of developing CIN.
Conclusion
Patients with or without diabetes who had a CT scan with IV contrast had a similar risk for the development of CIN after adjusting for other variables. It is possible a larger data set may yield different outcomes.

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P091

Glycaemic control in group 2 license holders with diabetes mellitus

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Background
Diabetes is a metabolic disorder characterized by chronic hyperglycaemia as a result of defective insulin secretion, insulin action or a combination. Poor glycaemic control increases the risk of microvascular and macrovascular complications. For group two driving license holders with diabetes there are specific requirements set out by the Driver and Vehicle Licensing Agency. It is therefore hypothesised that this patient group is likely to aim for less tight glycaemic control to avoid hypoglycaemia due to the socioeconomic implications of losing their license.
Aims
This project aims to assess glycaemic control in patients with diabetes who are group two license holders. A further aim is to assess the associated complications and episodes of hypoglycaemia.
Methods
Patient records were reviewed and patients with diabetes in possession of a group 2 license identified. Data regarding glycaemic control and associated complications was collected from SCI Diabetes with any further information obtained from clinic letters.
Results
Thirteen patients were identified as holding a group two license. Seven patients had type 1 diabetes and six type two. Average HbA1c (mmol/mol) at the last clinic visit was 70.6 and the average over the preceding 5 years 77.4. The average duration of diabetes was 11.1 years. Eye disease was the most frequent complication. No patients had a severe episode of hypoglycaemia in the preceding 12 months. One patient had impaired hypoglycaemic awareness and a small proportion of patients (23%) had had their license revoked.
Conclusion/Discussion
Diabetic patients who are group two license holders have poorer glycaemic control than the target set by national guidelines. This may be related to the importance of avoiding hypoglycaemia in order to retain their license. To the best of our knowledge this is the first study in the UK to examine glycaemic control and associated complications in this patient group.

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P092

Metformin use and vitamin B12 deficiency

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Incidence of Type II Diabetes Mellitus (T2DM) is increasing; majority of which is managed in primary care. NICE recommends starting Metformin as a first-line therapy. Studies have linked Metformin use with Vitamin B12 deficiency and suggest that regular monitoring of levels is warranted. The pathogenesis is not fully understood. Literature suggests that the risk of developing B12 deficiency is greatly influenced by high doses and long duration of therapy. An audit was conducted at Hucknall Road Medical Centre in Nottingham, to determine whether GPs are checking serum B12 level in patients on Metformin. The first phase of the audit concluded that 64% of patients have not had their Vitamin B12 tested. The first phase revealed that 6.4% of the patients were already deficient and on replacement injections while on Metformin. The second phase of the audit determined whether patients would comply if invited to have their Vitamin B12 tested. Second phase showed 72.2% compliance and the rate of Vitamin B12 deficiency was 6% in those tested. Overall, phase 1 and phase 2 combined showed that 9.6% diabetics on Metformin were Vitamin B12 deficient. The British Society of Haematology recommends that B12 levels are checked when there is clinical suspicion of deficiency in patients. However, peripheral neuropathy caused by Diabetes and B12 deficiency is irreversible therefore it may be too late if checked when symptoms develop. The prevalence of Vitamin B12 deficiency among Metformin-treated patients ranges between 5.8% and 52%. A study concluded that patients on long-term Metformin are twice as likely to develop peripheral neuropathy compared to those on other anti-diabetic regimes. There are no guidelines to clarify the surveillance of Vitamin B12 while on Metformin. The work has led to change in practice at the medical centre, whereby patients will have their B12 checked on the annual diabetic check.

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P093

Clinical characteristics of men and women attending a secondary care diabetic nephropathy service

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Background
Evidence suggests sex-specific differences in the development and progression of diabetic nephropathy (DN). Men and women have been shown to respond differently to certain therapies and epidemiological data suggest underuse of statins and renin-angiotensin system (RAS) blocking agents in women. We evaluated our local practice to identify differences in clinical characteristics and prescribing between men and women with DN.
Methods
Clinical data were collected from electronic medical records and the Scottish national diabetes registry for patients who attended the diabetes renal clinic at Stobhill Hospital between January and April 2018.
Results
Data were available for 180 patients (age 65 ± 12 years; 59% male). 33 patients (18%) had a diagnosis of type 1 diabetes while 142 (79%) had type 2 diabetes. Median diabetes duration was 18 ± 9 years. Comparison between males and females showed that HbA1c (69 ± 16 vs 69 ± 22, $P=0.730$); blood pressure (SBP 140 ± 19 vs 139 ± 19, $P=0.549$); eGFR (38 ± 21 vs 38 ± 22 ml/min/1.73m^2, $P=0.991$); and albumin: creatinine ratio (39 [0.5–957] vs 13.3 [0.3–805] mg/mmol, $P=0.089$) were not significantly different. Rates of type 1 diabetes were also similar between groups (19% men, 15% women). There were no differences in prescribing of statin (91 [86%] vs 60 [81%], $P=0.197$) or RAS blockade (67 [63%] vs 44 [60%], $P=0.518$) between men and women. However, despite higher BMI in women (34.5 ± 7.6 vs 31.5 ± 5.3 kg/m^2, $P=0.013$) significantly fewer were on metformin (15 [20%] vs 37 [55%], $P=0.029$).
Conclusion
In our local population glycaemic control, blood pressure and renal parameters were similar between men and women with DN. In addition we saw no difference in prescribing of cardiovascular protective agents. However, despite higher BMI there are less women treated with metformin. The reasons for this are unclear and it remains to be seen whether prescribing patterns translate into different trajectories of DN progression between sexes.

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P094

Diabetes related distress in a Nigerian Tertiary Hospital: A preliminary report

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Introduction
The prevalence of diabetes continues to increase worldwide. Diabetes distress (DD) defined as patient concerns about disease management, support, emotional burden, and access to care. It is distinct from depression.
Aim
To document the prevalence of Diabetes related distress.
Objectives
1. Determine the level of distress among the study population.

2. Determine the proportion of those with high distress, moderate distress and those with little or no distress.
3. Determine the relationship between glycaemic control and distress scores.

Methods

A cross-sectional study was conducted from May to June 2018. Data were collected through interview and record review of 50 adults attending the Diabetes Clinic at Federal Medical Centre, Abeokuta, Nigeria. Diabetes Distress Scale-17 (DDS-17) was used to measure Diabetes distress. Initially DDS-2 was used for screening purposes.

Results

The mean age of study participants was 55.16 + 16.87 years. The mean of duration of diabetes was 7.96 + 7.01 years while the mean blood glucose was 119.74 + 40.52 mg/dl. The proportion of diabetes distress among the study population was 30%; 10% had high distress and 20% moderate distress. The remaining 70% had little or no distress. The Mean ± SD of total diabetes distress score was 1.72 ± 0.69. The Mean ± SD for each domain score such as emotional burden, physician related distress, regimen-related distress and interpersonal distress was (2.08 ± 1.13), (1.31 ± 0.49), (1.79 ± 0.82), (1.59 ± 0.97) respectively. Emotional burden was considered as the most important domain in measuring diabetes distress.

Conclusion

Diabetes distress especially emotional burden is a significant health problem among the subjects studied. Careful attention should be paid to this aspect in diabetes care delivery services.

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P095

Hearing impairment in nigerians with type 2 diabetes mellitus attending fmc Lokoja

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Introduction

Diabetes mellitus is a chronic metabolic disease affecting every aspects of human system including the sense organs. Sadly, the prevalence is increasing in Nigeria and currently 5.5%. Hearing impairment (deafness) is public health disease and diabetes mellitus (DM) is a common risk factor.

Objective

To determine the prevalence and severity of deafness among Nigerians with DM attending FMC Lokoja.

Methods

A cross-sectional study where sixty-seven consented persons living with diabetes mellitusparticipated. Demographic data, fasting blood glucose (FBG), history of smoking and alcohol intake, and duration of DM were taken. Deafness was determined by pure tone audiometry. Normal hearing was ≤25 decibel [dB], while deafness was values >25 dB. Mild deafness >25 to 70 dB, moderate, >70 to 90 dB while profound >90 dB. Normal FBG 3.5–6.0 mmol/L, fair control 6.1–6.9 mmol/L and poor ≥7.0 mmol/L.

Results

The sixty-seven participants were 20 men and 47 women. No one smoked cigarette nor drank alcohol. Mean (±SD) FBG was 6.7 ± 2.3 mmol/L in men and 7.4 ± 2.6 mmol/L in women. Participant's blood glucose control was good, fair and poor in 38.8%, 17.9% and 43.3% respectively. The prevalence of deafness was 65.7% on the right ear and 55.2% onthe left. Mild, moderate, severe and profound deafness on the right ear was respectively 32.8%, 28.4%, 3.0% and 1.5% while on the left mild, moderate, severe and profound deafness was respectively 23.9%, 25.4%, 4.5% and 1.5%. The mean (±SD) duration of diabetes in severe deafness on the rightwas 13.0 ± 4.24 and 12.67 ± 3.51 on the left. The duration (years) of DM in diabetic with deafness was statistically significant when compared with fasting BG ($P = 0.001$), deafness on the right ($P = 0.022$) and deafness on the left ($P = 0.002$) [correlation is significant at 0.05 level]

Conclusion

Diabetes mellitus predisposes to deafness and is worsened by the duration of DM, degree of blood glucose control and commoner in right ear.

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P096

Hyperglycaemic emergencies as seen at a tertiary hospital in south western nigeria

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Background and objectives

Hyperglycaemic emergencies (HE) are the most common acute complication of diabetes and are associated with relative or absolute insulin deficiency, volume depletion, impaired mental status and metabolic derangements. Hyperglycaemic emergencies are associated with high morbidity and mortality if not properly managed. We investigated the pattern of hyperglycaemic emergencies at Obafemi Awolowo University Teaching Hospital, Ile-Ife, South-western Nigeria.

Subjects, materials and method

The study population were adult patients who presented to the accident and emergency unit of the hospital with features of hyperglycaemic emergency. The participants were selected using non-probability sampling technique. The information obtained included socio-demographic, clinical and laboratory data. Data was analyzed using SPSS version 22.0

Result

A total of 67 patients who fulfilled the criteria for hyperglycaemic emergency participated in the study. Their mean age was 53.6 (12.6) years. About 60% of the patients were 50 years and above. Female constituted 53.7% of the study population. About 38.8% were newly diagnosed diabetics. Precipitating factors were identified in 80.6% of the subjects and the commonest precipitating factor was infection. Majority of the study population (49.3%) presented with features of hyperglycaemic hyperosmolar state (HHS), 28.4% had normo-osmolar non-ketotic hyperglycaemic state (NNHS), 16.4% had diabetic ketoacidosis (DKA) and 6% had Mixed HHS-DKA.

Conclusion

Hyperglycaemic hyperosmolar state was the most common form of hyperglycaemic emergency seen in this study. HE occurred commonly among previously and newly diagnosed diabetics. A holistic approach is recommended to prevent HE in our practice environment.

Keywords: Hyperglycaemic emergency, Diabetes mellitus, Presentation.

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Frequency and predictors of sexual dysfunctions among male Nigerians with diabetes mellitus (A Preliminary report)

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Introduction

Evaluation of sexual function is an integral part of general assessment of people with diabetes mellitus but this is rarely done. These comprises hypoactive sexual desire, erectile dysfunction (ED) and ejaculatory disorders. Presence of any of this will negatively impact on the sexual life of female partners.

Objectives

To determine the frequency and determinants of sexual dysfunction among male patients with type 2 diabetes mellitus (T2DM).

Methods

Cross sectional study carried out among consenting T2DM patients attendingdiabetes clinic using IIEF questionnaire. Anthropometric, clinical and biochemical parameters were obtained. Data was analyzed using SPSS version 20.

Results

Sixty-five male consenting T2DM were analysed. The mean age of the participants was 58.6 ± 12.3 years with duration for DM ranged from one to fifty years. 63.1% had both T2DM and hypertension while 33.8% had only DM. 44.6% were overweight and only 24.6% were on diuretics. Mean HbA1cand FBS values were 7.4 ± 2.1% and 118 ± 30 mg/dl respectively. The prevalence of hypoactive sexual desire is 78.4% while ED was 67.7% (38.6% had severe erectile dysfunction). 46.1% had ejaculatory disorders. Only 44.6% and 49.3% had intercourse satisfaction and overall sexual satisfaction respectively. There were significant association between advancing age, duration of DM and ED.

Discussion
All the domains of sexual function were affected with hypoactive sexual desire being more frequent. Though predictors such as age, duration of DM and glycaemic controls affects ED, lack of sexual drive and ejaculatory problems could impact negatively on their female partners. This could lead to friction in relationships and eventually lack of social support needed by persons with DM.
Conclusion
Focus on all aspect of sexual function in term of counselling and active treatment of affected individuals will probably improve quality of care for persons with DM.
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Audit of gestational diabetes in a District General Hospital
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Background
Upto 5% of women will develop diabetes in pregnancy, which is increasing as a result of higher rates of obesity and older age. Diabetes in pregnancy is related increased risk to the mother and to the foetus.
Aims
To assess the management of diabetes in pregnancy and monitor outcomes.
Methods
This was a retrospective study that included 92 pregnant females, who were diagnosed with gestational diabetes following and oral glucose tolerance test. Patients were seen weekly initially by the diabetologist, diabetes specialist nurse, diabetes midwife and obstetrician.
Results
Of the 92 women included in the study only 5 had babies weighing more than 4000 grams and 2 women suffered from mild pre-eclampsia. 52% of women were obese (BMI >30) and 31% were overweight. There was a correlation between mothers' BMI and baby weight. Of the 92 patients, 52% were Caucasian and 42% south Asians. Treatment: 28% were managed on diet, 42% with metformin, 3% on insulin and 20% on insulin and metformin. Mean fasting blood glucose before commencing treatment was 5.01 mmol/l and this reduced to 4.96, 4.71 and 4.67 mmol/l over the next few weeks. Mean blood glucose 1 hour after breakfast was 6.81 and this reduced to 6.74, 6.48 and 6.43 mmol/mol over the next few weeks.
Conclusion
Increased incidence of GDM in south Asian population. However outcomes for mother and baby were favourable in both groups. Frequent monitoring can improve outcomes in pregnant women diagnosed with diabetes in pregnancy.
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Glucocorticoids promote mitochondrial fatty acid oxidation in fetal cardiomyocytes
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The late gestation increase in glucocorticoid action promotes the structural and functional maturation of the fetal heart. Metabolic maturation of cardiomyocytes involves a switch from glucose utilization as a fuel source to fatty acid (FA) oxidation. In fetal cardiomyocytes, glucocorticoids induce expression of PGC1a (a master regulator of mitochondrial capacity), lipin1 and KLF15 (genes involved in FA oxidation). We hypothesized that glucocorticoids promote the metabolic switch to FA oxidation during cardiomyocyte maturation. Isolated embryonic day 14.5–15.5 mouse fetal cardiomyocytes were were pre-treated with the glucocorticoid receptor antagonist RU486, or vehicle for 30 mins prior to treatment with dexamethasone (dex) or vehicle for 24 h. A Seahorse XF Analyzer was used to measure glycolysis and mitochondrial respiration. Palmitate was used to measure FA oxidation; with etomoxir to block mitochondrial FA uptake. Mitochondria were stained with Mitotracker-deep red FM and size measured using MitoGraphTo measure mitophagy, fetal cardiomyocytes were isolated from MitoQC miceand the increase in red puncta after exposure to vehicle, dex or DFP (positive control) was analysed. Fetal cardiomyocytes exhibited little dependence on glycolysis and this was unaltered by dex treatment. With palmitate, dex treatment increased basal respiration rate (517.9 ± 48.0 versus 366.7 ± 71 pmol/min/protein, mean $\pm$ SD, $n=5$) and oxygen consumption (related to ATP production, 159.5 ± 62.8 versus 297.9 ± 35.5 pmol/min/protein, mean $\pm$ SD, $n=5$) compared to vehicle. Etomoxir and RU486 inhibited these dex-dependent increases. No overt changes in mitochondrial phenotype were observed between dex and vehicle treated cells. Mitophagy was unaltered by dex up to 45 h post-treatment. These data support a glucocorticoid-induced switch in substrate preference towards fatty acid oxidation in fetal cardiomyocytes. The mechanism for this involves neither a general increase in mitochondrial volume nor mitochondrial remodeling. Further investigations will identify dex-regulated pathways leading to increased fatty acid oxidation.
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P100

Glucocorticoid receptor deficiency alters cardiomyocyte DNA replication in neonatal mice
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During early life, the majority of cardiomyocytes exit the cell cycle and undergo terminal differentiation, becoming binucleated. This establishes the number of cardiomyocytes for the remainder of the lifetime, with subsequent consequences for cardiac resilience in adulthood. Activation of the glucocorticoid receptor (GR) is important for heart maturation: fetal mice lacking GR in cardiomyocytes (SMGRKO) show structural and functional cardiac immaturity. Young adult male and female SMGRKO mice have heavier hearts but similar cardiomyocyte size compared to littermate controls suggesting that SMGRKO mice have more cardiomyocytes. We hypothesized that cessation of cardiomyocyte proliferation and subsequent binucleation will be delayed in neonatal SMGRKO mice, contributing to increased cardiomyocyte endowment. DNA replication, a marker of both proliferation and binucleation, was measured by incorporation of EdU, a thymidine analogue. Neonatal SMGRKO mice and littermate controls were injected with EdU (50mg/g bw) 4h prior to euthanasia at postnatal (P) days 2, 4, 7 or 10. Hearts were fixed, embedded, sectioned and immuno-stained for cardiac troponin and EdU. Nuclei were counter-stained with DAPI. The percentage of EdU-positive cardiomyocytes was measured. SMGRKO mice exhibited a different profile of DNA replication compared to controls. The percentage of EdU-positive cardiomyocytes was similar in both genotypes at P2, lower in SMGRKO mice at P4 (14.0 ± 1.9 versus $11.4 \pm 1.6\%$, mean $\pm$ SD, $n=8$) and higher at P7 ($3.7 \pm 0.7\%$ v $6.0 \pm 1.1\%$, $n=7$–11) with a trend towards greater DNA replication at P10. Mice lacking GR in cardiomyocytes show an altered pattern of DNA replication in the neonatal period, with elevated DNA replication during the later neonatal period. This suggests altered cardiomyocyte proliferation and/or binucleation, with delayed terminal differentiation of cardiomyocytes in the absence of GR. Future studies will compare the time course of binucleation in SMGRKO and control animals.
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Characterisation of diabetes mellitus in turner syndrome – Turner syndrome life course project
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Introduction
Diabetes Mellitus (DM) is 2–4 times more common in Turner Syndrome (TS) than karyotype normal females. Diagnosis of DM in TS is usually based on age of presentation and insulin dependency without regard for DM- autoimmunity. Previous research has identified DM associations with the isochromosome and ring chromosome. However, only small numbers of diabetics have been included in reports so far. Here we present preliminary data on DM characterisation in TS.
Methods
Anthropometrics, body fat by impedance, fasting blood glucose and insulin were taken from diabetics. The following DM related autoantibodies tested were; GAD, IA-2, ZnT8. Duration of diabetes ranged from 1–14.7 years.

Results
There was no significant difference in karyotype distribution between those with DM and those without. Results are summarised in Table 1 *$=P\leq0.05$. Raised BMI was the only significant factor associated with DM.
Conclusions
This is the first study to explore DM specific autoantibodies in TS in detail. So far the data does not indicate the same autoimmune profile found in Type 1 DM. Similar to the general population obesity, characterised by an BMI and waist circumference, was identified as a risk factor of type 2 diabetes for women with TS.

Table 1

	TS without Diabetes ($n=27$)	TS with Diabetes ($n=13$)
Age	31.3	37.6
Weight (kg)	56.1	69.2*
BMI	25.8	31.4*
Waist Circumference (cm)	84.8	101.1*
Total Body Fat (%)	26.1	33.9
Fasting insulin	7.1	9
Fasting glucose	4.6	9*
GAD	0/27	2/13
IA2	1/27	1/13
ZnT8	1/27	1/13

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Skin-endocrine regulation of whole-body metabolism
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The inflammatory skin disease psoriasis is an independent risk-factor for development of insulin resistance. However, the underlying mechanisms remain poorly elucidated. We used human and mouse models of psoriasis to investigate a potential endocrine role of the skin in regulating subcutaneous adipose tissue (sAT) and pancreatic islet function. Mice were administered a daily topical dose (75 mg) of imiquimod (IMQ), or Vaseline control, to a shaved dorsal region for 4 days. IPGTT were conducted to assess glucose tolerance and insulin secretion *in vivo*; skin, sAT and whole pancreas were collected on day 5 for further analysis. Human explant skin was treated with IMQ to induce a psoriasis-like phenotype and cultured for 24h. Conditioned media (CM) was collected, diluted 1:1 with fresh media and used to treat human explant sAT or mouse islets (24h). These experiments were also conducted using CM obtained from culturing IMQ-mouse skin. IMQ induced an inflammatory phenotype in human and mouse skin compared to controls. IMQ-mice displayed increased inflammation and decreased GLUT4 in sAT, indicative of sAT insulin resistance, whilst fed serum insulin levels were elevated (1.44 ± 0.23 ng/ml vs 0.47 ± 0.15 ng/ml, $n=12$–14; $P<0.01$). However, IMQ-mice displayed improved glucose tolerance and increased glucose-stimulated insulin secretion (GSIS) and c-peptide secretion together with increased Ki67$^+$ beta-cells (1.46 ± 0.19 vs 0.52 ± 0.10, $n=3$–4; $P<0.001$). In support of a direct endocrine role of the skin, incubation of human or mouse sAT with IMQ-skin CM (obtained from human or mouse skin) also led to increased inflammation and reduced GLUT4 expression in sAT. Incubation of mouse islets with human IMQ-skin CM increased GSIS, indicative of islet compensation to insulin resistance. These findings show that skin inflammation induces sAT insulin resistance and increased pancreatic islet function, *in vivo* and *ex vivo,* likely via the effects of skin-derived factors.

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Development of a Novel Estrogen Metabolite LC-MS/MS Assay: Influence of 16αOHE2 in Pulmonary Arterial Hypertension
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Pulmonary arterial hypertension (PAH) is a devastating disease characterised by increased pulmonary arterial pressures due to clustered proliferation of cells within the vessel. Untreated this leads to right heart failure and premature death. PAH predominates in females implicating sex hormones, in particular estrogenic metabolites, as being key in the progression of PAH phenotypes. We hypothesised that hydroxy and methoxy estrogens, with known proliferative and anti-proliferative properties, may be involved in endothelial dysfunction in PAH. This may be mediated by dysfunctional signalling via the aryl hydrocarbon receptor (*AhR*) which modifies cytochrome P4501A1 and 1B1 expression (enzymes generating estrogenic metabolites). An assay to measure estradiol metabolites, as their methylpiperazine derivatives in plasma was developed using liquid chromatography tandem mass spectrometry. E2 metabolites were recovered from plasma using solid phase extraction, permitting limits of detection of 4.3 pg on column. Screening of plasma (with Ethical approval) detected 16-alpha-hydroxyestradiol (16αOHE2) and 2-methoxyestrone (2MeOE1) in PAH patients but not controls; $n=3$ controls, $n=7$ patients. The effects of 16αOHE2 in the pulmonary circulation were unknown. Proliferation and migration of human control and PAH-derived blood outgrowth endothelial cells (BOECs) were assessed in the presence of 16αOHE2. Redox-dependent signalling was studied using bardoxolone, a nuclear factor erythroid-2-related factor-2 (Nrf-2) activator. 16αOHE2 increased migration of PAH-BOECs which was attenuated by bardoxolone. 16αOHE2 increased proliferation of PAH-BOECs in an AhR/Nrf-2-dependent manner. 16αOHE2 decreased mRNA levels of *AhR in* BOECs to a greater degree cells from PAH patients compared to controls. Metabolite profiling by LC-MS/MS of plasma from patients with PAH identified 16αOHE2 as a novel biomarker of disease. The actions of 16αOHE2 in a primary cell model suggests this metabolite may influence redox-sensitive proliferation and migration of endothelial cells in PAH.

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Glucose regulates miR-184 via AMP-activated protein kinase (AMPK) in pancreatic β-cells
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Introduction
Pancreatic β-cells control glucose homeostasis by secreting insulin in response to high glucose. MiRNAs regulate β-cell function and contribute to β-cell failure in type 2 diabetes. MiR-184 regulates β-cell compensatory expansion during pregnancy and obesity and its expression is reduced by glucose through unknown mechanisms. AMPK is a suggested target of antidiabetic drugs and an important energy sensor. Its β-cell-selective inactivation (βAMPKdKO) impairs β-cell identity, insulin secretion and dysregulates several miRNAs, including miR-184. We hypothesize that AMPK mediates glucose-dependent regulation of miR-184 and aim to identify the underlying mechanisms.
Methods
Control and transgenic animals were fed a chow or a ketogenic (low sugar) diet for 28 days. MiR-184 was measured by RT-qPCR in mouse and human islets. ATAC-seq and ChIP-qPCR with an anti-CTCF antibody were performed in isolated mouse islets.
Results
MiR-184 expression is decreased in mouse and male human islets cultured for 48h at high glucose concentration and its expression increases in human islets treated

with AMPK activators. Islets isolated from mice fed a ketogenic diet present higher levels of miR-184. This effect is not observed when AMPK or its main upstream kinase LKB1 (βLKB1KO) is deleted. MiR-184 primary transcript is reduced in βAMPKdKO islets suggesting that AMPK regulates miR-184 transcription. ATAC-seq data identifies increased chromatin accessibility in two regions upstream *MIR184* in βLKB1KO islets. According to ChIP-qPCR data CTCF bind the most proximal region.

Conclusion

AMPK mediates glucose-dependent down-regulation of miR-184 *in vitro* and *in vivo* possibly contributing to the deleterious effect of hyperglycaemia during diabetes. Our data suggest that AMPK might regulate miR-184 transcription by limiting CTCF binding to *MIR184*. We aim to validate our hypothesis and understand the role of AMPK in the regulation of CTCF activity and its implications in energy homeostasis and diabetes.

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State of glutathione system in patients with type 2 diabetes

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Materials and methods

Included patients were divided into … groups: group 1 – 41 almost healthy person (control group), group 2 – 59 patients with prediabetes, group 3 – 41 patients with T2D, group 4 – 40 patients with T2D and CHD and group 5 – 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 3,4, and 5 ($P<0.05$). 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 impaired carbohydrate metabolism.

Table 1

Findings	Group 1	Group 2	Group 3	Group 4	Group 5
GP	44.38 (34.14;55.73)	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	0.98 (0.76;1.09)	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	2.53 (2.29;3.15)	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	0,36 (0.34;0.38)	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	7.03 (6.73;8.29)	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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Bright and specific far-red labels for visualizing endogenous glucagon-like peptide-1 receptors

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The glucagon-like peptide-1 receptor (GLP-1R) is a G protein-coupled receptor (GPCR) expressed in various tissues such as brain and pancreas where it contributes to the regulation of energy expenditure and metabolism. Due to its involvement in glucose-dependent release of insulin from pancreatic beta cells, the GLP-1R has become a blockbuster target for the treatment of type 2 diabetes. Despite this, debate still exists about the exact distribution of the GLP-1R throughout the body, particularly at the protein level. Present approaches are limited by lack of antibodies against various GLP-1R epitopes, use of fluorescent agonists that induce internalization/degradation, poor signal or binding, and the requirement for fixed tissue. Here, we installed a Cy5 moiety onto the *C*-terminus of Exendin4(9-39) to produce a far-red fluorescent GLP-1R antagonist label, termed **LUXendin**. As expected, **LUXendin** was unable to generate cAMP in CHO-SNAP_GLP-1R cells unless the positive allosteric modulator BETP was co-applied. **LUXendin** strongly bound YFP-AD293-SNAP_GLP-1R but not YFP-AD293 cells with a $B_{max}=50$ nM. At the same concentration, **LUXendin** produced intense membrane labelling in MIN6 beta cells and primary islets, with penetration in the latter approaching >100 μm imaged using conventional confocal microscopy. Again, no internalization of the GLP-1R was detected unless BETP was co-applied to allosterically activate the receptor. Co-staining for insulin, glucagon and somatostatin in **LUXendin**-treated islets revealed widespread GLP-1R expression. FACS analysis of islets from Ins1Cre;mTmG$^{flox'd}$ reporter mice demonstrated **LUXendin** staining in $\sim$90% of non-beta cells, in contrast to transcriptomic and antibody studies where *Glp1-r*/GLP-1R was found to be almost absent in alpha cells (but abundant in delta cells). Thus, bright and highly specific antagonist labels allow sensitive detection and visualization of low levels of endogenous GLP-1R, with broad applicability to other GPCRs.

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Anacardium occidentale upregulates GLP-I and Insulin Gene Expression in Normoglycemic Rats

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Anacardium occidentale is a multi-purpose tree of the anacardae family with great economic and medicinal value. The leaf of the tree has been reported to possess hypoglycaemic and anti-diabetic properties. However, literature is devoid of any molecular basis for the potent effects observed. This study evaluated the molecular mechanisms underlying the efficacy and safety of the leaves by investigating glucagon-like peptide 1, insulin and kidney injury molecule genes using beta actin as the control for gene expression. Normoglycaemic Wistar rats were separated experimental and control groups. Experimental rats were fed 30% feed formulation of *A. occidentale* leaf powder while control rats were fed ordinary rat chow. Feeding occurred *ad libitum* over a period of three days after which the rats were fasted overnight and sacrificed the following day. The pancreas, kidney and intestinal crypts were excised for molecular studies. *A. occidentale* fed rats showed 18.9% increase in insulin and 50% in GLP-1 compared to control rats. There was no significant difference in Kim-1 expression compared to control ($P<0.05$). These results shed light on the molecular basis of the well reported anti-diabetic potency of *A. occidentale* and its low toxicity to the kidney.

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P108

Nrf2 mediated protection against hypoglycaemia induced cognitive deficits in type 1 diabetes

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Background
Hypoglycaemia in Type 1 diabetes (T1D) and type 2 diabetes is associated with long-term cognitive dysfunction. We have previously demonstrated that recurrent hypoglycaemia (RH) in a rodent model of T1D induces oxidative stress and inflammation in the hippocampus, associated with impaired cognitive function. This study sought to investigate whether pre-treatment with a potent inducer of the antioxidant response would ameliorate these cognitive deficits.
Methods
A chronic stable model of chronic insulin-treated TD1 was achieved using streptozotocin (125 mg/kg i.p) and insulin implants (Linbit®). Diabetic (male C57bl6 mice $n=8$–10/group) mice were randomly allocated to one of 3 groups: (i) T1D, (ii) T1D + RH, (iii) T1D + RH + AO and subjected to repeated episodes of insulin-induced hypoglycemia (3 episodes per week for 4 weeks). Sulforaphane(50 mg/kg i.p.) or Vehicle (1% DMSO/PBS) was administered 24hr prior to each hypoglycaemic episode. Cognition was subsequently assessed by novel object recognition (NOR) and spontaneous alternation tasks.
Results
Pre-treatment with the antioxidant had no impact upon body weight ($P=$ns) or fasting blood glucose ($P=$ns). In contrast HbA1c levels were significantly lower in SFN treated animals ($P<0.01$). Furthermore, SFN significantly improved cognitive performance in the 24hr NOR task ($P<0.01$) and the spontaneous alternation task ($P<0.01$) when compared to those receiving vehicle.
Conclusions
Treatment with the SFN significantly improves RH induced cognitive impairments in a rodent model of T1D. These improvements were associated with a significant improvement in HbA1c levels. Therefore, activation of antioxidant pathways offer a novel therapeutic target for the treatment of cognitive impairments associated with RH in T1D.

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Activation of the adhesion GPCR GPR56 by a synthetic tethered agonist improvesislet β-cell function

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GPR56 is an adhesion G-protein coupled receptor (GPCR), which we have shown to be the most abundant GPCR in mouse and human islets. The extracellular N-terminal domain of adhesion GPCRs contains a tethered agonist, buried within the GPCR autoproteolysis-inducing domain. Synthetic peptides mimicking tethered agonist sequences can activate a variety of adhesion GPCRs including GPR56. Here we investigated the effect of a GPR56 tethered agonist peptide, P7, on β-cell function. A stable GPR56KO MIN6 β-cell line, in which GPR56 had been deleted, was established by CRISPR-Cas9 technology and GPR56 deletion was confirmed by Sanger sequencing and Western blotting. Administration of P7 significantly increased intracellular calcium in native MIN6 β-cells, as measured by single cell calcium microfluorimetry, while this effect was lost in GPR56KO MIN6 β-cells (basal to peak ratio; native β-cells, 2 mM glucose: 0.02 ± 0.01, +P7: 0.13 ± 0.01, $n=3$, $P<0.01$; GPR56KO β-cells, 2mM glucose: 0.01 ± 0.003, +P7: 0.02 ± 0.001, $P>0.2$). In addition, P7 protected mouse islets and native MIN6 β-cells from cytokine-induced apoptosis, as assessed by luminescent quantification of caspase 3/7 activities, but it did not reduce apoptosis in GPR56KO MIN6 β-cells (% relative to maximum cytokine-induced apoptosis: mouse islets, +P7: $34\pm4.6\%$, $P<0.0001$; native β-cells, +P7: $87\pm4.2\%$, $P<0.01$; GPR56KO β-cells, +P7: $105\pm5.4\%$, $P>0.1$). P7 also potentiated glucose induced insulin secretion from human islets (2.32 ± 0.72 fold, $P<0.05$). These studies indicate that P7-induced activation of GPR56 stimulates insulin secretion and protects β-cells from apoptosis, and this could have implications in developing novel therapies for type 2 diabetes.

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P110

Prevalence of Kock's diseases among diabetes patient attending state Specialist Hosital Akure South West Nigeria

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Background
Diabetes mellitus (DM), which is on the increase in developing country like Nigeria, increases the risk of tuberculosis (TB). This study was carried out to detect TB in DM patient attending medical outpatient unit in State Specialist Hospital, Akure South West, Nigeria.
Method
This was a cross-sectional study in which six hundred and forty eight DM patients attending the outpatient clinic were consecutively recruited after an informed consent were taken between January and June 2018. History of Cough and anthropometric parameters were obtained. Fasting blood glucose were done. Those with positive history of cough were screened for Tuberculosis using gene expert.
Results
Of the six hundred and forty eight patient recruited for the study, four hundred and forty one (68.1%) were females and two hundred and seven were male (31.9%). Age range is 22–72 years. Thirty six (36) patients with DM had history of cough, of which three were gene expert positive representing 8.3% of those with cough.
Conclusion
Routine screening of DM patient for communicable diseases like tuberculosis could prevent transmission of, and early detection of tuberculosis in DM patient, allowing for early treatment and reduction in mortality.

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Neoplasia, Cancer & Late Effects

P111

Cholesterol metabolism and chemo-resistance in breast cancer

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Breast cancer (BCa) patients who present at clinic with elevated circulating LDL-cholesterol have poor prognosis, whilst pharmacological and lifestyle interventions that lower circulating cholesterol (statins, exercise, low saturated fat intake etc.) are associated with better treatment efficacy. The molecular mechanisms that link cholesterol with chemotherapy resistance (CR) remain unexplored. Hydroxycholesterols (OHCs) activate the transcription factor LXR, and are formed in the liver from cholesterol during bile acids synthesis, or in macrophages, fibroblasts and adipocytes at extra-hepatic sites. Here we explore the hypothesis that hydroxycholesterols induce chemotherapy resistance through activation of non-canonical LXR target genes. The promoters of a panel of chemotherapy resistance genes were assessed for LXR occupancy (LXR-ChIP-Seq) and their expression correlated with LXR expression (BCa RNA-Seq). LXR-specific activation of candidate LXR-regulated chemoresistance markers was confirmed in a panel of BCa cell lines exposed to LXR agonists (hydroxycholesterols and synthetic ligands), and an antagonist (GSK2033) using qPCR. Utilising the natural fluorescence of the BCa chemotherapy agent Epirubicin, we found pre-treatment of BCa cell cultures with LXR agonists enhanced intracellular drug efflux (non-linear curve fitting: $P<0.0001$). Epirubicin cytotoxicity was impaired by LXR activation in colony forming assays (one-tailed t-test MDAMB231: $P=0.0049$; MDAMB468: $P=0.0051$; MCF7: $P=0.0092$); LXR antagonists reversed these affects. Finally we measured endogenous hydroxycholesterol concentrations in the tumours of 28 BCa patients using LC-MS/MS. We observed high intra-tumour variance in OHC concentration, presumably reflecting differences in tumour invasion of OHC synthesising macrophages, fibroblasts and/or adipocytes. Our data support the hypothesis that elevated LDL-C may drive innate chemotherapy resistance in breast tumours through LXR-mediated induction of chemotherapy efflux pumps. This molecular mechanisms represents a metabolic legion that is targetable through existing pharmacological

and lifestyle interventions which could allow patients a route to modify the efficacy of their chemotherapy.

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P112

Use of glucocorticoids following immunotherapy for cancer

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Background
Immune checkpoint inhibitors have demonstrated significant advances in the treatment of several cancers including metastatic melanoma. However, they are frequently associated with immune-related adverse events which often require treatment with prolonged courses of glucocorticoids. Long-term glucocorticoid use is associated with several side effects including hyperglycaemia.
Aims
1) To determine the prevalence of glucocorticoid use in patients treated with immune checkpoint inhibitors for melanoma.
2) To determine the cumulative dose and duration of glucocorticoid (as prednisolone equivalent) given to patients for treatment of immune-related adverse events.
3) To determine the prevalence of new onset hyperglycaemia in patients treated with glucocorticoids.
Methods
Retrospective review of patients with advanced melanoma treated with an immune checkpoint inhibitor between September 2010 and January 2017 at the Royal Marsden Hospital, London. The electronic patient record was used to identify patients treated with glucocorticoids, to determine the cumulative dose and duration of glucocorticoid treatment and to determine the number of patients developing new onset hyperglycaemia.
Results
412 patients received immune checkpoint therapy, with 157 (38%) requiring glucocorticoids to treat immune-related adverse events. The median cumulative glucocorticoid dose was 2795 mg (prednisolone equivalent) with a median duration of 61 days. After excluding patients with pre-existing diabetes, 20% of patients receiving glucocorticoids were noted to develop new onset hyperglycaemia. A statistically significant difference was found in the median cumulative dose and duration of glucocorticoid treatment between patients who developed new onset hyperglycaemia and those who did not ($P < 0.0001$).
Conclusions
Immune-related adverse events frequently occur in patients treated with immune checkpoint inhibitors. Consequently, patients typically receive high doses of glucocorticoids for prolonged durations, often resulting in glucocorticoid-induced hyperglycaemia. Given the doses used, many will also be at risk of adrenal suppression. Endocrinologists therefore need to be aware of these emerging indications for prolonged glucocorticoid treatment in the oncology setting.

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P113

Very long term follow up of patients treated for childhood leukaemia – a single centre experience

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Introduction
Cure rate of childhood cancer is a medical success story. However >50% of patients have long term consequences of their cancer treatment. We reviewed data on very long term childhood leukaemia follow-up patients at our institution.
Methods
We reviewed electronic patient records for 39 patients (23 female, 16 male; 38-ALL, 1-AML). Multiple chemotherapy regimes were used-low use of anthracyclines/alkylating agents apart from BMT group who received cyclophosphamide. Radiotherapy (RT) divided into Low dose (LD:18-24Gy), high dose (HD:24Gy), Bone marrow transplant (BMT: additional 14.4Gy).
Results
Length of follow up:RT:median 39 years (range 27-47); BMT: median 21 years (range 8-42). 12/39 patients had end of treatment summaries in EPR.
Employment: Professional: 11/39; other: 12/39; unemployed:5/39; no data 11/39.
Endocrine replacements: GH deficiency: 15/39. Dynamic testing: 11/39 of whom 0/11 patients cortisol <400 nmol/l (28.3±6.8 yrs after RT); 4/11 GH <3 mcg/L (35±1.7 yrs after treatment). Hormones replaced: GH-5/39; E2/testosterone-10/39; Thyroxine-9/39 (unclear if primary or secondary), hydrocortisone-1/39. 6/39 patients had primary gonadal insufficiency-all BMT group. 2 patients had a documented diagnosis of T2DM.
DXA: osteopenia:8/39, osteoporosis:1/39, no data:14/39
Echocardiogram: ejection fraction >55% ($n=28/39$), 35–55%* ($n=2/39$ (BMT; P 0.017), no data-9/39
Lipids: non-fasting cholesterol >5 mmol/l ($n=24/39$), no data-($n=4/39$)
Second tumours/diagnoses: Meningioma-10; cavernoma-4, breast cancer-1, follicular thyroid cancer-1, papillary thyroid cancer-1, sarcoma-1, CVA-1, osteonecrosis-1, epilepsy-3 (number having MRI not documented).
Mental health/neurocognitive issues: Qualitative statements describing low mood, lack of ability to work, memory loss, fatigue.
Discussion
There is a significant impact of RT on pituitary dysfunction apart from ACTH. There is a significant impact on mental health, neurocognitive function, second brain tumours, lipid profile and employment. We should be robust about assessments, documentation and use these data to devise services which meet our patients needs. This review also demonstrates how historical data is lost with moves towards EPR.

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P114

The analytical validation and clinical implications of introducing a chromogranin A referral service within Scotland

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Background
Chromogranin A is an acidic 48 kDa glycoprotein originating from the chromaffin granules of most neuroendocrine cell types. In health chromogranin A is released as a pro-hormone together with other peptide hormones in response to stimulation. In disease larger quantities of Chromogranin A are produced by neuroendocrine derived tumours thus allowing its use as a tumour marker. Due to the different clinical scenarios for measuring Chromogranin A requesting practices within Scotland vary considerably. Currently labs in Scotland either send samples for a single chromogranin A measurement in London, Manchester or Sheffield or a combined gut hormone profile in London.
Method
The CisBio ELISA chromogranin A method was validated to assess linearity, lower limit of sensitivity, imprecision and accuracy. Paired serum samples were collected from 100 patients who were also having a full gut hormone profile measured at Charing Cross in London. The serum samples were analysed using the CisBio ELISA chromogranin A method and compared to the results from Charing Cross. External quality control samples ($n=20$) from the IMMQAS chromogranin A pilot scheme were analysed and compared to both the method mean and other assays.
Results
Validation proved the assay had a sensitivity of 15 ng/L, samples diluted linearly, the imprecision was ≤10% across the linear range and the assay showed no consistent bias when compared to the NEQAS method mean. The patient comparison with the Charing Cross assay showed 78% consensus.
Conclusion
The CisBio chromogranin A ELISA has performed well analytically and has the sensitivity, linear range and precision required for a tumour marker assay. Comparison data shows the assay is of equal clinical utility to the assay offered by the main referral laboratory. Therefore, the CisBio chromogranin A assay has the potential to improve comparability, cost effectiveness and sample turnaround times for patients in Scotland.

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P115

Could this be the tip of the iceberg? Endocrine dysfunction of immune checkpoint inhibitors in Kent Regional Oncology Service

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Aim
Baseline clinical and biochemical endocrine assessment at the start of immune checkpoint treatment and each treatment cycle is important given the treatable

nature of it. Also given the improvements in survival of these patients necessitate further longterm screening. Our study was to look at various aspects of this screening with a view to improve our knowledge and also patient care.
Methods
Using an excel database, a retrospective data collection was performed for 31 patients receiving Ipilimumab and/or Pembrolizumab between 1st January 2016 and 30th September 2016 in Kent. We looked to see if tests for endocrine dysfunction (TSH, FT4, 9 am cortisol, pituitary functions) were carried out on a 3 weekly basis as per local guidelines and the outcomes of these results for 39 weeks following administration of the immune checkpoint inhibitor.
Outcomes/results
25.81% of the patients developed endocrine complications following immune checkpoint therapy and the onset varied between 3 weeks and 36 weeks after the commencement. None of the patients with an endocrine abnormality underwent pituitary imaging and only 2 in 8 of the patients who developed an endocrine abnormality were referred to an endocrine team.
Conclusion
A high prevalence of endocrine dysfunction indicates the need for collaboration between the oncologists and endocrinologists with robust guidelines to be adhered to when prescribing an immune checkpoint inhibitor. If abnormalities are detected, a full pituitary screening (biochemistry and imaging) should be undertaken. The follow up period for endocrine function after administration of immune checkpoint inhibitors needs to be extended globally to at least 36 weeks.

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P116

TNFα regulates oestrogen uptake and metabolism in colorectal cancer

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Oestrogens impact colorectal cancer (CRC) development and proliferation. Biologically active oestrogens, oestrone (E_1) and oestradiol (E_2), are metabolised through hydrolysis of their sulfated forms (oestrone sulfate (E_1S) and oestradiol sulfate) by steroid sulfatase (STS). We have shown that increased STS activity drives CRC proliferation via oestrogen hydrolysis. We have also identified that CRC expresses the necessary organic anion transporter polypeptides (OATPs) for sulfated oestrogen uptake. However, what regulates STS activity and OATPs expression in CRC is poorly understood. In breast and prostate cancer inflammatory mediators, such as TNFα, increase STS activity. Therefore, we hypothesised that inflammatory mediators regulate STS activity and OATPs expression in CRC. To test this, we calculated correlation coefficients between inflammatory mediators (TNFα, IL6, IL8) and STS and OATP expression in human colon adenocarcinoma (COAD) RNA-Seq data ($n=440$) from The Cancer Genome Atlas (TCGA). We also tested how inflammation effects STS activity, OATP expression, and E_1S uptake in CRC cells. Analysis of COAD data demonstrated a positive correlation between TNFα and OATP2B1 expression ($r=0.32$, $P<0.0001$) suggesting TNFα upregulates OATP2B1 in CRC. No correlations were observed between other inflammatory mediators and OATP expression. When examined in vitro, TNFα significantly upregulated OATP2B1 mRNA and protein expression in HCT116 cells, and E_1S uptake was also significantly increased from 26.78 pmol/mg to 35.01 pmol/mg. While IL6 and IL8 had no effect on STS activity, 20 ng/ml and 40 ng/ml TNFα significantly increased STS activity from 7.02 pmol/mg/h to 40.21 pmol/mg/h ($P<0.05$) and 57.24 pmol/mg/h ($P<0.001$) respectively in HCT116 cells. These novel findings show that in CRC TNFα increases both the uptake of E_1S via OATP2B1 and its subsequent hydrolysis by STS. Coupled with our previous findings where increased STS activity results in greater CRC proliferation, this data suggests TNFα is an important regulator of oestrogen uptake and metabolism.

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P117

Epigenetic inhibitor treatment reduces proliferation via induction of apoptosis in a human typical bronchial carcinoid cell line

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Neuroendocrine tumours (NETs), occurring at multiple sites including the pancreas, lung and pituitary, are increasing in incidence and usually present at an advanced metastatic stage, and current medical treatments have limited efficacy. Epigenetic modifiers are promising new drugs, as mutations in the multiple endocrine neoplasia type 1 (*MEN1)* gene, encoding the histone methyltransferase MLL1 interacting protein, menin, are known to cause both familial and sporadic NETs. Moreover, pancreatic and pituitary NETs frequently have mutations of chromatin remodelling genes, and alterations in histone modification. In addition, the epigenetic modifier JQ1, a bromo and extra terminal (BET) protein inhibitor that modulates the transcription of growth stimulating genes, is a potent *in vitro* and *in vivo* inhibitor of NET proliferation. An additional 41 compounds interacting with different epigenetic related proteins are now available and could provide improved therapeutic options. We therefore tested their efficacy on proliferation of the pancreatic NET cell line BON-1 and the bronchial typical carcinoid cell line H727. Proliferation was evaluated over five days and compared to JQ1 as positive control, and DMSO treatment as a negative control. GSK-J4, an inhibitor of the KDM6 subfamily of Jumonji demethylases was found to exceed the inhibitory effect of JQ1 in the H727 cell line, significantly reducing proliferation by up to 71% ($P<0.0001$), compared to 56% for JQ1; GSK-J4 did not alter proliferation of BON-1 cells. Further investigation using a dose escalation study, demonstrated that a concentration of 5mM– of GSK-J4 could specifically, and optimally reduce H727 cell proliferation, compared to equivalent treatment with its inactive isomer GSK-J5. In addition, 5-day GSK-J4 treatment significantly increased apoptosis of H727 cells (by 57%, $P<0.05$) compared to GSK-J5 control treatment. Thus, our data shows the first epigenetic modifier that effectively reduces proliferation by induction of apoptosis in a typical bronchial carcinoid cell line.

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P118

The expression pattern of miR-16 in plasma of breast cancer patients attending radiotherapy clinic in luth

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Breast cancer is the most frequent carcinoma in women and its prevalence could be reduced by early detection which can improve the chances of successful treatment and recovery. Post transcriptional genetic modifiers known as microRNAs (miRNAs) are widely believed to play an essential role in many malignancies, acting as either tumor suppressors or oncogenes. Many recent studies on breast cancer have analyzed various miRNAs that may influence breast cancer progression and development. This study aims to determine the expression pattern miR-16 in plasma of breast cancer patients undergoing chemotherapy as against healthy controls. MiRNA was isolated from plasma samples collected from fifty women with breast cancer undergoing radiotherapy and twenty women without breast cancer. Expression levels of miRNA-16 was quantified using the quantitative real time PCR assay. Amongst the cases, there was 1 (2%) stage I patient, 6 (12%) stage II patients, 27 (54%) stage III patients, 16 (32%) Stage IV patients. MiR-16 was higher in the control samples than cases and a progressive increase of miR-16 in the plasma from stage I to stage IV (having Ct values 40.15, 38.63 ± 1.45, 38.04 ± 2.66, 37.45 ± 1.52 from stage I to IV respectively). Triple negative receptor cases showed a greater expression of gene. The pattern observed suggests the action of miR-16 as a tumour suppressor. In conclusion miR-16 may potentially to be used as a prognostic as well as a predictive marker in breast cancer patients.
Keywords: miR-16, Breast cancer, ER, PR, HER 2, Triple negative
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P119

Oncogenic action of pituitary-tumor transforming gene (PBF) in head and neck cancer is associated with poorer overall survival

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PBF is a multifunctional proto-oncogene overexpressed in thyroid and other endocrine cancers. Previously we identified a functional interaction between PBF and the tumour suppressor p53 in well-differentiated thyroid cancer (WDTC).

Here, we delineate the oncogenic mechanisms of PBF, along with its binding partner PTTG, in head and neck cancer (HNSCC), in which TP53 mutations (mutTP53) are common (>50%). HNSCC tissue revealed significant upregulation of PBF and PTTG mRNA (>1.6-fold), which was consistent with a TCGA cohort ($n=520$). Importantly, a panel of 129 p53-target genes showed a more significant correlation with PBF ($P=0.0006$) and PTTG ($P=5.9\times10^{-9}$) expression in TCGA than the background transcriptome ($n=19{,}764$ genes), supporting a functional relationship. In agreement, there were significant mRNA changes in PBF- and PTTG-depleted HNSCC cells for key p53-responsive genes such as BCL2. Co-immunoprecipitation studies confirmed that PBF and PTTG are specific interactors of p53 in HNSCC. PTTG retained the ability to bind p53 in the absence of PBF, but the degree of interaction was significantly attenuated (4-fold) suggesting that PBF facilitates binding of PTTG to p53. Half-life studies showed that PBF and PTTG inhibit p53 stability, with joint over-expression giving the most pronounced decrease (~13-fold). HNSCC TCGA patients with mutTP53 and high PBF/PTTG showed poorer overall survival (median=28.98 months) than those with low PBF/PTTG (median=71.16 months). A significant increase in the incidence of metastatic disease was further evident for wtTP53 HNSCC with high PBF/PTTG expression. In summary, our results indicate that PBF and PTTG functional interaction is not confined to endocrine cancers. HNSCC patients with high tumoural PBF/PTTG have worse outcomes due in part to greater aberration of p53-dependent signalling. These findings may be of relevance to poorly differentiated or anaplastic thyroid cancers which have a higher incidence of TP53 alterations than WDTC.

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P120

Progestins used in menopausal hormone therapy is not a 'one-size-fits-all' for breast cancer risk

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Women worldwide are using progestins in combination with an estrogen to relieve menopausal symptoms. Although the progestin component of menopausal hormone therapies is effective in terms of preventing estrogen-induced endometrial cancer, it has been associated with an increased risk of developing invasive breast cancer. Notably, most studies investigating an association between progestins and breast cancer, have examined older progestins such as medroxyprogesterone acetate, norethisterone and levonorgestrel. Considering that a variety of progestins with distinct structures and functions are available, it is possible that not all progestins increase breast cancer risk. Our study directly compared the effects of selected progestins on the mRNA expression of genes that are markers for specific tumour cell behaviours such as proliferation and apoptosis, and showed that progestins differentially regulate the expression of these genes. Moreover, we investigated the role of signal transduction pathways in progestin-induced regulation of the above-mentioned processes. Specifically, we examined pathways known to play a crucial role in growth, survival and metastasis, such ERK1/2 and JNK. All progestins, except the newer progestin drospirenone (DRSP), increased proliferation and migration of the human T47D breast cancer cell line to the same extent. DRSP was also the only progestin that did not stimulate phosphorylation of the ERK1/2 and JNK pathways in the T47D cells. Moreover, blocking activation of these kinase pathways by highly selective inhibitors prevented the effects all the progestins, except DRSP, on proliferation, apoptosis and migration. These results suggest that activation of the ERK1/2 and JNK pathways may be a mechanism by which the older progestins increase breast cancer risk. Finally, the results also suggest that DRSP may promote breast cancer pathogenesis to a lesser extent that the older progestins used in this study.

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P121

Progestin-induced breast cancer: Identifying the role of progesterone receptor isoforms

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Breast cancer is the most common oncology-related cause of death in women worldwide. The use of progestins in combined hormone replacement therapy (HRT) has been implicated in increasing the risk of developing breast cancer in postmenopausal women. Since various progestins are available for clinical use, all differentiated by structure, it is possible that not all progestins would lead to increased breast cancer risk. Progestins are synthetic ligands of the progesterone receptor (PR), designed to mimic the actions of natural progesterone. Although the PR exists as two isoforms, PR-A and PR-B, studies investigating the role of the PR in breast cancer seldom distinguish between the two isoforms. This is important, as the isoforms are functionally distinct and present in equimolar concentrations in the normal breast, while PR-A is overexpressed in breast cancer. The current study investigated the role of PR-A and PR-B in mediating progestin-induced regulation of genes involved in breast cancer biology, as well as their respective roles in physiological processes involved in breast cancer development and progression. In addition, effects of overexpression of PR-A relative to PR-B on the above-mentioned responses, was also investigated. Results showed differential regulation of genes by progestins via the individual PR isoforms. Moreover, effects on physiological processes such as cell proliferation, apoptosis, migration and invasion were progestin- and isoform-specific. These results not only highlight the importance of studying effects of individual progestins, but also effects via the individual PR isoforms. Moreover, in the presence of most progestins, overexpression of PR-A relative to PR-B inhibited physiological processes involved in breast cancer development and progression, suggesting that enhanced PR-A expression may be a positive prognostic marker for breast cancer.

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P122

The human oestrogen receptor beta variant 5 (ERß5) can alter the oestrogen sensitivity of oestrogen receptor alpha positive endometrial cancer cells

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Endometrial cancer is the most common gynaeological malignancy in the developed world: lifetime exposure to oestrogen is a key risk factor. Oestrogen action is mediated by ligand activated receptors encoded by the *ESR1* (ERα) and *ESR2* (ERß) genes: ERα plays a key role in regulating endometrial cell proliferation. ERß5, is a truncated variant isoform of ERß formed by alternative splicing of *ESR2* that contains a DNA binding domain but lacks the ability to bind E2. ERß5 is expressed in endometrial cancer tissue but its functional impact is unknown. Double fluorescent immunostaining for ERα and ERß5 was performed on sections of endometrial adenocarcinomas recovered from post-menopausal women ($n=271$) undergoing total abdominal hysterectomy. Reproductive cell lines where infected with lentivirus expressing an ERß5 construct to generate cells with altered ratios of ERß5/ERα to examine the functional impact in an ERE reporter assay. A lentivirus YFP-ERß5 construct was used to investigate intra-nuclear mobility (FRAP) in the cell lines. Fluorescent immunohistochemistry detected cells co-expressing ERß5 and ERα in stage I cancers. Co-expression of ERß5 in an $ER\alpha^{pos}$ endometrial cancer cell line (Ishikawa) increased ligand-dependent activation of an ERE-luciferase reporter by the ERα-selective ligand PPT. FRAP analysis of YFP-ERß5 in Ishikawa cells revealed incubation with E2 resulted in a transient reduction in intra-nuclear mobility. In $ER\alpha^{neg}$ MDA breast cancer cells, there was no E2-dependent change in mobility of YFP-ERß5 or activation of the reporter gene. Our results show ERß5 can act as heterodimeric partner to ERα in cells of endometrial stage 1 cancers that may increase their sensitivity to E2. These data suggest immunostaining for ERß5 should be considered in risk assessment of women with stage I endometrial cancers as they could benefit from treatment with drugs that block receptor dimerisation.

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P123

ELL2 and EAF2 co-regulation of AKT in prostate cancer cells

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Elongation factor, RNA polymerase II, 2 (ELL2) is an RNA Pol II elongation factor with functional properties similar to ELL that can interact with the prostate

tumor suppressor ELL-associated factor 2 (EAF2). In murine models, deletion of Ell2 induced prostate intraepithelial neoplasia similar to that induced by deletion of Eaf2. Since ELL2 and EAF2 can functionally interact and appear to have similar function in regulating prostate homeostasis, we investigated the impact of combined deletion of ELL2 and EAF2 in prostate cancer cell lines. Combined deletion of ELL2 and EAF2 did not result in an additive increase in proliferation, invasion or migration in prostate cancer cell lines. Combined knockdown of ELL2 and EAF2 induced an additive increase in p-AKT activation. These results suggest that ELL2 and EAF2 can compensate for each other in the regulation of cellular proliferation, but that they work together to regulate the AKT pathway.

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Neuroendocrinology and Pituitary

P124

A single bolus of the novel kisspeptin analogue, MVT-602, induces a prolonged LH surge compared to kisspeptin-54 during the follicular phase in healthy women

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Background
Kisspeptin-54 (KP54) stimulates hypothalamic GnRH release. The kisspeptin analogue, MVT-602, has a longer half-life ($t_{1/2}$108min) than KP54 ($t_{1/2}$28mins). MVT-602 potently stimulates gonadotrophin release in men. We sought to determine for the first time the effect of MVT-602 on gonadotrophin release in healthy women.
Methods
A two-phase dose-finding study was carried out in 9 healthy women, 18–35 yrs with regular menstrual cycles (mean ± SEM 29.1 ± 0.5days). Phase 1: three women received a subcutaneous injection of KP54 (9.6 nmol/kg), or MVT-602 (0.003, 0.03, 0.1, 0.3, or 1 nmol/kg) during the early follicular phase (days 1–4) of successive menstrual cycles. Serum gonadotrophin levels were measured regularly for 14 hrs, and at 24 hrs and 48 hrs post-injection. Phase 2: six further women received KP54 and MVT-602 (0.01 or 0.03 nmol/kg) with extended blood sampling for 24 hrs. Interventions were compared by one-way ANOVA with post hoc Dunn's test.
Results
Phase 1: Peak mean (± SD) serum LH occurred at 285 ± 41.3mins following KP54, but later following MVT-602 (MVT-602 0.01 nmol/kg: 1098 ± 245.2 mins, MVT-602 0.03 nmol/kg: 1330 ± 58.9mins). Phase 2: Peak serum LH following MVT-602 was similar to KP54 (KP54: 10.4 ± 2.7iU/L; MVT-602 0.01 nmol/kg: 11.1 ± 5.1iU/L; MVT-602 0.03 nmol/kg:12.3 ± 5.8iU/L; $P > 0.05$ vs KP54). MVT-602 0.01 nmol/kg additionally elicited a serum FSH rise 24 hrs post-injection (MVT-602 0.01 nmol/kg: 1.9 ± 1.5 iU/L), sufficient to induce a rise in serum oestradiol 330 ± 127 nmol/L ($P = 0.03$ vs KP54).
Conclusion
MVT-602 resulted in a LH-surge that was of similar amplitude but more prolonged compared to KP54 9.6 nmol/kg. This dose of KP54 safely induces oocyte maturation in IVF treatment. Therefore further studies are indicated to determine if the more prolonged LH surge elicited by MVT-602 delivers therapeutic advantage in the treatment of women with reproductive disorders.

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P125

Anti-*POMC* siRNA reduces ACTH secretion in an *in vitro* model of Cushing's disease

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Context
Cushing's disease (CD) results from the release of high levels of adrenocorticotrophic hormone (ACTH) from a pituitary adenoma. Increased ACTH secretion stimulates excess cortisol production, causing weight gain, hypertension, diabetes and depression. The only curative treatment is transsphenoidal surgery, but the rate of recurrence is high and there is a lack of suitable medical therapies. RNA-interference is a mechanism of post-transcriptional gene silencing that can be utilised to knock-down the expression of specific genes using small interfering RNAs (siRNA). ACTH is encoded by the *POMC* gene, so anti-*POMC* siRNAs might be an effective treatment for CD through silencing *POMC* expression and reducing ACTH secretion.
Methodology
The effectiveness of RNA-interference at reducing *POMC* expression was analysed by transfection of murine AtT-20 cells with three anti-*POMC* siRNAs followed by measurement of extracellular ACTH concentrations by immunoassay. Control transfections were siRNAs with no target sequence and mismatched anti-*POMC* siRNAs. Cell viability was assessed by trypan blue staining. Induction of IFN-α and IFN-β expression by siRNAs was measured in ELISAs.
Results
At 24 h post-transfection, anti-P*OMC* siRNAs at 10 or 30 nM reduced secretion of ACTH by 81-89% compared with untreated cells ($P < 0.001$). Control siRNAs had no effect upon ACTH secretion. Suppression of ACTH secretion was maintained for upto four days post-transfection. Viable cell counts remained equivalent whether cells were transfected or untreated. Anti-*POMC* siRNAs did not induce detectable IFN-α or IFN-β.
Conclusions
The results indicated that anti-*POMC* siRNAs significantly decreased ACTH secretion by AtT-20 cells. Specificity of the anti-*POMC* siRNAs was indicated by the ineffectiveness of anti-*POMC* siRNAs with nucleotide mismatches. ACTH reduction was not caused by adverse effects of the transfection process. Anti-*POMC* siRNAs did not appear to induce an interferon response. RNA-interference by *POMC*-specific siRNAs could be a novel medical therapy for CD.

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P126

Natural history of conservatively managed Rathke's cysts: a retrospective analysis of a single centre experience

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Rathke's cleft cysts (RCC) arise from the embryonic remnants of Rathke's pouch in the anterior pituitary gland. The majority are asymptomatic and incidentally diagnosed when the pituitary is imaged for other reasons. RCCs can progress to requiring surgical intervention for hormonal and structural effects. It is unclear what factors determine RCC enlargement and over what period this occurs, hence need for long term follow-up is uncertain. We analysed our conservatively managed RCCs to determine rates of growth.
Methods
Radiology reports were searched for term 'Rathke'. Patients with conservatively managed RCC, and at least two interval pituitary MRIs were selected. Scans were double reported by two neuroradiologists and cyst dimensions recorded: Anterorposterior-AP; Craniocauda-CC; Lateral-Lat. Comparison was made between the most recent and first scan: increase/decrease in size defined as $\geq/\leq$3mm. Clinical data was retrieved from medical records.
Results
Seventy-four patients (mean follow up 41 months) were identified after excluding those having intervention, co-existing pituitary adenoma and uncertain diagnosis. RCC was diagnosed incidentally in 58% (43/74), through headache investigation in 32% (24/74) and hypogonadotrophic hypogonadism investigation in 8% (6/74). 7% (5/74) had TSH deficiency, 3%(2/74) had ACTH deficiency,3%(2/74) GH deficiency and 5% gonadotrophin deficiency (4/74). In terms of growth, we found that 9.5% (7/74) increased in size (average 4mm at median follow-up 71 months); 18.9% (14/74) decreased in size (average 5mm at median follow-up 34 months); 71.6% (53/74) are stable (median follow up 36 months). Two patients progressed to requiring intervention during this period. There was no predilection for increase in a single cyst dimension.
Conclusion
Conservatively managed RCCs may increase in size and interval imaging is required for monitoring. However, given only 2 patients progressed to requiring intervention and 18.9% actually decreased in size, the health economics and rationale for long term imaging require evaluation.

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P127

Identifying disease causing variants in aryl hydrocarbon receptor-interacting protein (*AIP*) variants and their significance on the clinical phenotypes

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Introduction
Mutations in the aryl hydrocarbon receptor-interaction protein (*AIP*) gene predisposes to growth hormone or prolactin secretin adenomas, usually, manifesting before the age of 30 years old. There are 834 variants of the *AIP* reported in the GnomAD database and over 100 variants have been described in patients with pituitary adenomas. While the pathogenic role of variants resulting in truncated protein is beyond doubt, determination of the clinical relevance of missense variants could be challenging. In this study, we aimed to functionally assess the *AIP* variants identified in pituitary adenoma patients in order to determine their pathogenic role.
Method
Eleven missense and one nonsense, previously not studied *AIP* variants, were transfected into HEK 293 T cells to evaluate protein half-life in cycloheximide chase experiments. AIP protein expression at different time points were studied using western blotting. The results were then correlated with the clinical phenotype.
Results
A quarter of the studied variants showed a significant reduction in AIP protein half-life compared to the wild type. The protein degradation speed (K) of the positive control p.C238Y (0.289 ± 0.087), and the variants p.A277P (0.289 ± 0.087) and p.K241E (0.117 ± 0.022) were significantly higher when compared to the WT (0.021 ± 0.005). Table 1 shows all the variants studied and their clinical data.
Conclusion
Non-truncating variants in *AIP* with shorter half-life are likely to be pathogenic changes, while variants with normal half-life need further studies to determine pathogenicity.

Table 1 Missense variants included in the study.

p.A277P	12y, GH, macroadenoma 14y, ACTH, macroadenoma 39y, prolactinoma	p.R119W	32y, GH
p.R9Q	21y, GH&PRL macroadenoma 53y, 54y and 58y family, GH macroadenoma	p.R188Q	24y, microprolactinoma
p.W168*	14y, GH, macroadenoma	p.K103R	6y, corticotrophinoma
p.E245K	24y, prolactinoma 40, macroprolactinoma	p.D30E	23y, GH
p.K241E	53y, non-functioning pituitary adenoma	p.E319K	11y, GH, macroadenoma
p.R128H	27y, GH, macroadenoma	p.E283Q	71y, lung carcinoma, somatic mutation

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P128

Are silent corticotroph adenomas high risk tumours for recurrence? Systematic review and meta-analysis

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Introduction
The 2017 WHO Classification of Pituitary Tumors grades silent corticotroph adenomas (SCAs) as high-risk adenomas due to their aggressive clinical behaviour (high probability of recurrence). Nonetheless, studies comparing recurrence rates of SCA with other non-functioning pituitary adenomas (NFPAs) subtypes have provided conflicting results necessitating review of the evidence this recommendation relies on.
Aims
To estimate recurrence rates of SCAs following primary treatment (surgery $\pm$ radiotherapy) and recurrence rate ratios (RRR) between SCAs and other NFPA subtypes by performing a systematic review and meta-analysis of relevant published studies.
Methods
Extensive literature search of Medline, Embase and Cochrane Library up to October 31, 2017 was conducted. Recurrence rates, effect size (ES), RRRs and 95% confidence intervals (CIs) were estimated from each study and pooled using random effects meta-analysis model.
Results
For determination of SCAs recurrence rates, 15 observational studies of low risk of bias including 310 patients were finally selected. Overall, recurrence rate of SCAs was 5.69 (95% CI, 4.1–7.49) per 100 person-years. In studies with mean follow-up <5 or ≥ 5 years, 25% (ES 0.25;95% CI, 0.13–0.38) and 31% (ES 0.31; 95% CI, 0.23–0.39) of the patients had recurrence, respectively. Recurrence rate after surgery alone was 5.41 (95% CI, 4.1–7.49) cases per 100 person-years and after surgery + radiotherapy 4.88 (95% CI, 0.67–11.54) cases per 100 person-years. For RRR determination, 10 observational studies of moderate risk of bias including 244 SCA and 1622 NFPA patients were selected. RRR between these two groups was not significant (1.44; 95% CI, 0.9–2.33, $P=0.13$). Focus on tumours treated solely by surgery also revealed no significant RRR (1.17; 95% CI, 0.79–1.75, $P=0.429$).
Conclusions
RRR estimation which takes into account length of follow-up has not confirmed higher probability of SCA recurrence compared with other NFPA subtypes necessitating further methodologically robust studies to support the 2017 WHO recommendation.

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P129

The Utility of the high dose Short Synacthen test in pituitary patients who failed the ITT but have a low pre-test likelihood of ACTH deficiency

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The Insulin tolerance test (ITT) is regarded as the gold-standard for diagnosing ACTH deficiency but some normal subjects do not exhibit an adequate cortisol response to hypoglycaemia. Identification of false fail cases in pituitary patients is important so as to avoid unnecessary treatment with glucocorticoids. Two hundred consecutive ITTs in pituitary patients were analysed. Twenty six (13 males) failed the ITT and subsequently have a Short Synacthen test (SST). 20 patients were deemed to have a low likelihood of ACTH deficiency (basal am cortisol $>$ 200 nmol/l or peak cortisol response to ITT $>$ 400 nmol/l, or otherwise normal remaining pituitary axes). Using modern cortisol immunoassays, a cut-off of 450 nmol/l was regarded as a normal response to both ITT and SST. 17/26 patients (65.3%) failed the ITT but passed the SST. The positive predictive value (PPV) for passing the SST when the patient had an am cortisol of $>$ 200 nmol/l or a peak cortisol response to ITT of $>$ 400 nmol/l was 70% (95% CI 58–80%) and 77% (95% CI 55–91%) respectively. Patients with a normal SST were taken off hydrocortisone and none developed an adrenal crisis or convincing hypoadrenal symptoms (median follow-up 27 months, IQR 5–37). A high percentage of patients who fail the ITT but have an am cortisol of $>$ 200 nmol/l or peak response to hypoglycaemia of $>$ 400 nmol/l will pass the SST. These patients should be retested using the SST before committing them to life-long treatment with glucocorticoids.

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P130

Measuring of information transfer via gonadotropin-releasing hormone receptors (GnRHR) shows a remarkable loss of information through signalling

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Gonadotropin-releasing hormone (GnRH) is a hypothalamic neuropeptide that acts via GnRHR on the pituitary gonadotrope. It is secreted in pulses and acts via GnRHR to activate ERK and Nuclear Factor of Activated T-cells (NFAT), mediating GnRH effects on gonadotropin expression. We monitor their activation by high content imaging (fluorescence staining for ppERK and nuclear translocation of an NFAT1c-EFP reporter) in fixed LbT2 gonadotroph cells. Single cell measures reveal high cell-cell heterogeneity, and information theoretical approaches can be used to explore its influence on information transfer. Here we use Mutual information (MI) between GnRH concentration and measured responses (I(response; GnRH)) to measure (in Bits) information transfer via GnRHR. One bit of information can resolve two different signal values. However, the MI values were always <1Bit despite 3Bit input. Joint sensing of ERK and NFAT increased MI values, but the increase was modest, suggesting that, by ignoring response dynamics, information transfer is underestimated. Therefore, using live cell measurements and MI calculations taking response trajectory into account, NFAT-EFP translocation was tracked in response to a single pulse of GnRH. The I(NFAT-NF; GnRH) was 0.4Bit at 30min and increased to 0.54 Bit by consideration of trajectories. We also tracked NFAT-EFP translocation responses in cells receiving two pulses of GnRH and found that the information gained from the second pulse was little. Similar experiments were performed using Fluo-4 measurements of $[Ca^{2+}]_i$. The I(Ca^{2+}; GnRH) was 0.8Bit, 24sec after stimulation, and increased to 1Bit by sensing trajectories. Thus, LbT2 cells are unreliable sensors of GnRH concentration because a considerable amount of information is lost through signalling. Although joint sensing, trajectory sensing and sensing repeated pulses increased information transfer, this was typically $<20\%$ suggesting that most information is lost early in the GnRH signalling cascade, prior to Ca^{2+} mobilisation.

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P131

The importance of achieving disease control in Acromegaly: a retrospective single centre analysis

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Aim
Acromegaly is associated with higher mortality and morbidity, and achieving disease control can be challenging. The aim of this study was to assess the morbidity and mortality associated with active acromegaly compared to patients in whom disease control was achieved.
Methods
Retrospective analysis of all patients treated with acromegaly at a university hospital between 1948 and 2014 was performed. Mortality rates and development of new cardiovascular morbidity (CVE) (diabetes, hypertension, strokes, myocardial infarction or cardiac failure) were assessed. Number of various treatment modalities including medical therapy (somatostatin analogues, dopamine agonist, pegvisomant) was assessed. All GH values were converted to mcg/l; IgF-1 was not included due to limited availability of data.
Results
Of the 167 patients included, 116 achieved disease control with treatment. Comparing patients achieving control of acromegaly vs patients who did not achieve control, baseline parameters at diagnosis were (p value not significant unless specified): age 47.5 vs 53.9, ($P<0.005$), GH 16.6 vs 28.6 ($P<0.05$), proportion with pituitary axes failure 9.5% vs 16%, proportion with macroadenomas 78.5% vs 82%, $P<0.0001$, CVE 33.6% vs 36%. Total period of follow up was 163 vs 102 months ($P<0.05$). During follow up: number of treatment modalities used 2.25 vs 1.8, proportion of patients with new pituitary axes failure 38.8% vs 32%, number of failed axes 1.8 vs 1.5 and new CVE 33.6% vs 36%. Duration to develop CVE was 144 vs 69 months ($P<0.05$). Mortality rates were lower in cohort who achieved disease control (30.2% vs 64%, $P<0.0001$).
Conclusion
The group failing to achieve acromegaly disease control had higher GH at diagnosis, had macroadenomas and were older. Despite aggressive treatment approach in this group, disease control was challenging. Increased GH exposure contributes to earlier development of CVE and higher mortality rates and therefore it is important to offer such patients additional treatments.

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P132

Cannulated prolactin is useful to confirm hyperprolactinemia and to minimize inappropriate imaging

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Background
Current Endocrine Society guideline recommends a single prolactin level to confirm the diagnosis of hyperprolactinemia. This may lead to over diagnosis and inappropriate imaging. Our institution protocol is to repeat the prolactin and measure macroprolactin. If the second prolactin is elevated, then a cannulated prolactin to role out venipuncture stress effect is undertaken.
Methods
Data were collected for 49 patients between January 2017 to May 2018. After cannula insertion, prolactin is measured at 0, 60 and 120 minutes. Normalization is defined as prolactin drop to normal range.
Results
Mean age was 33.4 years (S.D. $\pm$9.9), 44(90%) were female. The presenting symptoms were menstrual irregularities in 28.57% and galactorrhoea in 12.24%, and the rest include fatigue, hirsutism and acne. Overall, mean referral prolactin was 1214.8 milliunit/l (S.D. $\pm$677.8) and mean second prolactin was 940 milliunit/l (S.D. $\pm$590.3). The cannulated prolactin normalized in 19 (38.8%) patients. Mean second prolactin was 516.4 milliunit/l (S.D. $\pm$235.1) in patients who normalized in cannulated prolactin vs 1195 milliunit/l (S.D. $\pm$594.7) in those patients who did not subsequently normalize ($P<0.0001$). MRI pituitary findings were available for 26/30 patients who did not normalize; 22/26 (84.6%) showed abnormality and four showed normal imaging. Majority of the findings were microadenoma (18/22). Among patients who normalized in cannulated prolactin, four had normal MRI pituitary before referral. In multilogistic regression including age, gender, referral and repeated prolactin, repeated prolactin was the only significant predictor for normalization of cannulated prolactin ($P<0.008$).
Conclusion
Cannulated prolactin was useful in excluding true hyperprolactinemia in 38.8% of patients with confirmed second elevated prolactin. This confirms that cannulated prolactin results could avoid over diagnosis and unnecessary imaging.

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P133

Characterisation of paediatric craniopharyngiomas in a single centre study – analysis of factors affecting recurrence rates

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Craniopharyngioma is a rare benign pituitary tumour that occurs in children and adults. Recurrence rates are high (up to 90%) but factors underpinning this are unclear, particularly in cases of childhood onset. We aimed to investigate factors that may influence subsequent recurrence rates in childhood onset craniopharyngiomas in patients attending our centre. A retrospective study of patients followed up at the Oxford Late Effects of Childhood Cancer service was conducted. Patient records were studied and information on clinical variables, the primary tumour and recurrence extracted. Patients were grouped according to their surgical treatment (subtotal resection, transsphenoidal aspiration or fenestration), radiotherapy modality and dosimetry and radiotherapy fractions as well as subsequent growth hormone replacement therapy, tumour histology and post-surgical endocrinopathies. Fisher's exact test was used to analyse recurrence rates. Twenty one patients were identified who had been followed up for up to 31 years (median of 15 years). This patient population was characterised across a range of variables. Notably, all tumours had adaminitomous histology, and all patients suffered from panhypopituitism post-surgery. There was a trend towards improved outcome with combined surgery and radiotherapy compared to surgery alone but this did not reach robust levels of statistical significance ($P=0.101$). No statistically significant association was found between any of the surgical treatments and recurrence rates ($P=0.595$). Furthermore, no statistically significant association was found between growth hormone replacement therapy and recurrence rates ($P=0.100$). This is one of the largest single centre reports on childhood onset craniopharyngiomas from the UK. Our data again demonstrate that Growth Hormone therapy is safe in this patient population. Factors influencing recurrence rates in childhood onset craniopharyngiomas are elusive,

though further work constructing a multi-centre population could show effects which this is not powered to demonstrate. Understanding craniopharyngioma recurrence is vital to improve treatment decisions and patient quality of life.

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P134

Prolactin as a surrogate marker of prolactinoma diagnosis in PCOS

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Background
To identify a serum prolactin (PRL) cut-off value indicative of a PRL-producing adenoma in women with polycystic ovarian syndrome (PCOS) and hyperprolactinaemia and characterize such patients. Materials and methods: In the present retrospective case–control study, the medical records of 528 PCOS women were reviewed. Pituitary magnetic resonance imaging (MRI) was performed in PCOS patients with PRL levels $\geq$94.0 ng/ml and/or symptoms suspicious of a pituitary adenoma (PA). Prolactinoma diagnosis was made in the presence of an MRI-identifiable PA with biochemical and radiological response to dopamine agonists. Receiver operating characteristic (ROC) curve analysis was performed to determine a serum PRL threshold that could identify hyperprolactinaemic PCOS subjects with prolactinomas. Clinical, metabolic and endocrine parameters were also analysed.
Results
Among 528 patients with PCOS, 60 (11.4%) had elevated PRL levels. Of 44 (73.3%) patients who had pituitary imaging, 19 had PAs, 18 normal MRI and seven other abnormalities. Patients harbouring prolactinomas had significantly higher PRL levels compared to patients without adenomas (median PRL 95.4 vs 49.2 ng/ml, $P < .0001$). A PRL threshold of 85.2 ng/ml could distinguish patients with prolactinomas with 77% sensitivity and 100% specificity (Area Under the curve (AUC) (95%) 0.91(0.8–1.018), $P = .0001$). PCOS women with prolactinomas were younger and had lower LH levels compared to women without prolactinomas.
Conclusions
In women with PCOS, PRL levels exceeding 85.2 ng/ml are highly suggestive of a prolactinoma warranting pituitary imaging. Pituitary MRI could also be considered in young PCOS patients with milder PRL elevation and low LH levels.

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P135

Bolus 3% saline restores cognitive function more rapidly than traditional slow intravenous infusion of 3% saline in the emergency treatment of SIAD, with symptoms of cerebral irritation

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Acute hyponatraemia is a medical emergency with high mortality. Recent expert guidelines advocate treatment with intravenous boluses of 3% saline with the aim to reduce cerebral oedema more rapidly than traditional slow intravenous infusion, but there is a poor evidence base for this policy change. We retrospectively audited treatment of symptomatic hyponatraemia due to SIAD ($n = 57$, age 22–76 year), comparing low dose (20 ml/h) and bolus infusion of 3% saline. Bolus 3% saline caused more rapid elevation of plasma sodium at 6 hours, with a concomitant return of GCS to normal. Administration of a 3rd bolus was associated with a greater need for dextrose/DDAVP to reverse overcorrection (OR 24; $P = 0.006$). There were no cases of osmotic demyelination in either group. Four patients died; all in the infusion group (NS). Bolus 3% saline delivers faster elevation of plasma sodium, with more effective restoration of GCS, without osmotic demyelination. Frequent electrolyte monitoring is required to prevent overcorrection.

Table 1 Results [expressed as median (min-max)]; pNa, plasma sodium.

	Bolus $n = 22$	Continuous Infusion $n = 28$	P
Baseline			
pNa (mmol/l, 133–145)	119 (108–124)	121 (114–125)	NS
GCS (3–15)	12 (8–14)	12 (5–14)	NS
Change pNa			
6 h	6 (2–11)	3 (1–4)	<0.0001
24 h	10 (6–13)	10 (6–12)	NS
Change GCS			
6 h	3 (1–6)	1 (−2–2)	<0.0001
24 h	3 (1–7)	3 (1–6)	NS
Treatment for overcorrection	5	0	0.008

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P136

Recovery of the hypothalamic-pituitary-adrenal and thyroid axes up to 12 months following trans-sphenoidal adenomectomy

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Background
Hypopituitarism is a potential complication of trans-sphenoidal adenomectomy (TSA). Recovery of pituitary function can occur, and reassessment is required to avoid unnecessary hormonal replacement. However, frequency of re-testing is variable across centres. Aim of this study was to determine recovery rates and time to recovery of hypothalamo-pituitary adrenal (HPA) and thyroid axis after TSA.
Methods
We performed a single-centre, retrospective analysis of patients undergoing TSA from January 2016 to March 2018. Patients with apoplexy, corticotroph adenomas or radiotherapy were excluded. Thyroid and HPA axis adequacy was assessed with TSH/freeT_4 measurements and short synacthen tests (SST), performed pre-TSA and at 6-weeks, 3-, 6-, 9- and 12-months post-operatively.
Results
Data on 108 patients (mean age 53 ± 17 years; 64M) were analysed. Macroadenomas occurred in 102 (94.4%), microadenoma in 6 (5.6%). Histology confirmed gonadotroph (49.1%), somatotroph (11.1%), plurihormonal (12%), lactotroph (7.4%), meningioma (2.8%), craniopharyngioma (13%), thyrotroph (1.9%) and metastatic malignancy (2.8%). 67.6% of patients had normal pre-op HPA function and 67.2% had normal HPA function at 6-weeks post-op. Among patients with abnormal pre-op HPA function, 32.1% (9/28) recovered at 6-weeks. 43.3% of our cohort failed SST at 6-weeks. Among them, 23.8%, 11.9% and 14.2% recovered at 3-, 6-, and 12-months respectively. Normal thyroid functions noted in 64.6% of patients pre-operatively and in 94.9% 6-weeks post-operatively. Conversely, 18.8% of patients having abnormal pre-op thyroid function recovered. Among patients recovering HPA axis function at 6-weeks, 83.6% also recovered thyroid axis (OR 3.7, $P < 0.01$).
Conclusions
After TSA, HPA and thyroid axis recovery occur more frequently in patients with normal pre-op function. Recovery of the HPA axis positively predicts thyroid axis recovery. HPA axis recovery can occur at 12-months post-TSA, emphasizing the importance of periodic reassessment to avoid unnecessary hydrocortisone replacement in those who could eventually regain function.

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P137

Safety of prescribing for inpatients with cranial diabetes insipidus (CDI): a Southwest Peninsula Audit

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Cranial Diabetes Insipidus (CDI) is associated with significant polyuria and is treated with desmopressin. Inappropriate or missed treatment can result in significant electrolyte imbalance and potential harm. A recent UK survey of Endocrinologists reported 55% had concerns about knowledge in their trust, 39% felt they had observed patients come to harm. Patients not receiving desmopressin have been associated with death, leading to an NHS England (NHSE) safety alert in 2016. We audited inpatients with CDI in 4 South West hospitals investigating desmopressin prescribing, administration, intravenous fluid monitoring before and after the NHSE safety alert (Jan 2015–16 and March 2016–17) and the impact on readmission. Thirty-two hospital admissions (26 patients) were studied (mean age 47 years, mean duration of CDI 9.6 years, 62% female). One additional patient with CDI, who had 32 unrelated individual admissions, was excluded as significantly skewed the results (but data will be shown). 50% had pan-hypopituitarism and were on hydrocortisone. Admissions were 84% emergency and 16% planned with range of sodium 112–153 mmol/l. 50% received the correct desmopressin dose (remainder mostly had inadequate documentation to determine the reason for not giving). 19% were hyponatraemic on admission, half of whom received their desmopressin. 25% had adequate fluid balance charts (40% received intravenous fluids). Three patients were readmitted within 30 days (unrelated to CDI). 20% had a documented endocrinology review within 24 hours of admission. There were no differences pre and post NHSE alert or clear differences amongst hospitals. NHSE safety alert has not improved management of patients with CDI which remains suboptimal. Healthcare professionals have limited understanding of CDI and therefore risk inappropriate management and referral to endocrinology is prudent. A patient information sheet to guide management as inpatients is now available locally. Recent publication of SFE clinical guidance should help to raise awareness and further improve care.

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P138

Outcomes of bilateral adrenalectomy in ACTH-dependent Cushing's syndrome

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Introduction
Bilateral adrenalectomy (BADx) is a treatment option in ACTH-dependent Cushing's syndrome refractory to other therapeutic modalities or can be an emergency measure in cases with severe manifestations of hypercortisolaemia.
Aim
To review the outcomes of our patients with ACTH-dependent Cushing's offered BADx.
Methods
Records of patients with ACTH-dependent Cushing's managed by BADx and seen in our Department between 1995 and 2017 were reviewed.
Results
Twenty cases were identified; two were excluded due to unavailable clinical data. Fourteen patients (11 females) had Cushing's disease (CD) (median age at diagnosis: 21 years (11–50)) and 4 (2 females) were considered to have ectopic Cushing's (ECS) of unknown origin (median age at diagnosis: 48 years (36–54)). Pituitary adenoma was identified in 11 patients (79%) with CD (all microadenomas) and in 1 (25%) with ECS. CD patients underwent BADx after 0 (21%), 1 (14%) or several (65%) transsphenoidal surgeries, radiotherapy (21%) and medical therapies (86%), whilst 3 patients (75%) with ECS had received medical treatment prior to adrenalectomy. BADx was performed *via* open route in 13/18 patients (72%) and laparoscopically in 5/18 (28%). Surgical complications were documented in seven patients (39%) (6 had open adrenalectomy); 30-days post-operative mortality was 0%. Biochemical cure was achieved in 17 cases (94%). During median follow-up of 10.5 years (1–26), 2 patients had died (both with CD). Based on clinic review, hypertension had improved in 83% and diabetes in 50% of the patients. Development of Nelson's syndrome was reported in 7 (50%) patients with CD (median interval since BADx 3 years (1–17)) and none had received radiotherapy prior to this diagnosis.
Conclusions
Our series demonstrate that BADx offers a high rate of biochemical control with no peri-operative mortality and considerable improvement in hypertension and diabetes. Nonetheless, the high rate of Nelson's syndrome requires attention and optimal patient monitoring.

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P139

Postoperative metabolic profile of patients after pituitary surgery

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Objective
To study the metabolic profile of patients after surgery for pituitary tumors.
Methods
This retrospective study included 1138 patients from 2000 to 2017. Those with prolactinomas, pituitary apoplexy and surgery elsewhere were excluded. The analysis included 525 patients, non-functional tumors (143), acromegaly (267), Cushing's disease (113) and TSHoma (1). The patients' blood pressure, blood sugar, lipid profile and body mass index (BMI) was serially followed up. The median duration of follow up was 2.6 years (range 1–14 years). The follow up included nonfunctional tumors (71) and patients in remission acromegaly (106), Cushing's disease (70) and TSHomas (1).
Results
At diagnosis 51, 68 & 79% of patients respectively with non-functional tumors, acromegaly & Cushing's disease had either prediabetes or diabetes (51% vs 68%, $P < 0.001$ & 51% vs79%, $P < 0.001$) Hypertension was present in 29, 28 & 64% of patients respectively with non-functional tumors, acromegaly and Cushing's disease (29% vs 64%, $P < 0.001$). Hypercholesterolemia was present in 48, 32 & 65% of patients respectively with non-functional tumors, acromegaly and Cushing's disease (48% vs 65%, $P < 0.01$). The median BMI was 24.8, 26.1 & 29.3 kgs/M^2 in patients respectively with non-functional tumors, acromegaly & Cushing's disease (24.8 vs 29.3, $P < 0.41$). At follow-up, prediabetes & diabetes resolved in 24, 43 & 50% of patients with non-functional tumors, acromegaly & Cushing's disease (24% vs 43%, $P < 0.01$ & 24% vs 50%, $P < 0.001$). Hypertension resolved in 27, 19 & 65% of patients respectively with non-functional tumors, acromegaly & Cushing's disease (27% vs 65%, $P < 0.001$). The BMI in patients with acromegaly increased from 26.1 to 28 kgs/M^2 ($P < 0.70$).
Conclusions
At follow up, diabetes & hypertension resolved respectively in 50% & 65% of patients with Cushing's disease. Diabetes & hypertension resolved respectively in 43% & 19% of patients with acromegaly. Obesity and dyslipidemia persisted in all the sub-groups.

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P140

Metoclopramide Test: Time for a revival in patients without classic symptoms and mild hyperprolactinaemia?

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Background
Generally Endocrinologists strive to diagnose conditions biochemically prior to radiological investigation. Pituitary incidentalomas are observed in 10% of pituitary MRIs and together with stress induced hyperprolactinaemia, 10–20% of patients receive dopamine agonists (DAs) without a definite diagnosis. Menstrual imbalance is a common symptom of hyperprolactinaemia which can have multiple origins (e.g. hypothalamic, pituitary or ovarian). DAs have side effects including nausea, postural symptoms and rarely impulse control disorders. Cardiac valvulopathy has been reported at higher doses. The metoclopramide test (MT) provides a cheap and effective way of providing a biochemical diagnosis. Metoclopramide is a potent D2 dopamine antagonist; abnormal prolactin and TSH responses support a diagnosis of microprolactinoma or 'disconnection hyperprolactinaemia' due to larger pituitary lesions.

Aims & Method
To assess the usefulness of the MT in determining the aetiology of hyperprolactinaemia. The MT is done after excluding macroprolactin and clear cases of prolactinoma (PRL >2000 mU/l with classic symptoms). Retrospective study of patient's who underwent MT (June'08–Mar'18) at a teaching hospital. Data were collected from electronic records.
Results
Hundred patients were included (34 male). Sixty one patients had MT suggestive of microprolactinoma, 57 underwent MRI pituitary with four conceiving whilst awaiting MRI on DA's. 23/57 showed no adenoma and 21/57 had adenoma <5 mm, they were treated with DA's as presumed microprolactinomas. Thirty-one patients had normal response to MT. 10/31 had MRI, four had pituitary adenoma <10 mm, thought to be incidentalomas.MT influenced management of 79/92 patients.
Conclusions
MT confirmed the aetiology of hyperprolactinaemia in all our patients and influenced management in 85%.We propose that there is utility of dynamic testing with MT in selected patient groups (absence of symptoms; prolactin <1000 mu/l & uncertainty regarding symptoms and negative MRI but classic symptoms). This would avoid treatment with DA's in patients with stress hyperprolactinaemia or pituitary incidentalomas.
Reference
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P141

Active management of severe hyponatraemia by endocrinologists is associated with lower mortality

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Severe hyponatraemia (SHN, <120 mmol/l) is reported to be associated with mortality as high as 50%; although there are several international guidelines for management of SHN, there are few data on the impact of treatment. We have longitudinally audited our treatment outcomes of SHN. We present the results of three audit periods, of six months each, from 2005, 2010 and 2015. The three periods represented; 2005, prior to hospital policy for SHN, 2010, audit of impact of policy, 2015, audit of change in policy after 2013 US guidelines[1]. In each period we analysed the results of treatment in patients with SHN and moderate hyponatraemia (120–125 mmol/l, MHN). The results were derived from case notes and computerised laboratory records and analysed by Chi Square. The period between 2005 and 2010 was marked by a significant rise in the rate of endocrine referral, and an increase in the use of active management of SHN, associated with a reduction in mortality from 37.8% to 12.2%. Management rates rose further after the introduction of updated guidelines[1], and although the improved mortality was maintained, there was no further reduction in mortality. The rate of referral and treatment of MHN rose between 2005 and 2015 ($P<0.001$), though at substantially lower rates than for SHN; mortality remained unchanged (2005, 16%, 2010, 12%,2015, 10%, $P=0.26$). Increased specialist management of SHN was associated with a sustained reduction in mortality in SHN.
Reference
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	2005	2010	2015	*P*
n	53	41	57	
Admission plasma sodium (median)	117	116	118	NS
Endocrine consultation, *n* (%)	10 (18.9)	27 (65.9)	34 (59.7)	<0.0001
Active management of SHN, *n* (%)	10 (18.9)	28 (68.3)	48 (84.2)	<0.0001
Mortality, *n* (%)	20 (37.7)	5 (12.2)	7 (12.3)	0.0012

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P142

A single-centre audit of treatment outcomes in 185 acromegaly patients under regular follow-up

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Transsphenoidal adenomectomy (TSA) is the recommended primary therapy in most patients with acromegaly and results in remission for majority of microadenomas and a proportion of macroadenomas depending on extent of surgically accessible disease. Acromegaly is associated with significant mortality and morbidity, hence a combination of treatment modalities may be needed to achieve disease control.
Methods
A retrospective casenotes review was conducted and management audited against the 2014 Endocrine Society guidelines. Patients were identified from the departmental database and clinic. Post-operative cure, and disease control, were defined as normal age- and sex-adjusted IGF-1, and either a random serum GH <1 μg/L or GH nadir <1 μg/L on OGTT.
Results
Data were collected on 185 patients currently attending clinic (Males 52.7%) with mean follow-up 154 months (range 2–587). Mean age at diagnosis was 44 years (59% macroadenomas; 30% microadenomas; 11% imaging not available): 167 (90%) were treated with TSA leading to cure in 62% (29/47) of microadenomas and 33% (33/101) of macroadenomas. Overall, 131/185 (71%) patients are controlled: 62 (33%) patients with surgery alone; 34 (18%) with surgery and pharmacotherapy (SSA and/or cabergoline and/or pegvisomant); 14 (7.6%) with surgery and radiotherapy; 15 (8%) with surgery, radiotherapy and pharmacotherapy; 10 (5.4%) patients with pharmacotherapy alone; 2 (1%) with radiotherapy alone. A further 28 patients (15%) have IGF-1/GH discordance with either normal IGF-1 (21) or GH <1 (7). In 12% of patients (8/65) who were initially cured after TSA, recurrence occurred after a mean duration of 7 years.
Conclusion
Our surgical remission rates are comparable to other published series. The 71% control with multimodal therapy compares favourably with other series. A recurrence rate of 12% emphasises the importance of long term follow-up. It is important to prioritise patients with uncontrolled acromegaly to reassess scope for treatment escalation.
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P143

Prevalence of sinonasal mucosal disease before and after treatment of acromegaly

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Introduction
High incidence of polyp formation and mucosal hypertrophy in paranasal sinuses have been reported in patients with acromegaly. Lund-Mackay score is widely used to stage chronic rhinosinusitis.
Aim
To assess changes in Lund-Mackay score after surgical or medical treatment of acromegaly and their relation to biochemical disease activity.
Methods
Records of patients with paired (before and after treatment) pituitary/sinus imaging (CT or MRI) performed between 1/2007 and 5/2018 were reviewed. Each imaging was assigned a Lund-Mackay score. Comparisons were made between pre- and post-treatment scores and these were correlated with IGF-I levels [times upper limit of normal range (*ULN*)].
Results
Eighty-four cases were identified [median age 45.4 years (21–72), 41 males/43 females]. Majority had macroadenoma (88%). All had active acromegaly at

pre-treatment Lund-Mackay score assessment (prior non-curative transsphenoidal surgery had been performed in 15). Median score was 1 (0-21); 11 patients (13%) (5 males/6 females) had significant sinus disease (Lund-Mackay score >3). There was no correlation between pre-treatment scores and ULN IGF-I. At post-treatment score assessment, 50 patients (31 females) were on acromegaly remission and had median score 1 (0–10); 34 patients (12 females) had improved IGF-I but were not in remission and had median score 0 (0–15). Median intervals between two score assessments were 18.7 months (3–91) in the former and 24 months (4–117) in the latter groups. No significant differences were detected between pre- and post-treatment Lund-Mackay scores in both remission and no-remission groups ($P=0.642$ and $P=0.363$ respectively). Two patients (2/11, 18%) with Lund-Mackay score >3 showed improvement after treatment (one each in both treatment outcome groups).

Conclusions

Staging of chronic rhinosinusitis with Lund-Mackay scores does not correlate with acromegaly biochemical activity. In our series, 13% of the patients had significant sinus disease which changed in a small minority after acromegaly treatment.

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P144

25 years of sporadic insulinomas - A case series

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Introduction

An insulinoma is a rare neuro-endocrine tumour originating in the pancreatic beta-cells with unregulated secretion of insulin resulting in profound hypoglycaemia.

Methods

A search of electronic hospital records identified all patients with a primary diagnosis of insulinoma. Clinic and discharge letters, radiology investigations, laboratory investigations and case notes were reviewed to highlight the presentation, investigations and laboratory investigations of the patients.

Results

Eleven patients had a primary diagnosis of sporadic insulinoma, with a year of diagnosis between 1994 and 2018. Most patients presented with symptoms of dizziness and fainting, with near patient testing of hypoglycaemia. In all patients where laboratory investigations had been performed, there was a laboratory confirmed hypoglycaemia (1.2–2.5 mmol/L), and raised insulin and C-peptide. On initial imaging 6 patients had MRI or CT evidence supporting insulinoma. 4 further patients had normal abdominal imaging on the first scan, however later had CT or MRI evidence, or an arterial blush seen on pancreatic angiogram with one patient. One further patient had no imaging. 8 of the 11 patients were still alive at the time of the search, of the three patients who had died one had metastatic insulinoma, and two patients died of illnesses unrelated to insulinoma.

Conclusions

An insulinoma is a rare but important differential to consider in a patient presenting with recurrent hypoglycaemia.

- Normal imaging does not exclude the diagnosis, particularly in a patient with a history suggestive of insulinoma and hypoglycaemia with raised insulin and C-peptide.
- Functional imaging or pancreatic angiogram may assist with diagnosis in these cases.
- Most patients have a good prognosis following surgical removal with swift resolution of symptoms. Solitary insulinoma related death in our case series was that of metastatic insulnoma, which was already metastasised at the time of presentation.

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P145

Isoforms of the short chain alcohol dehydrogenase reductase enzyme 11βHSD1L is differentially expressed in the pituitary, gonads and gastrointestinal tract

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The human Short-chain alcohol Dehydrogenase Reductase (SDR) superfamily of oxoreductase enzymes regulate important endocrine hormones. Two SDR members, 11b-hydroxysteroid dehydrogenase (11bHSD) 1 & 2 have key roles in the pre-nuclear receptor modification of glucocorticoid steroids, thereby contributing to regulation of fluid homeostasis, blood pressure, metabolic pathways and brain function. We have recently characterised a third structurally related HSD enzyme, 11B-HSD1L or HSD3, which is specially restricted, with an absence in the majority of rodent genomes. 11bHSD1L/HSD3 displayed highest expression in the brain, pituitary and gonads (1). Immunohistochemistry analysis in the sheep, marmoset and macaque showed strong protein localisation to the granulosa cells of the ovary and to the gonadotrophs of the anterior pituitary. Further studies now show that the 11bHSD1L gene in primates but not the sheep undergoes alternate splicing at the 3'end to generate mRNAs with different exon 9-derived sequences to produce two isoforms, 11bHSD1L9A and 11bHSD1L9B. Both splice variants are expressed in the pituitary but only the 9A form in the ovary. We have further localised expression of 11bHSD1L9B to the gastrointestinal tract (GIT) and immunofluorescent imaging in the marmoset showed strong protein localisation to enteric endocrine cells in the small and large intestine. Finally, an antibody directed to the 11bHSD1L9B isoform detected localisation of 11bHSD1L9B to pituitary lactotrophs. Overall, these results suggest that 11bHSD1L may play regulatory roles in reproduction through actions in the pituitary-gonadal axis and in also in the GIT.

Reference

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P146

Role of Nurr1 in the regulation of Synaptogyrin 3 (SYNGR3)

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SYNGR3 is involved in the re-uptake of dopamine (DA) into striatal pre-synaptic terminals. Here we elucidate the genetic control of human SYNGR3 gene (*SYNGR3*).

Methods and Intermediate Results

Step 1 Potential cis-acting in 2kb upstream of the transcription initiation site (TIS) of *SYNGR3* were investigated using the MatInspector algorithm. Three potential Nurr1 binding sites were identified. Step 2 PCR amplification (human DNA as template) generated a 1.8Kb amplicon containing terminal 5' Nhe1 and 3' Xho1 sites *(NheI-SYNGR3−1870/TIS−XhoI).* Step 3 Cloning and subcloning of *(NheI-SYNGR3−1870/TIS−XhoI)* allowed this DNA fragment to be ligated into pGL3-Basic vector (promoter-less firefly luciferase vector) giving plasmid pGL3-SYNGR3−1870/TIS. Sequence of the *SYNGR3−1870/TIS* section was identical to that in Ensembl. Step 4 pGL3-SYNGR3−1870/TIS or pGL3-Basic vector together with pRL-TK *Renilla* reporter vector were transfected into SH-SY5Y cells and promoter activity determined using a dual luciferase, end-point system.

Result 1

Surprisingly, pGL3-SYNGR3−1870/TIS had less promoter activity than the basic vector ($P<0.05$). Re-analysis of the *SYNGR3* sequence revealed a XCPE1 site between the TIS and the Translation Start Site (TSS). Step 5 Steps 2 to 4 were repeated using a longer DNA insert (*SYNGR3−1870/TSS).*

Result 2

Plasmid pGL3-SYNGR3-1870/TSS had greater promoter activity than the basic vector ($P<0.05$). Point mutation of one of the potential Nurr1 binding sites reduced promoter ($P<0.05$). Point mutation of all three sites reduced promoter activity to that of the basic vector.

Result 3

Gel-shift assays showed specific binding of Nurr1 to the three sites.

Result 4

Treatment of SH-SY5Y cells with Nurr1 transactivator, C-DIM12, significantly increased the cellular SYNGR3 level.

Conclusions

Nurr1 an orphan member of the endocrine nuclear receptor superfamily is involved in control of SYNGR3 expression. Increasing SYNGR3 levels via Nurr1 activation is a possible therapeutic option in Parkinson's disease.

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P147

Abstract Unavailable.

P148

Investigation of gonadotroph ultrastructure secretory machinery in a novel mouse model of Patched1 deletion in folliculostellate cells

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The sonic hedgehog (shh) pathway is known to be essential for pituitary development but little is known of its role in adult pituitary. Patched1, encoded by the *Patched1 (Ptch1) gene,* is a receptor for shh expressed in all cell types of the anterior pituitary. Adult onset hypogonadotropic hypogonadism has been reported in a genetically engineered mouse line with deletion of *Ptch1* using *S100a4* promoter driven CRE recombinase expression which is restricted to folliculostellate cells (*Ptch1-cKO*). *Ptch1-cKO* mice exhibit severely reduced circulating gonadotropin levels; reduced levels of mRNA expression for glycoprotein hormones alpha subunit (*Cga*), follicle stimulating hormone beta (*Fshb*) and luteinizing hormone beta (*Lhb*). The aim of the present study was to explore the secretory pathway ultrastructure of anterior pituitary gonadotrophs in *Ptch1-cKO* compared to control wild-type (WT) mice by electron microscopy, in particular to investigate LH and FSH within the regulated secretory pathway. Ultrastructural features of reduced regulated secretion were predicted. Pituitary glands (5 week old male and female mice) were collected ($n=4$), fixed and prepared for quantitative electron microscopy. Immunogold labelling of LHβ and FSHβ was performed in order to identify gonadotrophs. In WT and *Ptch1-cKO* no significant difference in mitochondria number/micron^2 cell area, secretory granule diameter, secretory granule number/micron^2 cell area, or rough endoplasmic reticulum amounts were measured. Gonadotroph size in female and male *Ptch1-cKO mice*, was significantly reduced ($P<0.05$). No significant difference in immunogold labelling of LH and FSH-positive granules was found. However, folliculostellate cell morphology was altered in *Ptch1-cKO* pituitary in that long cellular processes that are distinctive in WT were significantly reduced in number and length ($P<0.05$). Overall, these findings show smaller gonadotrophs and reduced contacts with folliculostellate cells but ultrastructural features of the regulated secretory pathway were not altered.

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Nursing Practice

P149

Assessement of Diabetes Distress in patients with diabetes mellitus taking insulin in a clinic in the United Arab Emirates

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Screening of patients with diabetes for psychological distress should be undertaken regularly by the diabetes nurse specialist. Patients requiring intensive treatment of their diabetes experience emotional and mental health issues at a rate higher than the general population and recent clinical research shows value in cognitive and behavioral therapy. We undertook a survey of a mixed population in Dubai, United Arab Emirates to assess diabetes distress scores among our patients receiving insulin therapy. We utilized the Diabetes Distress Scale (DDS 2017) to assess and report perceived diabetes distress among this patient population. Patients experiencing DD scores greater than 2 were referred to appropriate services locally. The items scoring highest included 'Feeling overwhelmed by the demands of living with diabetes,' 'Feeling that friends or family don't appreciate how difficult living with diabetes can be,' 'Not feeling confident in my day-to-day ability to manage diabetes,' 'Feeling that diabetes controls my life,' and 'Feeling that diabetes is taking up too much of my mental and physical energy every day.' We identified the highest degrees of DD in the subcategories of emotional burden and regimen distress and are pleased to report that within our practice patients experience a minimal degree of provider-related distress. Interestingly, in the UAE many patients report not feeling confident in their ability to manage the day-to-day elements of their condition which is underscored by the low level of health literacy and diabetes self-management skills we see in our practice. These items underscore the emotional and interpersonal strain elements of living with diabetes and give us the opportunity to refer to support groups, behavioral therapists and psychiatrists where appropriate. We have made a concerted effort to offer high-quality diabetes education provided one-on-one by the diabetes nurse specialist and have seen great results in patient empowerment.

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P150

Nurse led parathyroid clinics – Improving the patient journey

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Introduction
Our endocrine service introduced a nurse led parathyroid clinic to provide an efficient pathway for patients referred with hypercalcaemia.This benefits patients and clinical staff.
Materials/Methods
Patients referred with a raised calcium level are vetted by the endocrine consultants and directed to the nurse led clinic. The patients are seen within 6 weeks using a standard proforma and checklist. Relevant investigations to include renal function, bone profile, PTH, vitamin D, 24-hour urine calcium and spot urine calcium/creatinine ratio are arranged. Patient with Ca++ > 3 mmol/l are advised 2 weekly check of Ca++ level by GP. If Ca++ remains elevated, an appointment for administration of bisphosphonates is arranged. Standard letters are sent to the GP with clear instructions to cover a range of scenarios including vitamin D replacement, possible cardiac failure and higher calcium levels. Patients meeting criteria and willing for surgery are discussed with the medical team and parathyroid localisation studies are requested. Patients are directed to either the medical or surgical parathyroid clinic where they are seen with results of biochemical and radiological investigations where a treatment decision can be made at their first encounter with the surgeon or endocrinologist.
Results
Sixty-nine patients were seen by the nurse led clinic between April 2017 and March 2018. Twenty-four were willing and met surgical criteria and are either post-surgery or are awaiting an operation date. Thirty-five were not for surgery either because they did not meet criteria for surgery (23), had other significant illness (4) or refused surgery (8). Ten patients are still awaiting completion of radiological investigation.
Conclusion
We describe our experience of starting a nurse led parathyroid clinic which has improved the patient journey, including prompter assessments and reduced number of medical appointments.

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P151

The varied psychological support Acromegaly patients receive across the UK and what they believe can help improve their care; A patient perspective

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Introduction
When reviewing data from an Acromegaly focus group, it highlighted the lack of psychological support they receive. I became interested to see how psychological support varies geographically across the UK. I also wanted to identify what patients viewed as the priority in order to improve their Acromegaly care.
Methods
1. 7 Acromegaly patients from across the UK, with a mix of age, sex and treatment experience were filmed as part of a focus group. Discussions were aimed to look at their experiences holistically. Topics included medication, surgery, radiotherapy, co-morbidities and signs and symptoms of their condition. The lack of information and psychological support being prominent throughout.

2. An online survey with predictions of 50–60 participants will go live in July. Geographical location, age, sex, when diagnosed, treatments received and any psychological support received will be established. What the Acromegaly patient would like to see improved with their local endocrine service will also be identified.

Results

I believe the results will match the theory that psychological support is high on the agenda for patients, yet the support available to them is inadequate. I believe there will be a national problem however geographical information will be useful to feed back to areas, what improvements their patients would like to see. The focus group videos originally made with newly diagnosed patients in mind, will be available across social media. After reviewing the footage, we believe they will have an impact in supporting any person with Acromegaly. This alone could improve the psychological support these patients receive. The plan is to complete similar focus groups for other conditions such as Cushing's, Diabetes Insipidus, Hypogonadism and Adrenal Insufficiency. A follow-up survey for original participants will be sent in the future following up their original recommendations and how the focus group videos have helped them.

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Conducting research in vulnerable populations can be safe, beneficial and well received if infrastructure and staff experience are appropriate to patient's needs

Greta Lyons, Anne McGowan & Carla Moran
Wellcome Trust – MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK.

Introduction

Patients with complex health care needs and severely limited communication and mobility may be less likely to participate in research studies, and may find continued participation in such studies challenging. Allan Herndon Dudley syndrome (AHDS), due to defective thyroid hormone transporter (MCT8), causes severe neurological and physical disability. A multicentre trial (the TRIAC trial) studying the efficacy of the thyroid hormone analogue TRIAC in this rare condition has just been completed.

Method

Ten males with AHDS were recruited to the only UK site of the TRIAC trial (Cambridge). We conducted a participant survey in order to assess their experience of taking part in research.

Results

Response rate was 80% (1 died, 1 lost to follow up). Experiences of trial enrolment were positive: 87.5% strongly agreed they had sufficient time at the initial contact to discuss the trial and 75% strongly agreed that the pre-enrolment questions adequately covered relevant information prior to the first study visit. The research environment was highly rated; 100% strongly agreed that the room was appropriate, 87.5% agreed that parking was easy, 100% strongly agreed that appointments were arranged at convenient times. Care received was also highly rated; 100% strongly agreed that staff were attentive to the needs of the participant, 100% strongly agreed that staff explained each test and investigation in a way that they were able to understand, 100% strongly agreed that they could contact the Research team when needed. 75% said they would now be more likely to take part in research in the future. 62.5% stated that they learned more about their child's condition.

Conclusion

It is possible to conduct research on vulnerable populations if infrastructure and staff experience are appropriate to the participants needs. Research participation can be a beneficial experience and can encourage patients to engage in further research.

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Obesity & Metabolism

P153

Subcutaneous adipose tissue from patients with Idiopathic Intracranial Hypertension exhibits metabolically distinctive characteristics

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Idiopathic intracranial hypertension (IIH) is characterised by raised intracranial pressure (ICP) and papilloedema, diagnosed primarily in obese women of reproductive age, with the incidence rising with the global epidemic of obesity. Weight-loss lowers ICP and treats IIH. No mechanism explains the link between obesity and raised ICP. We hypothesise that adipose tissue from IIH patients has a metabolically distinct profile that contributes to raised ICP. Our previous data demonstrates elevated cerebrospinal fluid leptin levels as well as changes in systemic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity which correlate with ICP. Here we detail the phenotype of subcutaneous (SC) adipose tissue from female IIH patients and healthy age, BMI and gender matched controls. Morphometric analysis showed that IIH and control SC adipose are indistinguishable in terms of cross-sectional area. However, while 11β-HSD1 gene expression was unchanged, LCMS based 11β-HSD1 assays show that when treated with cortisone, SC adipose tissue in IIH is capable of generating more cortisol compared to controls (679 ± 115 vs 234 ± 80 pg pg/h/100 mg; $P < 0.05$, $n = 6$ vs 10). SC adipose cytokine secretion was screened (IL-1β, IL-6, IL-8, IL-10, MCP-1, TNF-α and leptin) and revealed that IIH leptin was elevated compared to controls (8309 ± 1593 vs 2366 ± 431 pg/24h/100 mg; $P < 0.01$, $n = 11$–12). Functional changes were examined by NMR metabolomics and show that IIH SC adipose produces more glycerol compared to controls (186 ± 67 μM vs. 97 ± 25 μM; $P < 0.05$, $n = 6$ vs 6). Furthermore lipid generating amino acids leucine and isoleucine were preferentially consumed by IIH SC adipose vs control, potentially indicative of altered lipid handling and turnover. These data suggest that SC adipose tissue in IIH is metabolically distinct from matched controls. We propose that SC adipose derived factors, such as glucocorticoids and leptin, coupled with changes in lipid turnover may mechanistically contribute to raised ICP and warrants further investigation.

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P154

Dominant-negative mutations in PPAR alpha are present in unselected human populations and have a metabolic signature

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The study of humans carrying dominant negative mutations in PPAR gamma has contributed significantly to our understanding of its role in human physiology. To date, comparable studies of PPAR alpha have not been reported. Using a pooled approach, we undertook exon sequencing of *PPARA* in 11,848 adult participants of the Fenland study, a population-based cohort study with detailed metabolic phenotyping. Twenty-nine *PPARA* missense variants were detected (allelic frequency 1.1×10^{-1} to 3.7×10^{-5}). Bioinformatic analysis predicted four defective variants (R157Q, K292R, R341C and L426H), confirmed in functional *in vitro* assays with impaired constitutive and ligand-activated transcriptional activity. This was associated with impaired DNA binding (R157Q, R341C and L426H) and co-activator interaction (K292R, R341C and L426H). R341C and L426H exhibited significantly impaired dimerisation with the retinoid X receptor (RXR) which accounted for impaired DNA binding and was partially rescued at higher concentrations of synthetic ligand. Crystallographic modelling of the mutations was consistent with the functional data, providing a structural basis for the observations. All mutants exerted a dominant negative effect over wildtype PPAR alpha in co-transfection assays. Heterozygous carriers of these variants had significantly elevated median (IQR) fasting levels of free fatty acids 514(421–882) umol/l vs 303(212–423) umol/l ($P = 0.025$), alanine transaminase 34(31–50) U/l vs 24(18–33) U/l ($P = 0.046$) and gamma glutamyl-transferase 83.5(64–98.5) U/l vs 25(20–37) U/l ($P = 0.003$) when compared to participants free of *PPARA* variants. Rare *PPARA* variants that are predicted to be functionally impaired were found in the Genome Aggregation database (gnomAD) at a frequency of 1 in 3000. In summary, dominant negative mutations in *PPARA* are found in human populations at an appreciable frequency and appear to have an impact on metabolically relevant phenotypes.

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P155

Identity and cell fate of Ngn3-expressing population in small intestinal organoids

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The intestinal epithelium (IE) is populated by different cell types each with a unique set of functions. Each cell type is derived from a common progenitor, the stem cell. The hierarchy of epithelial cell fate is transcriptionally regulated for example, Notch signalling defines secretory versus absorptive destiny. Peptide hormone producing enteroendocrine (EE) cells are scattered throughout the epithelium where they integrate complex nutrient signals and respond by promoting metabolic equilibrium. Understanding EE cell fate in health and disease could identify novel targets for the treatment of metabolic and other gut related endocrine diseases. EE progenitor cells are defined by the expression of Neurogenin3 (Ngn3), a transcription factor of the bHLH family, from which all mature enteroendocrine cells are thought to descend. However, the concrete signalling pathways that defines the terminal differentiation of different EEC cell types is poorly understood. This exposes a knowledge gap of the intestinal epithelium dynamics and consequently, progenitor cell differentiation and fate. We sought to scrutinise the cell fate of enteroendocrine progenitor cells using Ngn3-Cre-RFP mouse small intestine organoids. Ngn3+ red fluorescent cells were separated from the negative population by fluorescence-activated cell sorting (FACS) and gene expression in both populations quantified using qPCR. As expected, Ngn3+ population was significantly enriched for the EE transcription factor Ngn3 ($P<0.01$) as well as the pan-enteroendocrine marker, Chromogranin A ($P<0.01$). Surprisingly, expression of Paneth cell marker, Lysozyme ($P<0.001$) and Goblet cell marker, Mucin2 ($P<0.01$) were also significantly augmented in Ngn3+ cells. Our data suggest that EE progenitors contribute more extensively to the different intestinal epithelial cell populations than previously identified. Given the role of secretory cells (Paneth, goblet and EE cells) in gastrointestinal-related diseases, defining intestinal epithelium cell fate decisions could help to delineate novel therapeutic paths for gastrointestinal disorders.

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P156

Randomised trial of empagliflozin versus metformin in polycystic ovary syndrome

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Background
Empagliflozin is a sodium-glucose-cotransporter-2 that improves cardiovascular risk and weight loss in patients with type 2 diabetes. Polycystic ovary syndrome (PCOS) is associated with obesity and increased cardiovascular risk; therefore, empagliflozin may be of benefit in PCOS.
Methods
A randomised, open-label study in 40 overweight and obese women with PCOS treated with either empagliflozin 25 mg or metformin 1500mg daily for 12 weeks.
Results
At 12 weeks empagliflozin treatment resulted in reductions in weight (-1.5 ± 3.3 vs 1.2 ± 2.1; $P=0.005$), body mass index (-1.4 ± 3.3 vs 1.2 ± 2.1; $P=0.005$), waist (-1.6 ± 2.8 vs 0.2 ± 2.1; $P=0.029$) and hip circumference (-2.0 ± 3.0 vs 1.1 ± 1.9; $P=0.001$) compared to metformin. The percentage reduction from baseline in basal metabolic rate ($-1.8\%\pm2.9$ vs 0.05 ± 1; $P=0.02$), fat mass ($-0.7\%\pm4.9$ vs $3.2\%\pm5.0$; $P=0.02$) and free fat mass ($-2.0\%\pm3.2$ vs $-0.3\%\pm2.2$; $P=0.05$) were greater for empagliflozin compared to metformin treatment. Empagliflozin resulted in an increase in sex hormone binding globulin ($P=0.04$) while there was significant reduction of total testosterone levels ($P=0.04$) after metformin treatment only. No changes in endothelial function, free androgen index or insulin resistance were seen between groups.
Conclusion
In this novel study empagliflozin improved anthropometric and body composition parameters, in overweight and obese women with PCOS after 12 weeks of treatment.

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P157

The impact of lipopolysaccharide on mitochondrial efficiency in brown adipocytes

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Background
The presence of brown adipose tissue (BAT) in adults offers an opportunity to examine inflammatory factors that may affect metabolic function in states of obesity. Gut-derived lipopolysaccharide (LPS), which is elevated in obesity, and initiates the innate immune response in white adipose tissue, has not been fully studied in BAT. The interactions between LPS, TLR4 and ß3-adrenergic receptors in BAT is unknown. ß3-adrenergic receptor ligands as CL 316,243 (CL) induce BAT activity through UCP1-stimulation. Therefore, the objective of this study was to investigate the effect of LPS on the CL response and examine how LPS may alter mitochondrial function in BAT.
Methods
Immortalized brown adipocytes were differentiated with or without LPS (100 ng/ml, 1000 ng/ml). After treating cells with CL, RNA and protein were extracted for qRT-PCR and Western blot analysis. Mitochondrial respiration was assessed using Seahorse Bioscience XF24 extracellular flux. Mitochondrial membrane potential ($\Delta\Psi m$) was assessed by confocal microscopy images. Reactive oxygen species (ROS) assay was performed to estimate the capacity to prevent cellular damage.
Results
LPS significantly reduced BAT phenotype and mitochondrial function. LPS decreased key brown fat genes CIDEA ($P<0.001$), UCP1 ($P<0.01$), PGC-1a ($P<0.01$). Furthermore, LPS-treated cells showed significantly decreased UCP1-expression in response to CL at both protein ($\approx60\%\downarrow$) and mRNA levels ($\approx65\%\downarrow$). In addition, LPS significantly reduced key mitochondrial genes: ATPase8, CPT1B ($P<0.05$), CytC ($P<0.05$), and ND1 ($P<0.05$). Functional analysis highlighted that LPS impaired mitochondrial function through reduced O_2 consumption rate as well as loss of active membrane potential $\Delta\Psi m$ ($\approx65\%$). With ROS production also increased ($P<0.001$).
Conclusions
These findings suggest that LPS poses a risk to damaging mitochondrial function in BAT. Overall, this current data indicates that blocking LPS-TLR4 signalling has potential to enhance BAT activity and mitigate inflammation to counteract obesity and metabolic diseases.

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P158

Increased pro-inflammatory cytokine production in vitamin B12 deficient adipocytes

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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 suggesting the crucial role of B12 in adipose tissue function. Although the mechanisms underpinning metabolic disorders remain poorly defined, the pathophysiology of obesity-induced metabolic diseases has been strongly related to white adipose tissue dysfunction through several mechanisms such as fibrosis, apoptosis and inflammation. Therefore, the aim of this study is to investigate the role of B12 inflammation in human adipocytes. Human pre-adipocytes cell line (Chub-S7) and primary adipocytes were obtained from lean, obese and morbid obese patients, grown to confluence, differentiated for one week, maintained in nutrition media for next 7 days (day 14) and then used for further experimental analysis. In order to analyse B12 deficiency effects, customized media with different concentrations of B12 (25 pM, 100 pM, 1 nM, 500 nM) were used. Gene expression was performed by q-RTPCR. Chub-S7 and primary adipocytes cultured in low vitamin B12 conditions showed significantly increased gene expression of pro-inflammatory cytokines such as interleukin-1 (IL-1) interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1/CCL2). Our data highlights that low B12 in adipocytes induces higher gene expression and secretion of pro-inflammatory cytokines, which might lead to adipocyte dysfunction. This link between vitamin B12 deficiency and metabolic

inflammation opens new insights into the pathogenesis of maternal obesity and the relevance of micronutrient supplementation for pregnant mothers.

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P159

Vitamin B12 deficiency leads to adipocyte dysfunction by enhancing triglyceride biosynthesis and impairing fatty-acid oxidation: a new protagonist in metabolic disease?

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Vitamin B12 (B12) is an essential micronutrient required for two key metabolic reactions. Longitudinal studies and animal models showed that B12-deficiency during pregnancy is associated with the maternal obesity, development of insulin resistance and metabolic syndrome phenotype. Although the mechanisms underpinning low B12 and metabolic disorders remain poorly defined, it's becoming increasingly clear that lipid dysregulation is associated with obesity and co-morbidities. The aim of this study is to investigate the role of B12 in lipid metabolism in human adipocytes. Human pre-adipocytes cell line (Chub-S7) and primary-adipocytes obtained from lean, obese and morbid obese patients were grown to confluence, differentiated for one week, maintained in nutrition media for next 7 days (day 14) and used for further experimental analysis. To analyse B12-deficiency effects, customized media with different concentrations of B12 (25 pM, 100 pM, 1 nM, 500 nM) were used. Gene-expression was performed by q-RTPCR, *de-novo* triglycerides synthesis was quantified using radioactive tracing technique incorporating of ^{14}C-oleate and ß-oxidation and palmitate-induced oxygen consumption rate (OCR) was determined using seahorse XF analyser. Adipocytes cultured in low vitamin B12 conditions showed significantly increased expression of genes involved in triglyceride biosynthesis (such as ELOVL Fatty-Acid-Elongase-6 (ELOVL6), Stearoyl-CoA-Desaturase (SCD), Glycerol-3-phosphate-acyltransferase (GPAT), phosphatidate-phosphatase (LPIN1), Diacylglycerol-O-Acyltransferase 2 (DGAT2)) and a decreased ß-oxidation gene-expression (such as Fatty acid translocase (FAT/CD36), Acyl-CoA-Synthetase1 (ACSL1), Malonyl-CoA-Decarboxylase (MLYCD), Carnitine-palmitoyl-transferase1ß(CPT1-ß), Carnitine-Palmitoyltransferase-2 (CPT2), Acyl-CoA-dehydrogenase family (ACADS, ACADM, ACADL), Enoyl-CoA-hydratase-short-chain 1(ECHS1), Thiolase/Enoyl-Coenzyme-A-Hydratase (HADHB) and Acetyl-CoA-acyltransferase-2 (ACAA2)). Triglyceride biosynthesis detected by radioactive tracing technique resulted in higher levels in low B12 condition. In addition, we observed that basal and palmitate induced OCR was significantly reduced in B12 deficient cells. Our data highlights that low B12 dysregulates lipid metabolism increasing triglyceride synthesis and impairing ß-oxidation, which might lead to adipocyte dysfunction suggesting a possible role of B12-deficiency in metabolic disorders.

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P160

Screening for Cushing's syndrome in a tier 3 weight management service

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There is limited evidence for the role of screening for Cushing's syndrome (CS). Patients referred to the specialist medical weight management service at Musgrove Park Hospital have routinely been screened for CS with either an overnight dexamethasone suppression test (ODST) or two 24hour urinary free cortisol (UFC) if evidence of dysglycaemia. We retrospectively analysed the results of all patients referred to the service between 2013–2016. 794 patients were seen as initial assessments, of which 534 had screening tests and were included in the analysis. The mean age was 46 ± 12.4 years, BMI 46.6 ± 7.8 kg/m^2, weight 132.4 ± 26.7 kg and 72% female. 176 patients were classified as having dysglycaemia. A 9 am cortisol of <50 nmol/L following 1mg of dexamethasone was considered normal. Two or more abnormal UFC collections was considered abnormal. 361 patients underwent ODST, with 350 of those having a normal result. 173 patients underwent UFC, with 162 patients having normal results. Of the abnormal ODST, 8 patients went on to have normal UFC. In 3 patients, a clinical decision was made that the patient did not appear Cushingoid and the test was likely incorrectly done. Of the abnormal UFC, 5 patients went on to have ODST, 2 had further UFC collections and 2 had a Yankowski test all of which were normal. 2 were not thought to be Cushingoid clinically and plan to repeat in due course once diabetes better controlled. No patients were diagnosed with CS in this cohort. This study does not support the routine screening of obese patients referred to a specialised tier 3 weight management service for CS. The average BMI of patients with CS in the European Registry on Cushing's syndrome was 28 ± 9 kg/m^2 and so patients with CS may not reach the BMI typically seen in patients referred to a specialist weight management service.

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P161

B12 Receptors and transporters regulate the uptake and storage of vitamin B12 in hepatocytes

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Background
The liver stores 10 µg cobalamin per gram protein and able to hold 50% (1–1.5 mg) of body's B12. Making up the bulk of the liver, hepatocytes express receptors regulating cellular uptake of B12 in the liver. However, relationship between circulating and intracellular B12 levels as well as regulation of hepatic uptake of B12 is unexplored.
Objective
To assess the regulation of cellular uptake and storage of B12 in hepatocytes in varying concentrations of circulating B12.
Methods
HepG2 cell line was cultured using B12 deficient EMEM medium and seeded in 500 nM, 400 nM, 200 nM, 100 nM, 50 nM, 20 nM, 10 nM, 1 nM, 100 pM and 25 pM B12-media. B12 concentration within hepatocytes and corresponding conditioned media was determined by electrochemiluminescent immunoassay using a Roche Cobas immunoassay analyzer (Roche Diagnostics UK). Gene and protein expression of transcobalamin II (TCN2) and transcobalamin receptor (TCblR)(CD320) were assessed by RT-PCR and western blots.
Results
Low B12 (25 pM and 100 pM) in condition media resulted in 210–280% increase in intracellular levels of B12 in hepatocytes. 1000 pM (1 nM) circulatory B12 resulted in 42.7% storage in hepatocytes. Higher circulating B12 such as 10 nM, 20 nM, 50 nM, 100 nM, 200 nM, 400 nM and 500 nM decreased uptake of B12 to 4.7%, 4.3%, 3.1%, 1.6%, 2.3%, 1.3% and 1.8% respectively. We observed increased gene and protein expression of transcobalamin II (TCN2) and receptors (TCblR) (CD320) in hepatocytes under low B12 than higher concentrations.
Conclusion
Our study highlights low circulatory B12 (0–100pM) triggers higher intracellular levels of 2–3 fold and vice versa, supported by increased gene and protein expression of receptors/transporters. Implies active transport of B12 predominate at lower concentrations, possibly due to high expression of receptors/transporters. Hence suggesting the optimal physiological B12 concentration is required rather than overloading with supplements. This provides us impetus to further study whether the tissue-specific effect of low B12 dysregulates hepatic metabolism.

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The relationship between obstructive sleep apnoea and quality of life in women with polycystic ovary syndrome: a cross-sectional study

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Background
Obstructive sleep apnoea (OSA) and polycystic ovary syndrome (PCOS) are associated with significant comorbidities and commonly coexist. The primary aim

of this study was to examine the relationship between OSA and quality of life (QoL) in women with PCOS.
Study design
Observational cross-sectional study.
Methods
Women with PCOS were recruited from a single secondary care centre in the UK. PCOS was diagnosed according to the Rotterdam criteria. Women with increased risk of OSA, based on the Berlin questionnaire and/or the Epworth Sleepiness Scale (ESS), had home-based polysomnography performed (ALICE PDx). Participants were divided into two groups: 1) PCOS only: women with normal ESS and low-risk Berlin questionnaire (no sleep studies performed), or women with normal sleep studies; and 2) PCOS + OSA: women with PCOS and OSA [oxygen desaturation index (ODI) ≥ 5 events/hour]. QOL was assessed using the World Health Organisation QoL questionnaire (WHOQOL-BREF) and the PCOS health-related quality of life questionnaire (PCOQ16).
Results
39 women were included [mean $\pm$SD] age was 32.2 $\pm$ 8.9 years, weight 92.5 $\pm$ 23.7 kg, and body mass index (BMI) 34.1 $\pm$ 7.9 kg/m^2. 38.5% ($n=15$) had OSA [15.4% ($n=6$) had moderate to severe OSA]. Compared to women with PCOS only, women with PCOS + OSA had higher BMI (37.3 $\pm$ 7.3 vs. 31.7 $\pm$ 7.6 kg/m^2, $P=0.03$), HbA1C, CRP, and LDL. ODI was independently associated with impaired QoL. Excessive daytime sleepiness (EDS) was independently associated with anxiety, depression, and impaired QoL.
Conclusions
In women with PCOS, OSA was associated with increased obesity, higher HbA1c, worse cardiovascular risk profile, and impaired QoL. Intermittent hypoxaemia and EDS were associated with lower QoL. Furthermore, EDS was associated with anxiety and depression. Interventional studies are needed to examine these associations further.

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Metformin treatment fails to restore fatty acid oxidation in low vitamin B12 hepatocytes

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Background
Metformin is utilized in clinical trials for treatment of non-alcoholic fatty liver disease (NAFLD) and obesity. Metformin increases AMP:ATP ratio activating AMP activated protein kinase-alpha (AMPKα), a mediator of fatty acid oxidation (FAO) in the liver. Meanwhile, prolonged oral metformin therapy in T2DM decreases vitamin B12(B12) in patients and evidence shows that low B12 dysregulates lipid levels. We therefore investigated whether low B12 impairs FAO induced by metformin in the liver.
Methods
Liver cell line Hep G2 was cultured in custom-made B12 deficient Eagle's Minimal Essential Medium (EMEM) and seeded in different concentrations of B12 media 500 nM (control), 1000 pM, 100 pM and 25 pM (low) B12. Hepatocytes were exposed to 24 hour treatment with 1 mM and 2 mM metformin before harvest. Gene expression, protein levels and oxygen consumption rate (OCR) were measured using real time PCR (qRT-PCR), western blotting and seahorse flux XF24.
Results
Activation of pAMPKα and pACC were decreased by low B12 (25pM). Administration of 1 mM and 2 mM metformin to low B12 hepatocytes significantly impaired the upregulation of pAMPKα and pACC, resulting in high acetyl CoA carboxylase (ACC) expression. Restoration of the rate-limiting enzyme [carnitine palmitoyl transferase 1 alpha (CPT1α)] and the downstream genes involved in FAO [carnitine acyl carnitine translocase (CACT), Long chain Acyl–CoA dehydrogenase (ACADL), Medium chain Acyl–CoA dehydrogenase (ACADM), Short chain Acyl–CoA dehydrogenase (ACADS) and long-chain 3-hydroxyacyl-CoA dehydrogenase (HADHA)] were decreased in low B12 hepatocytes treated with metformin. Finally, spare respiratory capacity was impaired in low B12 following palmitate and metformin administration.
Conclusion
B12 deficiency (1) lowers levels of pAMPKα and pACC, and (2) metformin administration in low B12 failed to restore pAMPKα and pACC, and FAO genes. Hepatocytes' mitochondrial function was hampered by low B12 and therefore lipid lowering effect of metformin is compromised, inducing FA accumulation in the low B12 hepatocytes.

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P164

Prevalence of adenovirus 36 infection and association with obesity and diabetes in the United Arab Emirates

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Background
Prevalence of obesity and diabetes has increased significantly in the UAE over the last 40 years. Adenovirus 36 (Adv36) infection has been associated with obesity in several studies across different ethnic populations, and usually is associated with improved glucose tolerance.
Objective
1) Identify the prevalence of Adv36 seropositivity among adults living in the UAE.
2) Investigate the association of Adv36 infection with obesity and diabetes in this population.
Methods
Participants ($N=973$) were recruited from the outpatient facility of ICLDC, Abu Dhabi, UAE including patients with different weight and glucose tolerance categories. Height, weight, body composition, glycosylated haemoglobin (HbA1c) and lipid profile were measured at recruitment. Adv36 seropositivity was assessed using an ELISA (Obetech, Richmond, VA, USA). Differences between Adv36 seropositive and seronegative groups were analysed using ANCOVA or Mann Whitney U Test.
Results
Among the 973 subjects in the study, 458 (47%) were Adv36 seropositive and 515 (53%) were seronegative. Adv36 seropositivity rate in obese and non-obese was 42.5% v 49.6% (p-NS). In obese, type 2 diabetic subjects, Adv36 seropositives had a higher HbA1c ($P=0.003$) than seronegatives. Adv36 seropositivity was associated with a higher HDL ($P=0.031$) in obese subjects with impaired glucose tolerance, a higher LDL ($P=0.040$) and total cholesterol ($P=0.017$) in obese normoglycaemic subjects, and a lower LDL and total cholesterol innormoglycaemicnormal weight subjects ($P=0.018$ and $P=0.039$, respectively).
Conclusion
Past infection with Adv36 is more prevalent in the UAE than in other countries but we did not confirm a difference between obese and lean subjects. Unlike prior studies in obese diabetic subjects, Adv36 seropositives had worse, not better, glucose tolerance. Lipid profiles differed in obese vs lean, diabetic vs non-diabetic Adv36 seropositive subjects. The spectrum of changes with Adv36 seropositivity appears unique in the UAE population compared to other countries.

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P165

Obesity and diabetes in adults with down syndrome: data from a large diabetes centre in the United Arab Emirates (UAE)

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Background
Down Syndrome (DS) is the most common chromosomal abnormality. Obesity and type 1 diabetes mellitus (T1DM) are known to be more prevalent in patients with DS than the general population. Available data on the prevalence of type 2 diabetes mellitus (T2DM) in DS is scant.
Objectives
This study aims to investigate the prevalence of obesity and diabetes mellitus (DM) in adults with DS seen in Imperial College London Diabetes Centre (ICLDC) in the United Arab Emirates (UAE).
Methods
Participants with a diagnosis of DS recorded on the patient database were included in this study. Information including body mass index (BMI), diabetes

status, pancreatic autoantibody status and medication were reviewed for each record. Data are presented as median (range).
Results
35 participants [18 female, age 25.0 (20–43) years, weight 73.6 (49.8–128.0) kg, height 1.5 (1.3–1.6) m, BMI 34.2 (26.7–48.1) kg/m^2] were identified. All patients were overweight (25.7%; BMI 25.0–29.9 kg/m^2), obese (40%; BMI 30–39.9 kg/m^2), or severely obese (34.3%; BMI $>$40.0 kg/m^2).Nine (25.7%) had a confirmed diagnosis of DM. One (2.9%) had T1DM and was overweight with positive GAD and normal IA-2 antibodies. Eight (22.9%) had (T2DM); Six (75%) of these patients were severely obese. 75% of patients with type 2 diabetes and DS were on metformin.
Discussion
We have reported data on obesity and diabetes in people with DS attending a large Diabetes Centre. Although our data may not be representative of the DS population in the UAE in general, they suggest a high prevalence of overweight and obesity with major management challenges.

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P166

Evaluating non-face to face (NFTF) contacts for patients with Thyrotoxicosis

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Aim
To evaluate the feasibility of non-face to face (NFTF) contact in the follow-up for patients with thyrotoxicosis on carbimazole therapy.
Background
While on carbimazole, achievement of a euthyroid state may involve multiple clinic appointments. We hypothesize by conducting these appointments in a NFTF setting, i.e. telephone consultation with trained nurse practitioner supported by an Endocrine consultant; a higher volume of consultations can occur at a lower cost, making the process more time and cost effective without compromising patient experience or safety.
Methodology
Patients diagnosed with thyrotoxicosis at Lincoln County Hospital from January to June 2014 were invited to partake in NFTF consultations.
Results
A total of 39 patients were recruited for the NFTF trial and sent Patient Satisfaction Questionnaires. The median number of telephone consultations was two. The compliance at the first and second NFTF contact was 69.2% and 74.4% respectively. Approximately, 85.7% of patients reported overall satisfaction with the NFTF consultation method and would be content to continue follow up in this mannerism. The patient's answers highlighted that telephone consultations are a 'quick way to alter dose' and avoided 'travelling 30 miles' for an appointment.
Conclusion and Recommendation
Telephone consultations are an effective method of following up patients as they are safe and fit into the current shared care model. It is cost effective- according to the HRG codes published by NHS England for use in the National Reimbursement System, the cost of one NFTF is 43.50 GBP, whereas the cost of the first face to face appointment is 187 GBP in endocrinology. We recommend recruiting trained nurse practitioners to run this service; however it will be supervised by an Endocrinology consultant to ensure best patient care. This method has been adapted by Lincoln county hospital and is running successfully.

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P167

Male 5-beta reductase knockout mice have altered pancreatic islet morphology and hormone secretion

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The enzyme 5β-reductase (AKR1D1) controls intra-cellular steroid hormone availability through hormone clearance. Additionally, it catalyses an essential step in bile acid (BA) synthesis. Disturbances in steroid hormones and BA metabolism have potent effects on metabolic health, therefore we hypothesize that AKR1D1 may play a role in metabolic homeostasis; the role of AKR1D1 in regulating glucose homeostasis and pancreatic function remains unexplored. We generated a global AKR1D1 knockout (KO) mouse and using stereological techniques, defined islet morphology in mice at 12 weeks of age (12 w) compared against wild-type (WT) controls. Pancreatic islets were isolated from male WT and KO mice at 30 w. Insulin and glucagon secretion were assessed in static incubations. At 12 w, relative pancreas mass, islet volume and beta-cell mass were decreased in male KO mice compared to WT. Conversely, the alpha-cell fraction within male KO islets was increased. At 30 w, insulin secretion was increased in KO islets upon treatment with 1 mM glucose (% islet content: WT: 0.07 ± 0.01, KO: 0.12 ± 0.01), without any change in total islet insulin content. However, in response to 20 mM glucose, the increase in insulin secretion was lower in KO islets when expressed relative to basal levels (WT: 3.5-fold change, KO: 2.6-fold change, $P=0.08$). Additionally, KO islets failed to suppress glucagon release in the presence of 20 mM glucose. Indeed, we observed a paradoxical increase in glucagon secretion with increasing glucose concentration (1 mM glucose; pg/islet.hr: WT: 5.8 ± 1.1, KO: 7.4 ± 3.9. 20 mM glucose; WT: 4.0 ± 0.7, KO: 8.7 ± 3.0). Alterations in steroid hormone and BA exposure have been shown to modify pancreatic islet cell function; AKR1D1 KO male mice have a dysregulation of insulin and glucagon secretion, which may have profound effects on normal glucose homeostasis. Further characterization is warranted to define the role of AKR1D1 and to determine whether it has potential as a therapeutic target in metabolic disease.

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P168

The impact of freeze dried broccoli extract to mitigate inflammation in human adipocytes through the mevalonate pathway

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Background
Delivery of nutrient excess in obesity can disrupt protein folding in the endoplasmic reticulum (ER) within adipose tissue; this activates the unfolded protein response (UPR) and contributes to type 2 diabetes mellitus (T2DM) risk. Thus, the aims of this study were to utilise freeze-dried broccoli extract (BE) as a nutrient to mitigate such cellular damage in human adipocytes, understand the relevance of associated pathways, and create a mathematical model of the UPR to understand pathway dynamics.
Methods
Differentiated human adipocytes (Chub-S7; $n=6$) were treated with BE (hybrid Brassica oleracea var. italic; 10 ng/ml) alone or combined with tunicamycin (Tun; 750 ng/ml), an inducer of ER stress. UPR proteins (BiP, PERK, P-PERK, eIF2α, P-eIF2α) were measured at 18 time points (0 hr–72 hr) using Western Blot; transcriptomics was utilised to gain insight of pathway changes at the most affected time point. Mass action kinetics was used to create ordinary differential Default (ODEs) to model the UPR over time for predictive analysis.
Results
Tun increased UPR proteins 9.5 fold ($P<0.05$), whilst BE+Tun reduced ER stress proteins by up to 94%, back to control levels in many instances ($P<0.05$). Transcriptomic analysis highlighted positive significant changes in the mevalonate pathway with use of BE in treated adipocytes ($P<0,05$), whilst time series data identified oscillatory behaviour of UPR proteins involved in translation attenuation. Finally, modelling pathway dynamics with more time point granularity improved the error between model output and experimental data by 23%, yielding a new enhanced qualitative model.
Conclusion
These studies highlight that BE acts to alleviate ER stress in human adipocytes by reducing the UPR through the mevalonate pathway. Furthermore, modelling pathway dynamics using experimental data for parameterisation may provide insight into predicting nutrient capabilities to reduce obesity mediated T2DM risk.

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P169

Angiopoietin-like ptotein 4 and 8 (ANGPTL4 and ANGPTL8) in human fetal liver are dysregulated by in utero exposure to maternal smoking

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Introduction
Angiopoietin-like proteins (ANGPTLs) are a family of 8 glycoproteins with pleiotropic effects in metabolism, angiogenesis, inflammation and cancer. ANGPTL3, 4 and 8 play major roles in regulating lipid levels, via inhibition of lipoprotein lipase. Increased serum ANGPTL3, 4, 8 levels are associated with obesity, diabetes, metabolic syndrome and fatty liver. Furthermore, cord blood ANGPTL8 is higher than in maternal serum, suggesting a role in fetal development and growth. However, human fetal studies are lacking.
Aim
To investigate ANGPTLs in the human fetal liver transcriptome.
Methods
80 human fetal livers from elective terminations of normal pregnancies (12–19 gestation weeks), were collected (NHS Grampian Research Ethics Committees, REC 04/S0802/21) and RNA extracted. 76 bp single end RNA sequencing reads were then produced (Illumina NextSeq platform). Reads were aligned to the human reference genome and quantified at gene regions. Significant differentially expressed genes were identified using a generalised linear model with a three-way interaction between fetal sex, fetal age and maternal smoking status (confirmed by measuring fetal cotinine).
Results
All ANGPTLs, with the exception of ANGPTL5 and ANGPTL7, were robustly detected in all samples. ANGPTL4 and ANGPTL8 exhibited significant changes in the three-way interaction model ($P < 0.001$). ANGPTL4 was significantly upregulated (3-fold) in older smoke-exposed males (>17 gestation weeks). ANGPTL8 was significantly higher in 14–16 gestation weeks smoke-exposed females (5-fold) and in >17 gestation weeks smoke-exposed males (7-fold).
Conclusions
We report, for the first time, ANGPTLs transcript in human fetal livers across the second trimester of gestation. *In utero* exposure to cigarette smoke resulted in marked sex- and age-specific changes in ANGPTL4 and ANGPTL8. Maternal smoking is associated with an increased risk of obesity and metabolic syndrome in offspring. Therefore, we suggest that ANGPTL dysregulation during fetal life may play a role in adverse metabolic reprogramming.

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Effects of visfatin on brown adipose tissue energy regulation

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The role of brown adipose tissue (BAT) in pathological states of energy homeostasis and impaired adipocyte function, such as obesity has been a major area of research interest in recent years. Herein, we sought to determine the direct effects of adipokines, visfatin and leptin on BAT thermogenesis. The effects of mouse recombinant visfatin, nicotinamide mononucleotide (NMN) and leptin with or without FK866 were studied on differentiated T37i cells. Treated cells were analyzed for key genes and proteins regulating BAT [UCP-1, PRD1-BF1-RIZ1 homologous domain-containing 16 (PRDM-16), PPARgamma-coactivator-1alpha (PGC-1a) and receptor-interacting protein 140 (RIP-140)] using quantitative PCR and western blot analysis. Data is presented as mean *P*-values. Both visfatin and leptin had significant concentration dependent effects on thermogenesis in brown pre-adipocytes and at physiological levels, increased uncoupling protein-1 (UCP-1) levels in brown adipocytes. These effects of visfatin were similar to that of nicotinamide mononucleotide (NMN), further strengthening the enzymatic role of visfatin. We also showed that leptin induced UCP-1 mRNA expression and protein production appears to be mediated by visfatin. High concentrations of both visfatin and leptin led to a dramatic decrease in UCP-1 protein levels, supporting the notion that visfatin levels are raised in obesity and that obese people have reduced BAT activity, plausibly through a reduction in UCP-1 levels. Additionally, we found differential regulation of key brown adipogenic genes, specifically, PRD1-BF1-RIZ1 homologous domain-containing 16 (PRDM-16), PPARgamma-coactivator-1alpha (PGC-1a) and receptor-interacting protein 140 (RIP-140) by visfatin. Our observations provide novel insights in the potential actions of visfatin in BAT.

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P171

Glucocorticoid-induced metabolic syndrome: establishing the role of AgRP

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Glucocorticoid (Gc) excess, either from endogenous overproduction in disorders of the hypothalamic-pituitary-adrenal axis or exogenous medical therapy, is recognized to cause adverse metabolic side effects including obesity, hyperphagia, and hyperglycemia. The Gc receptor (GR) is widely expressed in the brain including the hypothalamus which is known to regulate energy balance. We have previously established through the administration of corticosterone (Cort) in the drinking water, that exogenous Cort delivery increases hypothalamic Gc levels[1]. This chronic elevation was associated with increases in AgRP mRNA expression and hyperphagia. The aim of this study was therefore to establish the role of AgRP in the development of Gc-induced obesity, hyperphagia, and hyperglycemia. CRISPR technology was used to create a novel model of AgRP knock down, deleting all three coding exons of the AgRP gene ($AgRP^{-/-}$). Corticosterone (75 μg/ml) or vehicle (1% ethanol) was administered in the drinking water to $AgRP^{-/-}$ and $AgRP^{+/+}$ mice across 3 weeks. Cort increased food intake in $AgRP^{+/+}$ mice after 3 days, and this remained elevated at 3 weeks. However, $AgRP^{-/-}$ mice were partially protected from Cort-induced hyperphagia. In comparison, both $AgRP^{+/+}$ mice and $AgRP^{-/-}$ mice treated with Cort had increased body weight between days 10 and 14 which then remained elevated for 3 weeks. In addition, at the end of the 3 week study, both $AgRP^{+/+}$ mice and $AgRP^{-/-}$ mice treated with Cort were hyperglycemic and hyperinsulinemic. These results indicate that although AgRP partially mediates Cort-induced hyperphagia, other non-AgRP related mechanisms play a role in driving the development of Cort-induced obesity and hyperglycemia.
Reference
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P172

Reduced PTEN levels enhance the proliferation as well as differentiation of preadipocytes

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Background/aim
Patients with germline mutations in the tumor suppressor *PTEN* frequently develop single or multiple lipomas. PTEN antagonizes the

phosphatidylinositide3-kinase/AKT/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway, which promotes cell proliferation and is involved in adipocyte differentiation. The aim of this study was to investigate the mechanisms leading to aberrant adipose tissue growth using PTEN knock-down cell models.

Methods

Primary cells of the stromal vascular fraction (SVF) from human fat biopsies were transfected with siRNA against PTEN after 40 or more days in culture and compared to scramble siRNA transfected cells. Additionally the PTEN gene was mutated in SVF cells using the CRISPR/Cas9 system.

Results

PTEN was transiently down regulated in SVF cells via siRNA to 65 ± 5% resulting in an elevated AKT phosphorylation (7.7 ± 5.1 fold) compared to control cells. Lipid accumulation was 1.4 ± 0.2 fold higher in differentiated PTEN knock-down cells compared to controls as measured by Oil-Red O staining. PPAR gamma expression increased 1.7 ± 0.1 fold. Cell count was increased 2.3 ± 0.3 fold in PTEN knock-down cells after 7 days. An elevated AKT phosphorylation as well as increased lipid accumulation (2.5 ± 0.3 fold, measured via Nile Red staining) and cell count (1.7 ± 0.2 fold) were also observed for PTEN CRISPR cells.

Conclusion

Primary human preadipocytes lose their ability to differentiate into adipocytes after several weeks in culture. Their differentiation capacity could be partly recovered with reduction in PTEN levels. An enhanced proliferation of these cells corresponds with the enhanced activation of AKT.

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P173

Fructose is metabolised by human subcutaneous adipocytes and can be used as a substrate for *de novo lipogenesis*

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Introduction

Excessive consumption of free sugars (glucose and fructose) is linked to an increased risk of developing chronic metabolic diseases. Current knowledge of fructose metabolism has focussed on the liver where it is implicated in impaired insulin sensitivity, increased fat accumulation and dyslipidaemia. The long-term effects of elevated fructose consumption on human health are poorly defined and fructose metabolism in subcutaneous adipose tissue, the largest human fat depot, has not been studied.

Methods

Primary human preadipocytes were differentiated in the presence of increasing concentrations (5 mM, 11 mm, 22 mM) of glucose or glucose:fructose (1:1). Differentiation medium was supplemented with $^{2}H_2O$ (5%) to measure *de novo lipogenesis* and U-^{13}C-fructose to trace fructose metabolism. Intracellular triglycerides (TG) were extracted and fatty acid (FA) composition was measured by gas-chromatography (GC). ^{2}H and ^{13}C enrichment of TG-palmitate was assessed using GC-mass spectrometry (MS). Gene expression of lipogenic genes was performed by real-time qPCR.

Results

GC analysis identified a reduction in 16-carbon FAs (62.4 vs. 53.7 mol%, $P = 4.2 \times 10^{-8}$; 22 mM) and an increase in 18-carbon FAs (25.8 vs. 36.4 mol%, $P = 7.7 \times 10^{-7}$; 22 mM) at the higher concentrations of fructose. Consistent with increased FA elongase activity mRNA expression of *ELOVL6* was upregulated in fructose-treated cells ($P < 0.05$). Total TG content was similar between glucose- and fructose-treated cells across all concentrations and there were no differences in lipogenic gene expression (*FASN*, *ACACA*). GC-MS analysis identified equivalent ^{2}H enrichment in TG-palmitate across all fructose concentrations (5 mM: 0.51 vs. 0.54, 11 mM: 0.51 vs 0.53, 22 mM: 0.48 vs. 0.48; 271/270 TTR) whereas ^{13}C enrichment in fructose-treated cells increased in a dose-dependent manner ($P < 0.05$).

Conclusions

Human subcutaneous adipocytes metabolise fructose. Fructose favours elongation of 16-carbon to 18-carbon FAs but does not alter total *de novo lipogenesis*. The functional significance of fructose-induced metabolic changes in subcutaneous adipocytes requires further investigation.

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P174

Placental DNA methylation is associated with infant adiposity but is not altered with metformin exposure

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Background

Metformin is widely used for treatment of gestational diabetes mellitus. Metformin is considered safe in pregnancy but crosses the placenta. The limited available data of follow-up of children exposed to metformin in utero suggests potential for increased adiposity but mechanisms are unknown. As placental DNA methylation has been linked to later obesity and metformin causes global DNA methylation changes in cancer cell lines we hypothesised that this may be a candidate pathway.

Methods

DNA methylation arrays (Illumina® Infinium Human Methylation 450 BeadChips, USA) were performed on bisulphite-converted DNA (EZ DNA Methylation kit, Zymo Research, UK) extracted from placenta samples ($n = 100$) from women who participated in 'EMPOWaR', a randomised controlled trial of treatment with metformin vs placebo in obese pregnant women without diabetes. We analysed the association of DNA methylation and metformin treatment with infant growth at three months ($n = 89$, $n = 43$ (48.3%) Male, $n = 45$ (50.6%) metformin treated). Data were analysed using R programming (CpGassoc package) and adjusted for baby sex with Holm-Bonferroni adjustment for significance.

Results

Decreased DNA methylation at five CpG sites within the ACADS gene (acyl-CoA dehydrogenase short chain, a key enzyme in mitochondrial fatty acid beta-oxidation) was significantly associated with increased infant weight at three months. Decreased methylation in eleven CpG sites within the genes ACADS and CYP11A1 (Cytochrome P450 Family 11 Subfamily A Member 1, involved in synthesis of cholesterol/steroids) was significantly associated with increased infant ponderal index. Metformin treatment was not associated with placental DNA methylation or infant adiposity.

Conclusion

As ACADs has been identified as a gene associated with type 2 diabetes and obesity in both infant and adult in recent genome-wide association studies, our observation of decreased placental DNA methylation and infant adiposity warrants further investigation. Further follow-up studies are needed to determine any longer-term outcomes of metformin exposure in utero.

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P175

Hepatic Cyp17a1 regulates the adaptive starvation response aia a nuclear receptor network

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Coupling metabolic processes to nutrient availability is essential for survival. The nuclear receptors PPARα and FXR regulate adaptive liver metabolism in the fasted-state and fed-state, respectively, through a complex mechanism that is incompletely understood. Here, we show that hepatic expression of the steroidogenic enzyme Cyp17al is strikingly regulated by feed-fast cycles via a repressive nuclear receptor cascade involving bile-acid:FXR signalling. Using both gain- and loss-of-function approaches, we find that Cyp17A1 likely produces a ligand for PPARα, and is essential for maintaining blood glucose levels during fasting. Together, these data identify Cyp17a1 as a novel hepatic FXR target-gene

that contributes to the adaptive starvation response. These studies also suggest that targeting of hepatic Cyp17a1 may improve lipid handling under specific pathological conditions.

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P176

A Direct Comparison of Metabolic Responses to NAD repletion in C57BL/6J and C57BL/6N diet-induced obesity mouse models

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Background and Aim
Supplementation with precursors of nicotinamide adenine dinucleotide (NAD), was shown to be beneficial in preventing metabolic dysfunction in mice, which is induced by feeding a high fat diet. We compared the effect of nicotinamide riboside (NR) supplementationon whole-body energy metabolism and mitochondrial function in two widely used diet-induced obesity mouse models.
Methods
Mice were fed a high fat diet (HFD, 60% fat) or standard chow with or without supplementation of 3 g/l NR in the drinking water for 8 weeks. Body and organ weights, liver lipids as well as glucose tolerance were measured. Metabolic phenotype was determined by indirect calorimetry, mitochondrial O2 flux in liver, muscles and heart was measured by high resolution respirometry.
Results
NR supplementation had a slight positive effect on fasting blood glucose and on energy expenditure of B6/N mice on HFD. In B6/J mice, NR influenced substrate usage as determined by respiratory exchange ratio both in chow and HFD-fed mice. Mitochondrial O2 flux and citrate synthase activity were significantly increased by NR supplementation specifically in heart muscle fibers of B6/N, but not B6/J mice on HFD. No effect on mitochondrial function was found in the other examined tissues. The mitochondrial enzyme nicotinamide nucleotide transhydrogenase (Nnt) was found to be 2-fold upregulatedin hearts of B6/N mice on HFD + NR, which was reflected by lower levels of the oxidative stress marker 4-hydroxynonenal.
Conclusion
The effect of NR supplementation in diet-induced obesity is influenced by mouse genotype and possibly related to cellular redox status.

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Reproduction

P177

Naringenin inhibits progression, proliferation and induces apoptosis via ROS generation in endometriotic lesions in rats

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Endometriosis is one of the commonly occurring disorders of reproductive women, which represents attachment of functional endometrial cells and tissue outside the uterine cavity, culminates into infertility. This invasive disorder is still under quest for novel treatment strategies. Naringenin is a plant-derived flavonoid having anti-proliferative, anti-inflammatory, and anti-angiogenic properties in chronic and metabolic diseases. The study was planned with an objective to demonstrate the therapeutic prevention of endometriosis by naringenin in rats and to examine its impact on various cellular aspects with a view to define the mechanism involved. Endometriosis was induced in rats by autologous transplantation of uterine tissue in the mesenteric arteries. Endometriotic rats were given naringenin (50 mg/kg/bwt daily) and dienogest (0.3 mg/kg/bwt daily) for 21 days. The endometrial implant volumes, weight, nitric oxide release, TNF-α level in serum and the histopathologic scores were significantly reduced in the naringenin treated group as compared to the endometriotic control group. Cell proliferation, migration and invasion were inhibited by naringenin (at dose of 1 μM and 5 μM) in endometriotic cells in-vitro. Naringenin caused dose-dependent loss of mitochondrial membrane potential and induced apoptosis. Naringenin ameliorated the expression of various proteins (TAK1, PAK1, VEGF and PCNA) involved in development and progression of endometriotic cells. A significant modulation in level of antioxidant transcription factors, their downstream and repressor molecules was found in endometriotic lesion developed in naringenin treated rats as compared to that of control endometriotic rats. Naringenin prevented the invasion of endometrial cells by inhibiting the expression of MMP-2 and MMP-9. We conclude that naringenin may have a therapeutic potential in the treatment of endometriosis due to ROS mediated apoptosis and its anti-invasive effects.

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P178

Altered vascular function in boys with hypospadias- role of reactive oxygen species

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Background
Hypospadias in boys may be associated with a lack of androgen exposure during the masculinisation programming window. As testosterone has effects on the vasculature, we assessed whether boys with hypospadias show evidence of vascular dysfunction.
Methods
Excess foreskin tissue was obtained from boys undergoing hypospadias repair (cases) or circumcision (controls) and small arteries dissected. Vascular contractility was assessed by wire myography in response to U46619 (thromboxane A2 analogue). Vascular smooth muscle cells (VSMCs) were cultured and generation of reactive oxygen species (ROS) was measured. NADPH oxidase (Nox) mRNA expression was measured by qPCR.
Results
19 cases and 22 age-matched controls were enrolled in this study (median age 1.9 (range 1.3, 12.2) years). There were 8(42%) cases of distal, 4(21%) midshaft and 7(37%) proximal hypospadias. There was no underlying disorder of sex development in the cases and there were no differences in clinical cardiometabolic or biochemical parameters between the cases and controls. Arteries from cases demonstrated increased constriction to U46619 compared to controls (Emax: 175.6–66.3, $P<0.001$), an effect inhibited by the ROS scavenger N-acetylcysteine (NAC). VSMC superoxide anion (5.3 fold) production and H_2O_2 (3.3 fold) levels were increased in cases ($P<0.05$). Expression of Nox5, a major ROS-generating oxidase in VSMC, was also increased in cases (2.6 fold, $P<0.05$). Exposure of vessels to testosterone increased vasoconstriction to U46619 (Emax: 66.3 – 124.6 $P<0.001$) in controls, but not cases. Incubation with NAC abolished the testosterone-induced vascular effects. Vascular hypercontractility in boys with hypospadias was associated with reduced endothelium-dependent and independent vasorelaxation.
Conclusions
These novel data demonstrate that small arteries from boys with hypospadias exhibit increased vascular contractility and decreased vasorelaxation with associated increased Nox-derived ROS generation. The significance of vascular dysfunction in these boys is unclear, but may play a role in surgical outcome as well as altered long-term cardiovascular risk.

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P179

The effectiveness of management of pregnant women with type 1 diabetes mellitus with continuous subcutaneous insulin infusion

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Aim
Assess the effectiveness of management of pregnant women with type 1 diabetes mellitus (DM 1) with continuous subcutaneous insulin infusion (CSII).
Materials and Methods
Pregnant women with DM 1 with CSII ($n=21$) - the main group and on multiple daily insulin injections (MDI) ($n=216$) - the comparison group. We used

different models of the Medtronic pumps. The inclusion in the comparison group carried out by a continuous method. The term of delivery, the frequency of preeclampsia, the level of glycated hemoglobin (HbA1c) in the 3rd trimester were used as efficiency criteria.

Results

In the main group, premature delivery was only 9.5%, compared with 53.7% in the group of MDI. The incidence of preeclampsia in the main group was significantly lower and amounted to 19.1%, compared with 52.8% in the comparison group. Also, the level of HbA1c in the third trimester in the main group were significantly less than in the comparison group and amounted to 5.92%, in comparison with 6.73%.

	CSII	MDI
Preterm delivery n, %	2 (9.5%)	116 (53.7%)*
Preeclampsia n, %	4 (19.1%)	114 (52.8%)*
The average HbA1c in the 3rd tr.,%	5.92%	6.73%*

(* - the difference were significant, $P<0.05$).

Conclusions

The continuous subcutaneous insulin infusion is an effective method of management of pregnant women with type 1 diabetes, which allows obtaining a full-term child in 90% of cases against the background of the optimal state of carbohydrate metabolism, reducing the frequency of preeclampsia.

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P180

Aortic growth in Turner syndrome is accellerated compared with general population

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Introduction

Women with Turner syndrome (TS) have an increased risk of aortic dissection. Aortic dilatation, bicuspid aortic valve (BAV) and hypertension confer increased risk of dissection. However, only some women with these risk factors develop dissection, and others with no risk markers may dissect. Knowledge of the development of the aortopathy over time is limited. We investigate aortic dimension changes in unselected adult TS and associations between aortic growth and risk factors for dissection.

Methods

TS-women aged >16 y with a baseline and follow-up transthoracic echocardiography (TTE). Exclusion criteria: scans with poor visualization. Ascending aorta (AA) and sinuses were assessed by two cardiologists. Age at baseline-TTE, BAV, hypertension and baseline aortic measurements were analyzed.

Results

Sixty-four TS-women who had TTE at baseline age 32±13 years (17–59) with TTE follow-up of 4.9 years (0.7–12.9) were included. Mean baseline measurements were: AA 26.4±4.2 mm (median 25) and sinuses 27.5±4.4 mm (median 27). The aortic growth rate/year was at AA 0.29±0.92 mm/y (−2.41 – 2.72; median 0.22) and at sinuses 0.08±1.06 mm/y (−2.9 – 3.7; median 0.00). One woman experienced dissection; aortic growth was at sinuses 3.4 mm/y and at AA 1.4 mm/y. Women with BAV (13/64) showed higher growth at sinuses (0.90±1.4 mm, $P=0.001$). Age at baseline and hypertension were not associated with aortic growth. Aortic growth was not dependent on baseline aortic diameter.

Conclusions

This long follow-up study showed a rapid rate of aortic growth in TS compared to general population (0.07 mm/year). Enlargement at aortic sinuses was accelerated in the presence of BAV. We suggest that risk stratification for aortic dissection in TS should include assessment of changes over time in proximal aortic diameter and in the presence of a rapid aortic growth closer follow-up is needed.

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P181

Gonadectomy for adults with DSD conditions at risk of hypogonadism in the international disorders of sex development registry

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Introduction

Disorders of Sex Development (DSD) can be associated with an increased risk of germ cell tumours depending on the underlying diagnosis. To date however knowledge regarding the indications and timing of gonadectomy is lacking.

Methods

The I-DSD Registry was interrogated for anonymised information regarding the diagnosis, karyotype, sex of rearing and timing of gonadectomy, if undertaken, of all individuals of any karyotype who were over the age of 16 years at the time of search and who had one of the following disorders that may lead to long-term hypogonadism: androgen action, androgen synthesis; gonadal dysgenesis; Leydig cell hypoplasia; persistent Müllerian duct syndrome or a non-specific disorder of undermasculinisation.

Results

At the time of search in January 2017, 2,141 cases were accessible on the I-DSD Registry. A total of 614 of these (57%) met the study inclusion criteria. Data regarding gonadectomy was available in 520 (85%). The cases were registered from 30 different centres in 21 different countries, over 4 continents. 158 (30%) (median age 24 years, range 17–72 years) of these individuals were currently registered male. 362 (70%) individuals were currently registered as females (median age 28 years, range 16–90 years). Gonadectomy was performed in 315 (61%) cases. There was no statistically significant difference in timing of gonadectomy ($P=0.09$) between males and females with a median age at time of gonadectomy of 14 (range 0.3–68) years in females and 5 (range 0.1–54) in males. The most common indication for gonadectomy was complete androgen insensitivity syndrome in females ($n=194$, 68%) and partial gonadal dysgenesis

in males ($n=15$, 50%), with females more likely to have gonadectomy than males for all conditions.
Conclusions
The I-DSD Registry contains a large number of young adults who are at risk of germ cell tumours and provides an opportunity to investigate current trends in gonadectomy internationally.

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P182

Elongated transverse aortic arch in Turner syndrome: a useful marker for cardiovascular risk?

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Introduction
Elongated transverse aortic arch (ETA) has recently been described as the commonest abnormality (≅50%) in Turner syndrome (TS), exceeding the prevalence of bicuspid aortic valve (BAV; 10–30%) and aortic coarctation (CoA; 7–18%). Nevertheless only few studies focused on ETA. ETA was associated with BAV, CoA, 45,X and aortic dilatation.
Aim
To evaluate the prevalence and associations of ETA in adult TS, unselected for cardiovascular disease.
Methods
Cardiovascular-MRI of 89 TS-women (37.7 years) were evaluated by two cardiologists, blinded to the subject's clinical history. ETA was defined by the presence of (1) posterior origin of the left subclavian artery (LSA) behind the trachea and (2) inward indentation or convex kinking of the inferior aortic contour along the lesser curvature. Absolute and indexed (i) diameter for body surface area of aortic sinuses and ascending aorta (AA) were collected.
Results
The prevalence of posterior origin of LSA was 38.2% (34/89). 11.2% (10/89) had kinking of the inferior aortic contour. Only 6.7% (6/89) had both the criteria for ETA. BAV was reported in 26% and CoA in 13%. 5/6 women with ETA had 45,X and one 45,X/46,idicX. 3/6 had BAV, CoA and hypertension. Aortic dissection had occurred in 3/89: one women with ETA and one with posterior origin of LSA. Comparing the group of patients with and without ETA, the presence of ETA was associated with CoA ($P=0.018$) and higher aortic diameters: AA 3.5 ± 0.7 cm vs 2.8 ± 0.4 cm respectively ($P<0.001$); iAA 2.6 ± 0.7 cm/m^2 vs 1.8 ± 0.3 cm/m^2 ($P<0.001$) and sinuses i2.3 ± 0.4 cm/m^2 vs i1.9 ± 0.3 cm/m^2 ($P=0.036$).
Conclusions
Our data showed a lower prevalence of ETA compared to previous studies (notwithstanding a similar prevalence of BAV and CoA). ETA was associated with aortic dilatation and coarctation, but these are better assessed directly with imaging methods, and ETA does not currently appear to be a useful additional clinical indicator.

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P183

Impact of ethnicity on the change in total testosterone, haematocrit and prostate-specific antigen with Testosterone undecanoate treatment

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Background
Current guidelines recommend regular monitoring of total testosterone, haematocrit and prostate-specific antigen (PSA) when androgen-deficient males are commenced on testosterone replacement therapy (TRT). The aim is to restore serum total testosterone to the mid-normal range, whilst maintaining haematocrit and PSA at the recommended levels. Limited studies have assessed the impact of ethnicity on these biochemical parameters.
Aim
To measure the impact of ethnicity on total testosterone, haematocrit and PSA following Testosterone undecanoate replacement.
Method
A retrospective analysis of 50 male patients, treated with testosterone undecanoate between 2006 to 2017, in a large secondary care centre was performed. Changes in total testosterone, haematocrit and PSA over 10 years of treatment were analysed. Mann-Whitney U test was used to assess differences in these parameters of the two ethnic groups- Caucasians and Asians.
Results
Thirty-one Caucasians (age: median (IQR) 54.0 years (42.5–68.0); duration of treatment 1253.0 days (537.5–2066.8) and 19 Asians (age: median (IQR) 52.0 years (42.0–68.0); duration of treatment 1264.0 days (540.0–2077.0) were treated with TRT during the study period. There was no significant difference in total testosterone levels between the two ethnicities. There was a significant rise in haematocrit in Asians compared to Caucasians in the first ($P=<.000$) and sixth year ($P=.029$) of therapy. PSA was significantly higher in Caucasians compared to Asians in the second ($P=.022$), fourth ($P=.014$), fifth ($P=.016$), seventh ($P=.032$), eighth ($P=.012$) and ninth ($P=.016$) year of therapy.
Conclusion
Differences in haematocrit and PSA between the two ethnic groups varied from year to year. Caucasians have a tendency towards higher PSA rise compared to Asians with TRT. Particular focus on haematocrit may be needed in the first year of TRT in Asians.

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P184

Where Are They Now? Review of patients diagnosed with Disorders of Sex Development since 1988

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Background
As diagnostic workup and management of patients with Disorders of Sex Development (DSD) evolves, access to the latest advances should continue.
Aims
To explore whether DSD patients in the West Midlands Region (WMR) remain under follow up, having optimal diagnostic workup and management.
Method
An unselected cohort of 48 patients with discrepant phenotypic gender and sex chromosomes in the WMR were identified from the regional genetics laboratory database. Ten patients were excluded as genetic records were unavailable.
Results
Median age at presentation was 15 years (range 0–61 years), with 27 patients currently ≥ 18 years (adult group), and 11 patients <18 years (non-adult group). The DSD type was 46XY in 25 patients (65.8%), and 46XX in 11 patients (28.9%). The karyotype for two individuals was unavailable. Primary amenorrhoea was the commonest presentation in 46XY female patients (73.7%), and fertility disorders in the 46 XX male patients (42.9%). In the non-adult population, 36.4% presented with ambiguous genitalia. A clinical diagnosis was made in 78.9%, but there was no confirmed genetic diagnosis in 28.9%. A gene panel was employed in 23.7% of the whole group, but in only 22.2% of the adult group compared to 30.0% in the non-adult group. In 46XY female patients with androgen insensitivity, 52.6% of the adult group underwent gonadectomy, compared to 28.6% in the non-adult group. 47.1% of adults and 52.9% of non-adults have been in contact with the genetics team over the last 2 years. This accounts for 47.2% of the whole population in our study that have been under follow-up.
Conclusion
We have identified that in the WMR, patients with DSD, particularly adults, are not receiving benefits of advances in current practice in relation to making a genetic

diagnosis, and are potentially lost to follow up. Development of adult services for these patients is essential.

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P185

Managment of women with premature ovarian insufficiency: a multi-disciplinary review of practice

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Introduction
Women with premature ovarian insufficiency (POI) may complain of various symptoms and consequently be seen by clinicians in a range of settings. Management is multifactorial and may vary depending on the awareness of practitioners within each specialty/subspecialty. In 2015, the European Society for Human Reproduction and Embryology (ESHRE) published guidelines on the management of POI. These state that women should have the following investigations: karyotype; screening for Fragile X pre-mutation, thyroid peroxidase (TPO) and 21-hydroxylase antibodies; and measurement of bone mineral density (BMD). Treatment should incorporate: lifestyle advice; oestrogen replacement; contraception; fertility; bone protection; and psychological support.
Aims
To assess compliance with ESHRE guidelines at Leeds Teaching Hospitals NHS Trust (LTHT) and determine whether this varies according to clinical setting of presentation.
Methods
A retrospective review of all females diagnosed with POI between 01/07/16 and 30/06/17 in one of the following clinics: paediatric endocrinology; general endocrinology; oncology; reproductive medicine; menopause; and general gynaecology. We assessed which investigations had been performed and what treatments had been discussed.
Results
We identified 103 women, who were evenly distributed between the different clinics. Overall, 40.6% had a karyotype. Screening for Fragile-X pre-mutation, TPO and 21-hydroxylase antibodies and BMD occurred in 7.4, 11.1, 13.6 and 35.9% respectively. There was significant variation in performance of a karyotype and TPO antibodies between the different settings. Overall, lifestyle advice was offered to 30.1%. Oestrogen replacement, contraception, fertility, bone protection and psychological support were discussed with 76.0, 38.4, 59.0, 75.0 and 25.2% respectively.There was significant variation for all apart from contraception.
Conclusion
Management of POI at the LTHT is not consistent with ESHRE guidelines and requires improvement. Furthermore, there is significant variation in practice amongst the different specialties/subspecialties. We suspect similar results may occur elsewhere. We have proposed remedial action and will reassess following implementation.

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P186

Hormone replacement therapy and cognition in menopause

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Background
Menopause marks the permanent cessation of periods for a woman. It is commonly associated with cognitive impairment. Oestrogens and progestins have been known to have a profound effect on the central nervous system and can exert neuroprotective effects on the cellular level. This led to the hypothesis that administration of oestrogens, progestins or a combination of both in the form of hormone replacement therapy (HRT) can have a protective or therapeutic effect against cognitive decline during and after the menopausal transition.
Objective
To conduct a systematic review of randomised controlled trials (RCTs) investigating the effect of HRT on the prevention or treatment of cognitive symptoms, cognitive decline and dementia in perimenopausal and postmenopausal women.
Materials and Methods
A pubmed, EMBASE and PsycINFO online search was conducted and the references of selected studies were searched during the 'snowball' process. 50 RCTs trials were included in the review.
Results
The majority of the RCTs revealed that HRT in menopausal women had a negligible effect on various cognitive measures and did not protect from the development of cognitive impairment or dementia. A few trials revealed that HRT actually had a deleterious effect by increasing the risk for cognitive decline and dementia to a statistically significant degree. Only a very small number of studies showed a positive effect of HRT on a number of cognitive tests.
Conclusion
HRT is not recommended as a preventive or therapeutic measure against cognitive decline and dementia and it is not recommended as a treatment to alleviate cognitive symptoms in menopausal women.

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P187

A prospective study of testicular development and function in boys with Duchenne Muscular Dystrophy

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Introduction
There is a need to understand testicular development in adolescents with Duchenne Muscular Dystrophy (DMD).
Objective
To evaluate testicular development and function in DMD over 12 months.
Methods
All data are presented as median(range). 23 boys aged 12.4 years (10.0, 16.8) with a bone age delay of 0.9 years (−2.4, 7.1) had physical and biochemical assessment of puberty at Month 0(M0) and Month 12(M12) and divided into groups depending on pubertal progress: A-remained prepubertal (*n*,11); B-treated with testosterone (*n*,5); C- spontaneous virilisation (*n*,7).
Results
Testes Z-scores adjusted for bone age at M0 and M12 were −1.3 (−3.6, 1.5), and −2.5 (−3.6, 1.1)(p=0.08).
Group A: Aged 11.2 years (10.0, 12.4), all were on glucocorticoids by M12. 8/11 (73%) and 9/11 (82%) had undetectable LH at M0 and M12; 9/11 (82%) had undetectable testosterone at M0 and M12. Median inhibin B *Z*-scores at M0 and M12 were −0.4 (−3.2, 1.3) and −1.7 (−3.1, 0.7) (*P*=0.02).
Group B: Aged 15.9 years (13.6, 16.8), all were on glucocorticoids and although they virilised with testosterone therapy, testes remained less than 4 ml in all 5 (100%). 3/11 (60%) had undetectable LH at M0 and M12. Median inhibin B *Z*-scores at M0 and M12 were −1.1 (−2.7, −0.0) and −2.1 (−2.4, 0.0) (*P*=0.89).
Group C: Aged 15.1 years (10.9, 16.6), 4 (57%) were on glucocorticoids by M12. Median LH at M0 and M12 was 1.7 U/l (0.6, 8.2) and 1.7 U/l (0.3, 5.6) (*P*=0.89). Median testosterone at M0 and M12 was 4.8 nmol/l (0.7, 16.2) and 9.1 nmol/L (1.2, 13.1)(*P*=0.04). Median inhibin B *Z*-scores at M0 and M12 were −2.2 (−2.8, −1.3) and −2.1 (−2.9, −1.4) (*P*=0.27).
Conclusion
Boys with DMD have relatively small testes. This may be associated with Leydig and Sertoli cell dysfunction as a result of functional hypogonadotrophic hypogonadism.

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P188

The impact of testosterone level on body composition in men with type 2 diabetes (T2D)

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Sex hormones are important determinant of body composition. The significant negative correlation between testosterone and obesity, positive correlation between testosterone and muscle mass and that testosterone therapy increases muscle mass in hypogonadal men is well-known.
Objectives
To assess the impact of total testosterone (TT) level on body composition in men with T2D.
Methods
A cross-sectional study involving men with T2D ($N=200$) assessing the impact of TT level on fat mass % (FM) and fat-free mass % (FFM). Men were divided into 2 groups according to their TT level: group 1 - untreated (TT <12 nmol/l), and sub-optimally treated hypogonadal men (TT <12 nmol/l 2–4 h after the testosterone gel application or trough testosterone level <12 nmol/l if on the testosterone injections) ($N=102$) and group 2 - eugonadal and optimally treated hypogonadal men (TT ≥ 12 nmol/l) ($N=98$). Also, we assessed the significance between body composition and the quartiles of SHBG, HbA1c, ALT and AST/ALT ratios.
Results
Mean age 63.9 ± 8.7 years (range 41–83). Mean TT level for group 1 8.1 ± 2.6 nmol/l (range 0.4–11.8); for group 2 18.3 ± 6.2 nmol/l (range 12.0–52.1). Comparing FM and FFM between the groups, we found significant difference in FM ($P=0.021$) and FFM ($P=0.021$) between the groups. Taking into account that FM + FFM = 100%, the difference for FM and FFM is the same. In regard to FM and FFM, there was significant difference between the SHBG quartiles 1&4 ($P=0.003$), the HbA1c quartiles 2&4 ($P=0.035$), the AST/ALT ratio quartiles 1&4 ($P=0.004$) and 2&4 ($P=0.048$). The difference between the ALT quartiles 1&4 was trending towards statistical significance ($P=0.108$).
Conclusion
i) TT, SHBG and AST/ALT ratio are positively correlated to FFM and inversely correlated to FM. ii). HbA1c and ALT are inversely correlated to FFM and positively correlated to FM. iii). Testosterone should be replaced to the mid-normal range as per guidelines.

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P189

From Evidence to Practice, group education as part of routine outpatient clinic in Polycystic Ovary Syndrome a proof of concept intervention

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Background
The benefits of patient education in women with polycystic ovary syndrome (PCOS) are known but a cost effective way to offer the education to these patients need to be assessed. As part of a quality improvement project in an outpatient setting we tested the idea of incorporating group education for women with PCOS in their routine care process. We tested two different methods.
Methods
1. January-June 2017: Ad hoc open patient invitation
A researcher identified all women with PCOS coming to outpatient reception. Patients were given a letter inviting them to a group session. All clinicians and Trainees were encouraged to invite patients to the sessions.
2. January – June 2018: Dedicated education clinic
A clinic code was set up and an official appointment letter sent to patients. All clinicians and Trainees were made aware of the clinic code and availability of the education session through reminder e-mails.
The education sessions were held in the same location and at similar times. Patients were invited to bring a friend or family member. Assessment of the session was rated from 1 (very bad) to 5 (very good).
Results
Group A: Ad hoc invitation
135 women with PCOS were offered the education session and only 6 (4%) attended.
Group B: Dedicated education clinic
18 of the 31 women (58%) who received an appointment attended the education session.
All patients but two scored the sessions four and five (good or very good respectively) and expressed a desire for more sessions.
Conclusion
Patients with PCOS find education sessions helpful want to come back for more. A dedicated education clinic with an appointment letter with date and time is more effective than an ad hoc open invitation. This proof of concept study might inform methodology for an educational intervention in outpatient setting.

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P190

Clomiphene citrate treatment in women with hypothalamic amenorrhea

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Functional hypothalamic amenorrhoea (FHA) is a disorder associated with functional inhibition of the hypothalamic-pituitary-ovarian axis due to deficiency of pulsatile GnRH. The incidence of FHA ranges from 15 to 48% of all secondary amenorrheas. The abnormal GnRH secretion leads to decreased pulses of gonadotropins, absent midcycle surges in luteinizing hormone (LH) secretion, absence of normal follicular development, anovulation, and low estradiol (E2). Causes of FHA can be classified into the three groups: i) stress-related factors ii) consequences of weight loss or underweight, and iii) extreme physical exercise. FHA is a 'diagnosis of exclusion' and requires multidisciplinary approach. Diagnosis of FHA is based upon the findings of amenorrhea, low gonadotropins and E2 with evidence of a precipitating factor (exercise, low weight, stress). Treatment of FHA should be aimed at elimination of the primary cause, i.e. a decrease in emotional strain, reduction of physical exercise, or optimisation of BMI. If periods do not return after a period of six months, hypoestrogenism may affect the bone metabolism. Hormone replacement is useful in both the treatment of menstrual disorders and normalisation of bone mineral density. Transdermal therapy is more appropriate. Clomiphene Citrate (CC) has also been used to restore periods in women with FHA. We report a series of 16 patients diagnosed with FHA who were treated with CC. An oral preparation (50 mg/day) was administered for 5 days. This was followed by a double dose (100 mg/day) for another 5 days a month later. If periods returned, treatment was continued for the two more months with 100 mg/day from day 3 to day 7 day of the cycle. 13 patients responded well periods retuned to normal, one patient became pregnant. The present data show that CC treatment can be useful to restore normal cycles in young women with FHA.

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P191

Reproductive function in women after kidney transplantation

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According to population registries prevalence of chronic kidney disease (CKD) in the world is about 10%. Global trends show growth of CKD due to diabetic nephropathy, chronic tubulointerstitial nephritis, secondary nephropathies. Kidney transplantation is a 'golden standard' in CKD treatment. Is it performed about 100 times per year in The republican research and practice center for organ and tissue transplantation. The aim of the study was to evaluate menstrual function and describe aspects of endocrine status in women with transplanted kidney. The study included 55 women aged 18–44 (mean age 31 ± 3.8) who had undergone kidney transplantation within last 5 years. They had adequate graft function and were administered immunosuppressive drugs. Control group consisted of healthy regularly menstruation women matched by age. 68% of women with kidney transplantation have regular menstruations with confirmed ovulation, 15% show oligomenorrhea, 17% are amenorrheic. Menstrual function restoring occur within one year after kidney transplantation. Luteinizing and follicle stimulating hormones (on 5th and 25th days) were similar in two groups. Oligomenorrhea was accompanied by significant decrease in progesterone level to 5.48 pmol/L (21 day), statistically significant ($P<0.01$) increase in estradiol level (up to 2.5 nmol/L) in the follicular phase. Elevated prolactin level to 948 mME/L ($P<0.01$) and significant decrease

of testosterone level to 0.1 pg/mL ($P<0.01$) were found in 33% of kidney transplanted women. Women included in the study group who had normal menstruations demonstrated Antimullerian hormone levels significantly ($P<0.01$) lower (1.30–2.45 ng/mL) than in oligo- or amenorrhea. Vitamin D concentrations were comparable. Further studying of menstruation, ovulation and hormone functioning in patients who had undergone kidney transplantation is an actual topic, which aims to preserve reproductive potential and improve quality of life of women, giving them an opportunity to conceive and give birth to healthy children.

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P192

Alteration to PGF and IGF-1, signalled the adverse growth of the foetus and placenta in a genistein exposed pregnancy in experimental rats

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The mechanism of the adverse influence of genistein; a soya phytoestrogen on foetal development is still poorly understood. Previous reports showed adverse effects on thyroid and leptin hormone, C-reactive protein and thyroxin kinase activities. This study evaluated the changes to the level of the insulin-like growth factor-I (IGF-1) and placenta growth factor (PGF) in rat pregnancy exposed to genistein. Pregnant rats grouped into 2 mg/kg and 4 mg/kg genistein treated groups were orally dosed daily with genistein dissolved in distilled water from gestational day (GD) one till sacrificed, while the control group received equal volume of distilled water. At GD-16 and GD-20, serum samples were collected and the placenta tissue carefully harvested and homogenized for the analysis of IGF-1 and PGF using ELISA method. Result showed that the serum level of PGF decreased at gestation day16 while it was increased at GD-20 in the 2 m/kg and 4 mg/kg groups. The placenta PGF level was significant increase in 2 mg and 4 mg/kg group at GD-16 while the level was significantly decreased in both 2 mg and 4 mg/kg at GD-20. Genistein at the two doses used, significantly reduced placenta level of IGF-I compared to control at GD-20 while it was only significantly reduced in 2 mg/kg at GD-16. Thus genistein alters these two growth factors and thus alters the normal growth and development of the placenta and the foetus especially towards term. The reported reduction in placenta and foetal weight in genistein exposed pregnancy is precipitated by the adverse effect on PGF and IGF-1 biosynthesis and proper growth-signal interactions with hormones and energy in the development of the placenta and the foetus.

Keywords: Genistein, Placenta, foetal growth, PGF, IGF-1, phytoestrogen, foetal programing

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P193

Anti-fertility effect of aqueous seed extract of *Buchholzia Coriacea*

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The leaves and seeds of *Buchholzia coriacea (*BC) are known to have antimalarial effect. Many antibiotic and antimalarial agents are known to have antifertility actions. This study was designed to investigate the effect of the aqueous seed extract of buccholzia coriacea on fertility parameters in female rats. Forty regularly cycling rats were randomly divided into two equal groups: BC-treated group (BCT group) received aqueous extract of the seed (200 mg/kg) and the control group (CT group) received equal volume of distilled water as the vehicle. The estrous cycle was monitored throughout the six weeks of administration and blood samples were collected for hormonal analysis at various phases of the cycle. At the end of this period, organs were collected for oxidative studies. The oviduct of rats in the estrous phase was harvested for ova count. Results showed distorted and significantly reduced number of cycles in the BCT group and also a significantly increased frequency of occurrence of the metestrous phase. The number of ova released at ovulation was significantly decreased in the BCT group (2.60 ± 0.24), compared to the CT group (5.80 ± 0.37). FSH level was significantly reduced during the proestrous phase in BCT group (117.66 ± 2.47 ng/ml) compared to the CT group (138.20 ± 2.05 ng/ml) and estrous phase (BCT group - 34.70 ± 2.25 ng/ml; CT group - 58.50 ± 2.05 ng/ml;). There was a significant increase in GSH (31.57 ± 1.33 µmol/ml), SOD (39.83 ± 1.39 µmol/ml) and CAT (659.48 ± 6.61 µmol/ml) in BCT group compared to the control GSH (19.5 ± 1.14 µmol/ml), SOD (56.9 ± 2.19 µmol/ml) and CAT (563.13 ± 12.9 µmol/ml). However, the MDA was significantly reduced in BCT group (91.56 ± 0.22 µmol/ml) compared to the control (2.4 ± 0.19 µmol/ml). Thus, this study showed that the aqueous seed of the *Buccholzia coriacea* has antioxidative properties but possesses antifertility effects.

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P194

Investigating the roles of steroids in gonadal development and maintenance using an androgen and cortisol deficient zebrafish model

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Sex development in zebrafish is highly plastic, making this species an ideal model for investigation of endocrine disruption and gonadal development and function. However, the hormonal regulation of these processes in zebrafish is poorly understood. We have used a model of androgen and glucocorticoid deficiency to explore these processes. In humans, ferredoxin *(FDX1)* is an electron-providing cofactor required for steroid biosynthesis. The zebrafish homologue of FDX1, fdx1b, has a crucial androgen biosynthesis. *Fdx1b* mutant zebrafish are profoundly androgen and glucocorticoid deficient. We have analysed the phenotype of adult *fdx1b* mutant zebrafish to investigate the role of steroids in sex development and gonadal differentiation. *Fdx1b* mutants exhibit feminised secondary sex characteristics but may possess either testes or ovaries, both sexes are sterile. Histological investigation showed abnormal seminiferous tubule structure and disorganisation of *fdx1b* mutant testes, compared to those of wild-type siblings. To investigate mechanisms behind testicular disruption and sterility we measured expression of genes regulating testicular development or spermatogenesis. We observed downregulation of pro-testis gene *sox9a,* and *igf3,* a key factor for spermatogonial proliferation and differentiation, in *fdx1b* mutant testes. The mechanism behind female infertility remains unclear and is currently under investigation however misregulation of several genes involved in female development has been detected. Whilst androgens regulate some secondary sex characteristics, they do not promote testis differentiation, as mutants developed distinct ovaries or testes. However, it is clear that androgens have an important role in development, maturation, organisation and function of both male and female gonads, since adult males and females were sterile. Taken together, our observations provide novel insights into the roles of androgens in these processes. We anticipate that these insights will support development of model organisms to study the interplay of genetic factors and environment in disorders of sex development.

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P195

Exhaustive characterization of placental production of progesterone *in vitro*

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Placenta is an endocrine organ, secreting steroids (progesterone [P4], estrogens) and hCG, thanks to villous tissu (cytotrophoblasts [VCT] and

syncytiotrophoblast [ST]). P4 is required for implantation and maintenance of pregnancy. P4 is synthetized from maternal cholesterol thanks to mitochondrial transporter MLN64 and P450SCC and HSD3B1 enzymes. We aimed to characterize P4 production in human placenta during VCTs differentiation into ST *in vitro*. VCTs isolated from term placenta ($n=6$) were cultured for 72h to allow trophoblast differentiation. hCG, P4 and Pregnenolone secretions were measured in supernatants from 24h to 72h by immuno-assay (IA) and/or mass spectrometry (GC-MS/MS). Intracellular expression of transporter (MLN64) and enzymes (P450SCC and HSD3B1) were studied by western-blot and RT-qPCR. The same experiments were performed with 10 μM of Forskolin (FSK, a cAMP/PKA pathway activator) to stimulate trophoblast differentiation. hCG and P4 secretions increase during trophoblast differentiation (respectively 25 and 8 folds). An increase of P4 (12 folds) and pregnenolone (6 folds) is observed using GC-MS/MS during VCTs differentiation. However, 17-OH-Progesterone is not detected, confirming the absence of CYP17 enzyme in placenta. HSD3B1 and MLN64 expression increase (respectively 4 and 1,5 folds) during trophoblast differentiation at mRNA and protein levels whereas P450SCC expression remains constant. Using IA and/or CG-MS/MS, after FSK-induced differentiation, hCG level increases at 24h and 72h whereas P4 and pregnenolone levels increase (respectively 1,3 and 1,5-folds) only at 72h. Furthermore, HSD3B1 and P450SCC protein expressions increase (respectively 1,3 and 2,1 folds) in FSK-incubated trophoblasts at 72h. Our results highlight that steroidogenesis is already effective in VCT. Each steps of the synthesis increase during trophoblast differentiation leading to increase pregnenolone and progesterone secretions. Interestingly, FSK-induced trophoblast differentiation involves a rise in progesterone production. These results suggest that steroid production is linked to VCT differentiation and may involve hCG.

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P196

Alterations in some heavy metal levels correlated with cellular adenosine triphosphate production in male rats exposed to a municipal dumpsite

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Heavy metals are present in different waste types and products found in landfills and they are known not only to pose considerable health risk in the waste management sector but also specifically engender health hazards for the environment and people living near the landfills and dumpsites. However, there is little evidence associating male proximity to dumpsites with reproductive function. This study was carried out to examine the effects of heavy metal levels on reproductive function in direct exposure to a municipal dumpsite. Ten male rats were raised from birth to adulthood on the dumpsite (DSE group) and they were fed on solid wastes and leachates while another ten male rats which served as control were raised in the laboratory environment and feed and water were provided *ad litum.* At adulthood serum lactate dehydrogenase (SLDH), intratesticular lactate dehydrogenase (ITLDH) (marker of cellular ATP), fructose in the seminal vesicle and coagulating glands, and epididymal heavy metal levels were measured. There was a significant increase in the nickel and arsenic levels of the DSE group compared to the control, while there were significant alterations in the fructose levels and SLDH levels in the DSE rats compared with the control. There was significant positive correlation between the ITLDH and copper levels ($P<0.05$) as well as between ITLDH and mercury levels ($P<0.05$) in the DSE group. Taken together, the alterations in some heavy metal levels and correlation with lactate dehydrogenase level suggest possible impaired reproductive function in men that live close to dumpsites.

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P197

Reproductive Life Course Project: Preliminary data from UK Turner Syndrome Pregnancy audit

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Turner Syndrome (TS) affects 1:2500 females and is caused by the partial or complete loss of one X chromosome. About 80% of women with TS experience primary amenorrhea and therefore the only option for fertility treatment is ovum donation (OD). The remaining 20% may have the opportunity for a spontaneous pregnancy. Pregnancy in women with TS has been associated with excess obstetric risk such as miscarriage and hypertension. Maternal mortality has been estimated to be 2% risk of TS mainly due to the risk of aortic dissection. To date there has been no data to document UK pregnancy data in TS. Here we present preliminary data from the Reproductive Life Course Project (RLCP) that aims to conduct a UK-wide TS pregnancy audit to document pregnancy outcomes in TS.

Methods

Women with TS who had achieved pregnancy were identified by collaborating centres and the TS Support Society (TSSS). Telephone interviews were conducted to collect data regarding; mode of conception, mode of delivery and TS-specific complication such as cardiac events and hypertension. Currently 7 centres are recruiting of which 3 have completed data collection. The TSSS subjects self- reported to UCLH.

Results

Seventy one women with TS have reported 110 pregnancies of which 39% were spontaneous conceptions and 61% were achieved with ovum donation (OD). Miscarriage rates were 35% for spontaneous conceptions and 26% for OD conceptions. No case of acute cardiovascular morbidity such as aortic dissection has so far been identified.

Conclusions

The RLCP is on target to make a major contribution to the world data on pregnancy safety for women with TS. Initial results show an expected high miscarriage rate and stratification of obstetric risks is underway. The project is actively recruiting centres for wider collaboration. For further information see www.RCLP.uk

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P198

Dax1 controls female fertility as a hypothalamic rheostat of estrogen receptor-alpha

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Coupling the release of pituitary hormones to the developmental stage of the oocyte is essential for female fertility. It requires estrogen to have simultaneous positive and negative feedback effects on spatially-distinct regions of the hypothalamus. However, the mechanistic basis for this differential effect is not known. We have found that negative-feedback is mediated by the nuclear receptor Dax1, which is present in the arcuate hypothalamic nucleus and serves as a ligand-dependent repressor of ERa transcriptional activity. It decreases follicle stimulating hormone release in response to rising ovarian estrogen production. Concordantly, mice lacking Dax1 in cells expressing the reproductive-neuropeptide kisspeptin have abnormal estrogen-stimulated gonadotropin secretion and fail to cycle normally. As such, the interaction between Dax1 and ERa in the arcuate hypothalamus explains the paradoxical observation of hypothalamic estradiol negative-feedback.

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P199

Recombinant FSH dosing during controlled ovarian stimulation in IVF treatment

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Background
During IVF treatment, a pharmacological dose of recombinant FSH (rFSH) is used to induce multi-follicular growth (controlled ovarian stimulation; COS). An insufficient dose of rFSH negatively impacts the number of oocytes retrieved, whereas an excessive dose risks the potentially life-threatening complication 'ovarian hyperstimulation syndrome'. Hence, appropriate rFSH dosing is regarded as a key treatment decision affecting both the success and safety of IVF treatment. Current dosing calculators for rFSH are derived to the number of oocytes retrieved, however we hypothesised that rFSH dosing can more accurately be related to follicular growth.
Methods
A single centre retrospective cohort study of 1,034 cycles (January 2012-January 2016) at Hammersmith IVF unit, where rFSH (GonalF) alone was used to induce follicular growth. Follicle sizes at each ultrasound scan and rFSH doses during COS were collated. Relevant univariate and multivariate analyses were conducted.
Results
Recombinant FSH dose adjusted for weight (iU/kg) most accurately predicted serum FSH level ($r^2=0.352$, $P<0.0001$) suggesting that rFSH dose should be weight-adjusted. Weight-adjusted rFSH dose predicted median follicle size after 5 days and the proportion of antral follicles recruited. Day 5 follicle size predicted follicle size on subsequent scans and thus time to oocyte maturation trigger. No additional improvement in ovarian response was identified at doses beyond 2.25 units/kg. A multivariate model incorporating age, AFC and pre-treatment serum FSH predicted the proportion of antral follicles recruited ($r^2=0.22$, $P<0.0001$). An insufficient rFSH starting dose necessitating subsequent dose-increase resulted in increased variability of follicle size on day of trigger, negatively impacting the number of mature oocytes retrieved by a median of 5 between high and low dosing groups ($P<0.0001$).
Conclusion
Recombinant FSH dose should be weight-adjusted. Commencing COS with a sufficient starting dose of rFSH is advantageous, reducing variability in follicle size and improving the number of mature oocytes retrieved.

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Thyroid

P200

Controlled Antenatal Thyroid Screening (CATS) II: long-term cardiometabolic effects of treating maternal sub-optimal thyroid function

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Objectives
The Controlled Antenatal Thyroid Screening (CATS) study I was a randomised trial investigating the effects of levothyroxine treatment for suboptimal gestational thyroid function (SGTF), evaluating mothers with normal gestational thyroid function (NGTF), SGTF who received (SGTF-T), or didn't (SGTF-U), levothyroxine during pregnancy. The present follow-up study (CATS II) reports the long-term effects of SGTF and levothyroxine treatment on anthropometric and cardiometabolic outcomes in children and mothers.
Methods
332 mothers aged 41.2±5.3 years (mean±SD) and 326 paired children were evaluated 9.3±1.0 years after delivery/birth: 197 NGTF, 56 SGTF-U, 79 SGTF-T. BMI was calculated; in children this was expressed as BMI-SDS against current UK standards (1990). Subsets underwent: i) dual-energy x-ray absorptiometry (DXA) scan of lean/fat mass; ii) Vicorder® analysis of heart rate, systolic/diastolic blood pressure, augmentation index, total peripheral resistance and aortic pulse wave velocity; iii) measurement of serum TSH, FT4, FT3, TPOAb, lipids, insulin and adiponectin. The difference between means of the 3 groups (NGTF, SGTF-U, SGTF-T) was analysed using linear regression.
Results
No significant differences between groups were detected in any of the parameters in the children. SGTF-U mothers had significantly higher BMI and percent fat mass compared with NGTF/SGTF-T and had higher TSH, since 64% of SGTF-U were never started on levothyroxine treatment.
Conclusions
Thyroxine supplementation of women with SGTF during pregnancy did not benefit children's BMI or other cardiometabolic parameters. However, screening for SGTF during pregnancy identified women that would benefit from levothyroxine replacement: absence of such treatment was associated with sustained long-term BMI increase.

	NGTF	SGTF-U	SGTF-T	*P*
TSH	1.54	**2.45**	1.68	**0.042**
median (IQR)	(1.12-2.07)	(1.43-3.50)	(0.89-2.96)	
BMI Kg/m^2	25.73	**28.30**	25.80	**0.034**
median (IQR)	(22.76-29.99)	(24.62-32.60)	(23.11-29.84)	
Subtotal % FAT mass	40.24±7.16	**42.84±7.18**	40.40±7.43	**0.017**
mean±SD (range)	(20.45-54.78)	(17.45-55.11)	(21.80-54.85)	

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P201

Targeted sequencing of dyshormonogenesis-associated genes in Macedonian cases with congenital hypothyroidism and gland-in-situ reveals a low mutation frequency

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Neonatal screening for congenital hypothyroidism (CH) in the Republic of Macedonia was piloted in 2002 and implemented nationally in 2007, demonstrating a CH incidence of 1 in 1916. 52.7% cases exhibit a normally-located gland-in-situ (GIS CH), however, although this may indicate genetically-mediated dyshormonogenesis, genetic stratification has not previously been undertaken. We selected singleton GIS CH cases ($n=22$), born at term, with birth weight >3000 g in whom genetically-mediated dyshormonogenesis was likely, e.g. with scintigraphic features of dyshormonogenesis, goitre, familial cases, or with unexplained transient or subclinical CH. *TG, TPO, IYD* and *DUOX2* were sequenced in seven cases with thyroid stimulating hormone (TSH) concentrations greater than 50 mU/l (including two sibling pairs) and TSHR, *DUOX2* and *DUOXA2* were screened in fifteen milder cases with TSH11.9-41 mU/l, including one sibling pair. *SLC5A5* (NIS) was sequenced in cases lacking pertechnate scan data; otherwise normal isotope uptake was assumed to indicate preserved SLC5A5 function. One case with TSH >150 mU/l harbored compound heterozygous pathogenic *TPO* mutations (p.E17Dfs*77 and p.R438H) and two siblings with severe CH harboured a heterozygous pathogenic *TPO* mutation (p.A397Pfs*76). Three mild cases harboured rare, heterozygous variants; *TSHR* p.E506K (novel, predicted to be pathogenic), *TSHR*c.692+1_692+4delGTGA (uncertain significance) and *DUOX2* p.E1546G (known pathogenic). 24 hour urinary iodine concentrationswere assessed in ten mutation-negative casesand did not show iodine deficiency (range 124–329 µg/l). Our small, iodine replete GIS CH series demonstrated few candidate gene mutations (maximum frequency 27% assuming pathogenicity of all variants). Autoantibody titres were not routinely assessed, but were negative in the only case with a maternal history of thyroid disease. Although GIS CH due to dyshormonogenesis may be difficult to ascertain clinically, and targeted sequencing may miss unexpected defects, we postulate that novel genetic aetiologies underlie dyshormonogenesis, especially in familial cases with severe goitrous CH.

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P202

Rate of progression of subclinical hypothyroidism to overt hypothyroidism: a 10-year retrospective study from UAE

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Introduction
Limited data is available on the natural history of thyroid disorders in the Middle East. We aim to report the rate of progression of subclinical hypothyroidism to overt hypothyroidism specifically for the UAE population.
Methods
Retrospective analysis was performed on all patients attending Imperial College London Diabetes Centres in the UAE over ten years from 2007 to 2017, with a diagnosis of spontaneous subclinical hypothyroidism (TSH >4.2 and <10 μIU/ml) without thyroid replacement. Categorical variable analysis and logistic regression analysis were used to identify factors associated with increased risk of conversion to overt hypothyroidism including gender, BMI, baseline TSH, diabetes status and thyroid peroxidase antibody (TPO) positivity status.
Results
12,900 patients with subclininical hypothyroidism during the study period were identified. 847 (6.5%) of patients developed overt hypothyroidism, defined as TSH >10 μIU/ml. The mean time to development of overt hypothyroidism was 90 weeks. The majority of the patients with overt hypothyroidism were female (67.7%). 44.7% of all patients with overt hypothyroidism had diabetes and 42.8% were obese (BMI ≥ 30 kg/m^2). In those who developed overt hypothyroidism, TPO antibodies were positive in 53%. Logistic regression analysis showed that female gender ($P<0.03$) and higher baseline TSH (TSH ≥ 6 μIU/ml; $P<0.02$) were both associated with increased risk of progression to overt hypothyroidism. TSH levels spontaneously normalized without treatment in 41.9% of patients (mean time of 8.5 weeks).
Conclusion
Rate of progression to overt hypothyroidism in our population is 6.5% over 10 years. In keeping with studies in other populations females and those with higher baseline TSH are more likely to develop overt hypothyroidism. Further studies are required to investigate and identify other clinical and biochemical predictors that could be associated with development of overt hypothyroidism in the UAE population.

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P203

Characterization of thyroid nodules in acromegalic patients

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Background
Thyroid nodules were reported with high prevalence in acromegalic patients.
Patients and methods
63 acromegalic patients (16 males and 47 females), aged at diagnosis 43.6 ± 12.7 years were retrospectively reviewed. Median duration of acromegaly was 8 years. 25 patients were residents in iodine deficient areas. GH, IGF1, TSH, FT_4 were measured by chemiluminescence (Liaison). Thyroid ultrasound was performed. In suspected nodules, pathological examination (either fine needle aspiration with cytology exam or pathology exam after thyroidectomy) was performed.
Results
Median thyroid volume was 20.72 ml. Thyroid nodules were present in 52 patients (82.5%). Multiple thyroid nodules were found in 45 out of 52 cases (86.5%). Toxic multinodular goiter was prezent in 5 patients (7.9%). Average maximum diameter of dominant nodule was 1.7 ± 1.3 cm. Thyroid differentiated cancer was diagnosed in 6 patients (9.5%). Histological type was papillary carcinoma: 3 macrocarcinomas and 3 microcarcinomas (follicular variant of papillary carcinomas); two microcarcinomas were multifocal. Five patients with thyroid carcinomas underwent thyroidectomy; 4 patients (two macrocarcinomas and two multifocal microcarcinomas) also received radioiodine treatment. Thyroid surgery is pending in one patient. Autoimmune thyroiditis was present in 4 patients (6.3%).
Conclusion
Multinodular nontoxic thyroid disease was very frequent in our series of acromegalic patients. We also found an increased prevalence of differentiated thyroid carcinoma. Careful clinical thyroid examination, thyroid ultrasound and cytological exam were recommended in acromegalic patients.

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P204

Evaluation of the Mental Health and Quality of Life of patients with hyperthyroidism attending an Endocrine Clinic

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There is scant literature on various mental health parameters following treatment of hyperthyroidism. We present our initial results from an ongoing quality improvement project, jointly undertaken by the Endocrinology and Psychiatry teams.
Aim
To evaluate anxiety, depression, ability to work and quality of life (QOL) of patients with hyperthyroidism on presentation and after institution of specific therapy.
Method
We assessed 68 newly referred patients with overt hyperthyroidism with 4 Health Questionnaires; PHQ-9 for depression, GAD-7 for anxiety, EuroQoL for QOL and WSAS for functional impairment at baseline and 2 follow up visits at 3 and 6 months (mean 97 days and 192 days).
Result
23% male, mean age 48.4 ± 15.4 years. 23.5% had mild, 17.6% moderate and 26.5% severe anxiety pre-treatment, which decreased to 1.5%, 8.8% and 11.8% and to 4.4%, 1.5% and 1.5% at 3 and 6 months respectively. Depression scores were mild 16.2%, moderate 20.6%, moderately severe 19.1% and severe 13.2%, with post-treatment figures being 10.3%, 4.4%, 4.4% and 7.4% and 5.9%, 0%, 1.5% and 1.5% respectively. EQ5D vas score improved from baseline of 54.4 ± 24.7 to 68.5 ± 22.9 and 73.0 ± 16.1 and WSAS scores from 7.4 ± 11.0 to 6.3 ± 9.0 and 1.1 ± 3.8. The improvement was parallel to improvement in thyroid status. Only 8(11.8%) persons received psychotropic medications. Severity of hyperthyroidism was not an independent predictor of the degree of impairment of any parameter.
Conclusion
A significant proportion of patients had anxiety and depression, along with functional impairment and poorer quality of life at baseline. Following specific therapy for hyperthyroidism, all parameters improved in a majority of patients. Some patients continued to have impaired mental health and there was no formal management strategy for them. We recommend a formal assessment of mental health in patients with hyperthyroidism and an agreed strategy for its management when the improvement is delayed.

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P205

A second course of antithyroid drug therapy is effective in patients with relapsed Graves' disease

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Background
Antithyroid drugs (ATDs) are preferred as a first-line treatment for Graves' disease (GD). However, around 50–60% of patients relapse following treatment withdrawal. Radioactive iodine (RAI) or thyroidectomy is recommended for these patients, however, repeat ATD therapy is a further option, dependent upon patient choice. The long-term efficacy of ATD in relapsed GD has not been robustly established.
Methods
We conducted a retrospective study to assess the prognosis after a second course of ATD and investigate the clinical predictors for remission. Consecutive ATD-treated GD patients with at least three years of follow-up who attended our endocrine service since 2004 were identified and medical records analysed. Remission was defined as maintaining a euthyroid status for at least one year after ATD withdrawal.
Results
219 patients underwent an initial course of ATD therapy. A total of 129 patients (59%) relapsed upon treatment withdrawal after a mean time of 2.0 ± 2.7 years (range 0–15 years). Seventy-two (58%) patients (70% female, age at diagnosis 43.7 ± 15.0 years) opted for a second course of ATD. Eight patients were lost to

follow-up. During 6.1 years (range 1.5–11.7 years) median follow-up, 24 patients (38%) achieved remission, 29 patients (45%) relapsed and 17% ($n=11$) continued ATD treatment. Male gender (RR = 1.88, CI 1.21–2.91) and a large goitre (RR = 2.07, CI 1.42–3.02) were independent risk factors for relapse. A higher free T4 level at the time of relapse (mean fT4 36.2 ± 20.7 pmol/l vs 29.6 ± 14.3 pmol/l) was also suggestive of increased risk of relapse following second ATD therapy ($P=0.05$). Age, smoking status and orbitopathy did not show significant association.

Conclusion

A second course of ATD therapy results in a satisfying long-term remission rate (38%) in GD patients. The best outcomes are in females presenting with lower fT4 level on relapse in the absence of a large goitre.

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P206

Iodine restricted diet prior to radioiodine therapy for hyperthyroidism

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Background

There has been conflicting evidence on the use of strict dietary iodine restriction prior to Radioiodine (RAI) administration for the management of hyperthyroidism and varying level of restrictions have been used. More recently the Medical Physics team in our institute implemented strict dietary iodine restrictions for 2 weeks pre-RAI administration. Significant inconvenience was reported by patients, which in some instances led to their reluctance to receive a second dose if required.

Objective

We have undertaken a retrospective audit to compare outcomes following no restriction and severe restriction of dietary iodine in our cohort of patients receiving RAI therapy.

Patients and methods

We audited 50 consecutive patients without restrictions and 50 with severe dietary iodine restriction and compared them for cure of hyperthyroidism and time taken to achieve the cure. We did not measure urinary iodine to assess adherence to iodine restriction, as our aim was to make the assessment in the setting of actual clinical practice. Dose of RAI ranged from 400–600 MBq.

Results

Both groups were comparable for age, gender distribution, aetiology, RAI dose, use of antithyroid medication, goitre size and severity of hyperthyroidism as judged by FT4 level ($P>0.05$ for all). Cure rate for patients who had no iodine restriction and strict iodine restriction was 94% and 86% respectively, which was statistically not significant ($P>0.05$). Time taken to achieve cure for both groups was 9.2 and 8.9 weeks respectively ($P>0.05$). We did not formally assess patient satisfaction but >50% of patients from the latter group reported significant 'inconvenience'.

Conclusion

Strict iodine restriction prior to administration of RAI for the management of hyperthyroidism is inconvenient for patients and does not improve the cure rate or the time to achieve cure in a clinical setting. We have now reverted to the position of not restricting dietary iodine.

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P207

Can we predict relapse of Graves' disease after antithyroid drug therapy?

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Background

Current therapeutic options for Graves' disease (GD) include antithyroid drugs (ATD), radioactive iodine (RAI) or thyroidectomy. ATD treatment is widely used but the relatively high recurrence rate (~50%) after ATD discontinuation is a major concern. Identification of risk factors predicting relapse in GD patients after stopping ATD is decisive to guide initial treatment choices.

Methods

We conducted a retrospective study to determine the recurrence risk and investigate predictors for relapse in GD patients after a treatment course of ATD. Consecutive patients with Graves' hyperthyroidism who attended our endocrine service since 2004 were identified and medical records analysed. Remission was defined as maintaining a euthyroid status for at least one year after ATD withdrawal.

Results

262 patients with GD were identified. 249 patients opted for initial ATD therapy with intention to treat but 219 (88%) completed ATD treatment as per protocol (75% female, age at diagnosis 44.5 ± 14.6 years). On initial evaluation, 36% (64/180) were active smokers, 65% (136/209) had a palpable goitre and 28% (53/192) had Graves' orbitopathy. At one year after ATD withdrawal, 142 patients (65%) were in remission. During 7.1 years (range 1.5–17.0 years) median follow-up, four patients continued medical therapy and 85 patients (40%) achieved long-term remission after completing first ATD course. Smoking (RR 1.39, CI 1.06–1.82) and large goitre size (RR 1.60, CI 1.20–2.13) were significant independent predictors for disease recurrence after first treatment course. Age at diagnosis, gender, orbitopathy and initial serum free T4 level showed no significant association with relapse in ATD-treated patients.

Conclusion

In our cohort, smoking and goitre size were significant pretreatment risk factors for disease relapse following an initial course of ATD. These factors must be duly considered at the time of initial assessment to facilitate an informed decision on the most appropriate therapeutic approach for individual patients.

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P208

Clinico-pathological correlation of U3 thyroid nodules: A retrospective review

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Background

The incidence of thyroid cancer is increasing globally mainly due to increased detection of papillary microcarcinoma. The British Thyroid Association (BTA) guideline (2014) recommends the use of U1-U5 classification on ultrasound to assess thyroid cancer risk. U3 nodules have low, but indeterminate risk and therefore need FNAC. This retrospective review analyses the outcome of U3 nodules in an outer London hospital.

Methods

Thyroid ultrasound performed between 2016 and 2017 were searched and those with reported U3 nodules were selected ($n=104$) for this retrospective review. The static images were interrogated against the BTA guideline for U3 characteristics, corresponding cytology and histology. People with overt hypo or hyperthyroidism were excluded.

Results

Nearly 81% ($n=84$) were female (mean age 48 years). Multiple nodules were noted in 54% ($n=56$) of which only 5% ($n=2$) were larger than 4 cm compared to 19% ($n=9$) among solitary nodules. The nodules were mainly heterogeneous (87%) and mixed vascularity was the most common reported U3 characteristic (94.5%) followed by isoechoic nodules (55.5%); other features were reported less frequently (<30%). FNA was done at least once in 86% ($n=89$). In those with multiple nodules, 86% had THY2 cytology and 9% had THY3a/f whereas 26% with solitary nodule had THY3a ($n=11$), 7% THY3f and 5% THY5 ($n=2$). Nineteen patients (18%) had thyroid surgery, which included four total thyroidectomies (two THY5, two large goitre). Both THY5 total thyroidectomy patients had papillary cancer (pT1a pN1a) and were treated with radioiodine. None of the fifteen who had hemithyroidectomy needed any further procedure. This included 7 of the 22 who had THY1 on first FNA.

Conclusion

In summary, this review showed a bias towards mixed vascularity in reporting U3 nodule, negligible indeterminate cytology rate in multiple nodules and a reassuringly low rate of clinically significant papillary cancer risk (<3%).

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P209

Low dose rituximab for thyroid eye disease: an effective treatment with fall in TSH receptor antibodies (TRAb)

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Background
Thyroid eye disease (TED) is an autoimmune inflammatory disease associated with Graves' disease. Rituximab (a monoclonal antibody that depletes B-cells), has recently been shown to be effective in treating TED. There is evidence to support an association with increased TRAbs and TED severity, and one study has demonstrated a fall in TRAbs with rituximab therapy. The aim of this study was to assess the clinical efficacy of low dose rituximab in patients with TED, and correlate this with TRAb level.
Methods
A retrospective study of patients with moderate to severe active TED who received low dose rituximab (100 mg) at the Oxford Joint Thyroid Clinic (Ox-TED). 14 patients were identified between 2016 and 2018. All patients were initially treated with 100 mg rituximab and 500 mg intravenous (IV) methyl-prednisolone. Patients were subsequently treated with further 100 mg rituximab (2 patients), further IV methylprednisolone or steroid-sparing agents if clinically indicated. Disease severity scores, B-cell counts and TRAb levels were collected at baseline and following treatment.
Results
Clinical activity scores significantly decreased from baseline to follow up (11.78 to 6.8, $P=0.01$). B-cell depletion was seen in all 11 patients with B-cell count recorded following treatment, $P<0.001$. Cumulative steroid dose was 2.38 g, half the dose recommended by EUGOGO for patients with moderate to severe active TED. In all patients ($n=11$) with TRAbs recorded pre and post treatment, all showed significant reduction (7.64 to 3.98 international units per litre, $P=0.01$).
Conclusion
Low dose rituximab suppresses B-cells, is clinically efficacious, is associated with reduced requirement for systemic steroids, and results in significant reduction of TRAbs. Data is now being prospectively collected on TRAbs in patients treated with steroids and steroid-sparing agents alone.

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P210

Weight gain with hyperthyroidism therapy: a prospective pilot study

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Introduction
It is currently unclear how hyperthyroidism and its treatment impact on the weight trajectory of an individual. Anticipated weight gain with the treatment of hyperthyroidism is one of the main concerns of patients.
Methods
We prospectively examined the BMI changes that occurred with hyperthyroidism and its therapy and sought risk factors for treatment-related weight gain. An established institutional protocol for the management of hyperthyroidism was followed; patients with BMI ≥ 25 kg/m^2 were verbally advised to visit a dietitian. Descriptive statistics are given as means (SD) and median (IQR) for parametric and non-parametric variables, respectively. Paired *t*-test, *t*-test, Wilcoxon two-sample signed rank test and Pearson's correlation were employed.
Results
33 patients with hyperthyroidism were recruited; mean age was 45.1 years (15.27) and 54.5% were females. The self-reported mean weight loss was 6.6 kg (5.15) and BMI reduction was 2.5 kg/m^2 (0.73–3.85) over a median duration of 12 weeks (IQR 4–24). The mean baseline weight was 72.42 kg (15.93) and BMI was 25.77 (5.04) kg/m^2. The final recorded mean weight and BMI increase were 6.52 kg (3.79) and 1.72 kg/m^2 (1.27), respectively, over a mean follow-up time of 24 weeks. The self-reported weight loss was only correlated with male gender ($P=0.037$). The baseline BMI was only correlated with the baseline TSH ($P=0.018$). The BMI post-therapy was significantly higher from as early as 6 weeks after therapy ($P=0.01$) and remained so at three and six months ($P<0.0001$). Overall there was no significant difference between the weight lost at presentation to that gained following treatment ($P=0.981$ and $P=0.279$, respectively). None of the patients elected to see a dietitian.
Conclusion
Overall, in this prospective pilot study the patients seemed to have recovered their pre-morbid weight status following treatment. Notwithstanding, many patients moved further away from their ideal weight range following hyperthyroidism therapy and this bears further investigation.

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P211

Ultrasonographic features and management of thyroid nodules undergoing ultrasound-guided fine needle aspiration

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Introduction
Thyroid nodules can be detected in 50 to 60% of healthy individuals, particularly in the elderly and females. An increase in differentiated thyroid cancer has been noted over the years, especially papillary thyroid cancer.
Objectives
To assess different approaches to management and histological nature of thyroid nodules in Malta, as well as to evaluate the association of ultrasound characteristics with biochemical and histological features.
Methods
All thyroid nodules undergoing ultrasound-guided fine needle aspiration (FNA) between July 2013 and December 2017 were evaluated. Data was collected on ultrasonographic nodule characteristics, FNA histology (using Bethesda system), follow-up of these nodules with repeat ultrasound or FNA and histology report of those nodules undergoing surgery. Sensitivity and specificity of thyroid nodule FNA was calculated.
Results
A total of 1420 patients who had 1522 FNAs were identified. They had a mean age of 57.4 (+/− 15.3) years at the time of FNA and the majority (76.1%) were female. Most nodules were benign (69.3%), while only 1.9% and 4% were suspicious of malignancy or malignant respectively. Lobectomy or total thyroidectomy was undertaken in 21.5% of patients. Of those operated 19.6% had a follicular adenoma, 4.6% had a follicular carcinoma, 35.6% had papillary carcinoma, 1.3% medullary carcinoma, 0.3% anaplastic and 41.8% had benign nodules, with multinodular goitre predominating in 69.5% of benign cases. Where documented on ultrasound, most malignant nodules were at least 2 cm in size (37.2%), had chaotic intranodular vascularity (35.7%), were hypoechoic (62%), had irregular borders (22.6%) and microcalcifications (27.7%). The sensitivity and specificity of FNA cytology for malignancy (including both Bethesda categories 5 and 6) were 85.3% and 95.1% respectively.
Conclusion
Our sensitivity and specificity results for FNA cytology compare well with ranges quoted by current guidelines. Papillary carcinoma was found to be the most prevalent thyroid malignancy in Malta.

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P212

Low Dose Radioiodine Therapy for Graves' disease: comparison of outcomes following administration of different doses across two centres

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Introduction
Low dose radioiodine (LDRAI) has been used to treat benign thyroid disease for over 70 years (1). However, controversies remain about the optimal dosage to administer. The Royal College of Physicians guidelines recommend a dosage of 400–600 MBq for uncomplicated Graves' disease (2); the dose administered varies between centres.
Methods
Outcome data at Edinburgh Royal Infirmary were collected retrospectively for patients who received an average of 400 MBq (Range 364-467 MBq) LDRAI between January 2010 and October 2015. Outcome data at Aberdeen Royal Infirmary were collected retrospectively for patients who received 550 MBq

between January 2012 and June 2017. Only people with a diagnosis of Graves' disease receiving their first dose of radioiodine were included.
Results

Demographics	400 MBq	550 MBq
Total number	348	169
Mean age ± SD	51.07 ± 15.58	50.4 ± 15.77
Female (%)	72.1	76.3
TSH receptor antibody positive*	96.8%	91.5%

*A clinical diagnosis of Graves' was made in the remaining small percentage of patients.

Outcomes at 12 months following LDRAI	400 MBq	550 MBq
Hypothyroid or receiving levothyroxine (%)	74.1	84.0
Euthyroid (%)	6.6	6.5
Hyperthryoid (%)	18.4	8.3
Deceased (%)	0.9	0.6
Unknown (%)	0	0.6

Discussion
Administration of 550 MBq LDRAI resulted in a significantly higher cure rate at 12 months (90.5%) compared to 400 MBq (80.8%) ($P=0.0024$), albeit with an increased number of patients requiring levothyroxine replacement. These results suggest that if our aim is to cure hyperthyroidism then we should be administering the higher dose of 550 MBq to our patients with Graves' disease.
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P213

Outcomes following radioactive iodine therapy (RAI) in hyperthyroid patients with Grave's disease and toxic nodular disease

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Background
RAI is used as definitive treatment for hyperthyroidism, but administered activities vary between institutions. We used a fixed activity of RAI therapy for Grave's disease (GD) and toxic multinodular goitre (TMNG), and calculated activity for toxic adenoma (TA). We reviewed treatment outcomes at one year.
Methods
Thyroid function tests 1 year post RAI were reviewed retrospectively to asess outcome for 79 hyperthyroid patients divided into 3 etiological groups: those with GD treated with 200 MBq, TMNG treated with 400 MBq and TA treated with calculated activity (50–434 MBq), between January 2012 and June 2017. 24 hour isotope uptake results were examined retrospectively to assess relationship to clinical outcome.
Results
48/79 patients had GD (60.8%%), 16/79 TMNG (20.2%) and 15/79 TA (19%). Patients with GD were younger (median 46 years) compared to those with TMNG and TA (median 62 and 59 years respectively). There were more females in both groups (85.5% female in GD, 93.7% in TMNG and 83.3% in TA). At one year post-RAI, more patients with GD were rendered hypothyroid 28/48 compared to TMNG and TA (62.5% vs. 18.75% vs. 53.33%) and fewer patients with GD were rendered euthyroid (25% vs. 46.6% vs. 53.3%) or had persistent hyperthyroidism compared to those with TMNG/TA (12.5% vs. 0% vs. 0%). 12/28 patients with GD who developed hypothyroidism had 24 hour uptake >60% and all patients with 24 hour uptake >60% became hypothyroid in GD and TMNG groups.
Conclusion
We used low activity RAI (200 MBq) as treatment for GD, an activity below international recommendations, with comparable outcomes and cure rate 87.5%. All patients with 24 hour uptake >60% in GD and TMNG group developed hypothyroidism post RAI indicating that lower activity RAI should be considered to reduce risk of hypothyroidism.

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P214

Evaluation of a high sensitivity thyroglobulin assay for use in patients following total thyroidectomy and radioiodine ablation treatment

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Background/aims
Thyroglobulin (Tg) is used for monitoring patients who have undergone total thyroidectomy (TT) and radioiodine (RAI) ablation therapy for thyroid cancer. The current method is the Siemens Immulite assay with limit of quantification of 2 ng/mL following in-house evaluation. Recent guidelines suggest the use of high sensitivity Tg (hs-Tg) as an alternative to TSH stimulated Tg levels. The aim is to evaluate the hs-Tg Beckman Access II assay with a stated functional sensitivity of 0.1 ng/ml.
Method
Bias was assessed relative to the Siemens assay using Deming regression and Bland-Altman analysis on 45 patient samples. Bias relative to the method mean was calculated using nine NEQAS samples. Intra-assay and inter-assay imprecision were calculated from three replicates of four patient samples for hs-Tg over one and five days respectively. Clinical utility of the assay was assessed by measurement of 126 patients with an Immulite result <2 ng/ml after TT and RAI.
Results
Bland Altman analysis showed a 50% negative proportional bias and Deming regression showed a slope of 0.604. Intra-assay imprecision (%CV) was 10.2% at 0.13 ng/ml, 2.0% at 0.77 ng/ml, 2.4% at 1.13 ng/ml and 1.7% at 2.62 ng/ml. Total imprecision was 11.3% at 0.13 ng/ml, 3.6% at 0.77 ng/ml, 11.3% at 1.13 ng/ml and 7.3% at 2.62 ng/ml. Time post RAI ranged from one month to twenty years, median four years. A Tg ≥ 0.1 ng/mL was obtained in 37/126 (29%) patients. Of these patients, 25 were <5 years post RAI and 12 were >5 years.
Conclusion
A period of paired analysis would be required due to the significant negative bias observed. The assay has acceptable imprecision and EQA performance. A subset of patients with detectable hs-Tg were identified; further investigation is required to determine the clinical significance.

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P215

Utility of fetal thyroid scanning in pregnancy: experience in a single centre

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Background
Guidelines from ATA and the Endocrine society suggest the use of fetal thyroid monitoring in maternal Graves' disease to detect fetal thyrotoxicosis or hypothyroidism in response to maternal thyroid receptor antibodies (TRAb) or thionamide therapy respectively. The literature examining how effective this policy is remains sparse, since these remain unusual clinical situations for most centres. Here we review our experience of scanning for fetal goitre.
Methods
Normative data for fetal thyroid size were established at Princess Royal Maternity Unit, Glasgow in 2008. Since then women with a history of Graves' disease have been routinely scanned using transabdominal ultrasound at 4 weekly intervals from 20 weeks if indicated by positive TRAb or thionamide treatment after 20 weeks. Case notes and electronic records were reviewed for women scanned between 2008–2018.

Results
18 women were scanned. At the outset of pregnancy 6 were on carbimazole, 4 on propylthiouracil, 3 on thyroxine (2 with previous radioiodine therapy and 1 with previous thyroidectomy) and the remainder on no medications. Possible fetal goitre ($>95^{th}$ centile) was detected in 2 women. In the first, reduction of PTU dose (despite elevated maternal fT4 levels) at 30 weeks of gestation led to reduction in size of fetal goitre. The second woman had severe T3-toxicosis and grossly elevated TRAb levels; fetal goitre was associated with signs of advanced bone age but without other late signs of fetal thyrotoxicosis. Carbimazole was increased and fetal goitre reduced in size. Baby delivered with normal thyroid function but went on to have neonatal thyrotoxicosis.
Discussion
Even in a relatively large centre (6500 annual deliveries), fetal thyroid ultrasound is needed in relatively few cases, requiring little additional resource since these women are relatively high risk and would be undergoing growth scanning. Nevertheless implementation has led to important changes in management in certain cases.

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P216

Management of 'Anomalous' thyroid results

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Background/objectives
While patients are commonly referred to endocrinology with a low FT4 and normal TSH, there is no consistency in the management of these patients. The aim of this audit was to assess management of these patients including investigation, diagnosis and pharmacological intervention and compare to the current Association for Clinical Biochemistry guidelines.
Methods
This was a retrospective audit studying 41 endocrine outpatients at University Hospital of Wales with TFTs at referral showing low T4 and normal TSH. Clinical history was analysed to look for mutual patient factors which may have contributed to anomalous results. The main diagnosis of interest was of pituitary macroadenomas.
Results
Good clinical history, repeat TFTs and anterior pituitary tests were obtained for all patients. 53.7% of patient had concurrent neuropsychological conditions. 19/41 patients were on antidepressants and 11/41 on anticonvulsants. No assay interference was identified in 7/7 samples analysed. 17/41 (41.5%) of patients had normalisation of their TFTs on repeat testing: patients with normal pituitary anterior pituitary hormone tests were more likely to have TFT normalisation (55.6%) in comparison to patients with abnormal pituitary results (30.4%). 3/41 patients were found to have macroadenomas but all these had other abnormal pituitary tests. No significant difference was found in baseline FT4 of patients with macroadenomas to those without.
Conclusion/ interpretation
Neuro-psychiatric conditions and/or their drugs were common in this cohort. Patients found to have a macroadenoma had abnormalities in other anterior hormone tests; 41.5% of patients referred had normalisation of their TFTs. The majority of patients had an unknown cause of anomalous TFTs not requiring intervention. A pathway may aid appropriate referral to endocrinology.

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P217

The use of a thyroid telephone clinic (TTC) to follow up thyroid function tests (TFTs) in patients treated with radio-iodine (RAI) for thyrotoxicosis

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The thyroid telephone clinic (TTC) was established to facilitate rapid decision making on timing of introducion of anti-thyroidals or L-thyroxine replacement therapy post RAI so avoiding unnecessary outpatient appointments or leaving patients with untreated hyperthyroidism or hypothyroidism. The TTC is also used to monitor TFTs during pregnancy and to dose-titrate treatment of unstable hypo- or hyperthyroid patients. This service is provided to patients who speak English fluently, and are able to safely follow instructions regarding medication changes, can be contacted by telephone, and commit to regular blood tests, either at the hospital phlebotomy department or locally. Prior to RAI therapy, anti-thyroidal drugs should be stopped for at least a week prior to RAI therapy and only restarted where required. Our protocol is to perform TFTs at weeks 1, 3, 6, 9, 12, 24 post RAI, with additional TFTs requested if required. Results are reviewed through the TTC with outpatient review at week 18–21 post RAI. TTC is run by the senior endocrine Specialist Registrar with consultant endocrinologist cover and the clinic runs every Friday with a list of 15–25 patients. 92 patients who received RAI therapy were followed in the TTC between January 2012 and June 2017. 40/92 patients did not miss any blood test or phone call. The average free T4 and TSH were smooth over 24 weeks post RAI within the target range. TTC has an important role to avoid unnecessary outpatient appointments and avoids leaving patients with untreated hypothyroidism, which has many undesirable effects.

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P218

Early and more frequent monitoring of thyroid function tests (TFTs) post RAI could be clinically beneficial

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Background
Radioiodine (RAI) is widely used for the treatment of hyperthyroidism. Most patients respond to RAI therapy with a normalization of TFTs and improvement in clinical symptoms within 4–8 weeks. Hypothyroidism may occur from 4 weeks on, with 40% of patients being hypothyroid by 8 weeks and $>80\%$ by 16 weeks. American thyroid association guidelines recommend testing for free T4, total T3, and TSH within the first 1–2 months after RAI. Biochemical monitoring should be continued at 4- to 6-week intervals for 6 months, or until the patient becomes hypothyroid and stable on thyroid replacement therapy. Our local protocol is to monitor thyroid function more frequently and earlier, week 1, 3, 6, 9, 12, 24 post RAI therapy to avoid any delay in starting treatment if required.
Methods
79 patients with hyperthyroidism underwent definiive treatment with RAI between January 2012 and June 2017. Monitoring of thyroid function tests were examined retrospectively to determine timing of initiation of treatment for either hypothyroidism or persistent hyperthyroidism post RAI.
Results
Treatment started for both hypothyroidism and persistent hyperthyroidism in 47/79 patients, 41 developed hypothyroidism while 6 became hyperthyroid. 19/41 developed hypothyroidism within 9 weeks post RAI, while 9/41 developed hypothyroid within 3 weeks post RAI. Median time to commence treatment was 13.6 weeks.
Conclusion
Frequent early monitoring of thyroid function tests post RAI may avoid delay in starting treatment for patients developing either hypo- or hyperthyroidism.

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P219

Improvements in monitoring and biochemical control of hypothyroidism in primary care with the use of an electronic protocol: 12-month follow up evaluation

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Introduction
Following the introduction of the Quality Outcome Framework (QOF), 98–100% patients with hypothyroidism received annual TSH checks during the period

2009–2014. However, there was no evidence this resulted in improved care. We have developed an electronic protocol in EMIS web to both emulate the former QOF thyroid e-alerts in prompting GP's to check annual thyroid function in patients with treated primary hypothyroidism, and also to alert if TSH is out of range.
Aim
To investigate the impact of an electronic protocol on the monitoring and management of levothyroxine replacement in patients treated for primary hypothyroidism in primary care.
Methods
The study population comprised five Surrey GP practices with a total population of 74,984 patients. The prevalence of primary hypothyroidism was 3.2% and did not change significantly over the course of the study. We analysed the percentage of patients who i) had had TSH checked in the preceding 12 months and ii) had latest TSH level within the local laboratory reference range (0.35–5.0 mU/l) at baseline and again 12 months after introduction of the electronic protocol.
Results
The proportion of patients with TSH checked in the previous 12 months increased from 77% to 83%. The latest TSH result was within local reference range in 68% (before) and 71% (after) introduction of the electronic thyroid e-alerts. The proportion of patients with TSH both within range and checked in last 12 months improved from 53% to 58%.
Conclusions
An electronic protocol which reminds GP's to check thyroid function and alerts them to TSH values that are out of range resulted in modest improvements in monitoring and biochemical control of primary hypothyroidism. Although both may improve further over subsequent years, additional measures are likely required to achieve higher levels of monitoring and improvement in optimisationof thyroid hormone replacement.

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P220

Radioiodine therapy in benign thyroid disease

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Introduction
Radioiodine (RAI) is a safe and effective treatment used to treat benign thyroid disease. A review of patients who received RAI in Malta between 2010 and 2018 was carried out to determine their outcome.
Methods
Data collection included patient demographics, indication for RAI, amount of RAI doses received, use of antithyroid drugs pre RAI and thyroid function tests (TFTs) at 3, 6 and 12 months post RAI. Cure was defined as euthyroidism or hypothyroidism during the first year post RAI.
Results
185 patients received RAI. 136 (73.5%) were female whilst 49 (26%) were male. Average age was 52.8 years. A standard dose of 10 mCi was used. 9 patients needed a repeat dose. Indications for RAI included Graves' disease: 113 (61%), multinodular goitre: 14 (7.5%), toxic adenoma: 12 (6.4%), amiodarone induced thyrotoxicosis: 2 (1%) and hyperthyroidism cause: 44 (23.8%). Before each RAI dose 148 (76%) were treated with carbimazole, 11 (5.7%) received propylthiouracil, 27(14%) had no treatment and in 6(3%) no treatment was recorded. Patients had their thyroid function tests checked after 3, 6 and 12 months. At 3 months: 25(12.9%) were euthyroid, 100 (51.5%) were hypothyroid, 21 (10.8%) hyperthyroid in 47 (24%) no TFTs were available. At 6 months: 19 (9.8%) were euthyroid, 115 (59%) hypothyroid, 19 (9.8%) hyperthyroid and in 40 (20.6%) TFTs were unavailable. At 12 months: 18 (9.2%) were euthyroid, 116 (59.8%) hypothyroid, 5 (2.6%) hyperthyroid and in 52 (26.8%) TFTs were unavailable. Median duration to achieve eu/hypothyroidism was as follows: 125 (64.4%): 3 months, 45 (23%): 6 months, 6 (3%): 12 months and in 13 (6.7%) no data was available. 6(3%) were still hyperthyroid at 12 months.
Discussion
The majority of patients achieve euthyroidism or hypothyroidism at one year. Radioiodine is a highly successful treatment in benign thyroid disease.

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P221

A retrospective study of outcomes of radioiodine treatment for benign thyroid disease

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Background
As radioiodine therapy is highly effective in curing Graves' hyperthyroidism and toxic multinodular goitre, the assessment of its efficacy by rendering those patients euthyroid while avoiding the development of permanent hypothyroidism, is important.
Aim
To determine the current practice of radioiodine treatment provided at our trust, in line with the recommended guidelines of the Royal College of Physicians and also to compare our success rate with the published data.
Method
Retrospective data of 100 hyperthyroid patients who underwent radioiodine treatment during 2013 to 2017, were analysed. One year follow up clinical data was reviewed.
Results
Among them, 45% had Graves' disease, 16% had multinodular goitre (MNG), 3% had toxic adenoma and 22% were hyperthyroidism of indeterminate aetiology. Median radioiodine dose used for Graves' disease and MNG patients were 534MBq (range 530–560 MBq). Two third (78%) had their thyroid function tested on the day of treatment. The median duration for the first follow-up was 8 weeks (range 6–9 weeks). After radioiodine therapy, 17% of patients were rendered euthyroid (off the treatment for 1 year), whereas 83% became hypothyroid. The median duration for developing post radioiodine hypothyroidism was 10 weeks (range 6–34 weeks). Graves' hyperthyroid patients (50%) had a higher incidence of developing post radioiodine hypothyroidism than MNG patients (34%). Sixteen patients had significant elevation of free T4 $>$ 70pmol/L at the time of diagnosis and required a second dose of radioiodine.
Conclusion
Our audit demonstrated a high success rate approaching 100% for radioiodine treatment; higher than the published results (60–84%). This has largely motivated us to continue practicing the current integrated approach in managing individual hyperthyroid patients while facilitating close collaboration with general practitioners to ensure their long term standardised follow-up.

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P222

Assessment of efficacy with radioiodine treatment in Benign Hyperthyroid disease across two centres

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Aim
Indications for Radioiodine (131I) in therapy for benign thyroid disease include Graves' disease, Toxic goitre and euthyroid goitre. There is reduced clinical & financial implication as compared to surgery with absence of anaesthetic/invasive complications, pain, recovery and in-patient stay. The aim of this study was establishing demographics and prevalence of the treatment population, to ensure dosage and indication compliance with national guidelines as well as determining efficacy of the treatment through thyroid function outcomes.
Methods
Using an excel database, retrospective data collection was performed for patients receiving Radioiodine treatment for benign thyroid conditions between 1st June 2015 and 1st June 2016 amongst two prescribing sites; one of which had an endocrinologist as prescriber, the other having an oncologist, and comparative outcomes investigated.
Outcomes/results
Radioiodine treatment was given for approved aetiologies in all patients (majority for Graves' disease in both centres with few for Toxic Multinodular Goitre and Toxic adenoma). The average dose of radioiodine used was higher in the prescribing oncologist Vs endocrinologist 447.74 MBq vs 404.94 MBq in Graves' disease, 637.5 MBq vs 403 MBq dose for Toxic multinodular goitre but lower in Toxic adenoma 299 MBq vs 503.25 MBq. All patients had active eye disease excluded. The overall data showed a cure rate (achieving euthyroidism or hypothyroidism) for Graves' disease of 100% by 12 months.
Conclusion
There was appropriate adherence to national guidance and this should continue. Thyroid eye clinics to exclude and stabilise eye disease prior to radioiodine should be utilised. By raising awareness of the effectiveness and safety of

radioiodine as a treatment for hyperthyroid disease in the context of Graves' disease and alternative pathologies early referral in recurrent thyrotoxicosis should be encouraged. This study needs a longer follow-up period to include relapse rates and be compared to centres using dosage calculations as a lower dosage may also be successful.

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P223

Assessment of plasma sodium and potassium levels in sudanese patients with hypothyroidism

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Background
Hypothyroidism is one of the most common forms of thyroid dysfunction. And it causes disturbance in electrolyte balance. The increase or decrease in plasma sodium and potassium levels were found to be associated with increase mortality.
Objectives
The aimed of the study to measure plasma sodium and potassium levels in Sudanese patients with hypothyroidism.
Method
The study is retrospective case control study included 50 patients (diagnosed with hypothyroidism), with mean age 35.9 years and other 50 healthy control have normal thyroid function test and normal renal function test. Random samples were taken for measurement of thyroid function test, sodium and potassium levels.
Result
Plasma sodium levels were significantly decrease in patient with hypothyroidism when compared with control (P value = 0.001), while there were increase in plasma potassium levels when compared with control (P value 0.011).
Conclusion
There is a significant effect of hypothyroidism on plasma sodium and potassium levels in Sudanese patients.

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P224

Identification of novel sodium iodide symporter (NIS) interactors which modulate radioiodine uptake

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Patients termed to have radioiodine-refractory differentiated thyroid cancer (RR-DTC) cannot accumulate sufficient radioiodine for a therapeutic response due to sodium iodide symporter (NIS) dysregulation via diminished expression and/or altered plasma membrane (PM) localisation. Currently, the regulation of NIS localisation remains poorly defined and despite protein-protein interactions being well-described to modulate trafficking events, the NIS interactome is limited. Previously, using mass spectrometry, we identified two novel functional NIS interactors – ADP-ribosylation factor 4 (ARF4) and valosin-containing protein (VCP). ARF4 overexpression and VCP knockdown approximately doubled radioiodine uptake in the TPC1 thyroid cancer cell line, with similar findings observed in human primary thyrocytes. In thyroid cancer, ARF4 was determined to be downregulated, and VCP overexpressed, providing a putative explanation for repressed NIS function. Now, we have determined that ARF4 does not alter NIS expression, but enhances membranous NIS localisation. Real-time imaging using total internal reflection fluorescence microscopy highlighted trafficking of NIS and ARF4 in co-incident vesicles at the PM, suggesting that ARF4 promotes NIS trafficking to the PM. The site of ARF4 binding was identified to be a VAPK motif within the NIS C-terminus; abrogation of this site resulted in a NIS protein whose function remained unaltered compared to wildtype NIS, but which could not be enhanced by ARF4. In contrast to ARF4, VCP decreased NIS protein expression, which was suggestive of a role for VCP in NIS processing and degradation. A panel of pharmacological VCP inhibitors – Eeyarestatin-1, NMS-873 and the FDA-approved Astemizole, Clotrimazole and Ebastine – all overcame VCP inhibition of NIS function, implicating the endoplasmic reticulum-associated degradation pathway as critical to NIS processing. The co-application of SAHA with VCP inhibitor Eeyarestatin-1 additively enhanced radioiodine uptake in vitro. Collectively we identify a novel potential therapeutic strategy for RR-DTC, based on already FDA-approved drugs.

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P225

Using lightsheet microscopy to explore the relationship between NIS and its functional interactors ARF4, VCP and PBF

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Effective treatment of differentiated thyroid cancer relies on a multifaceted approach often including administration of ^{131}I to ablate residual cancer cells post-surgery. The success of this treatment hinges upon adequate uptake of iodide by malignant thyroid follicular cells. In a subset of patients, dedifferentiation of the carcinoma can result in aberrant expression and trafficking of the iodide transport protein, the sodium iodide symporter (NIS), resulting in a radioiodide refractory phenotype. We recently discovered two protein interactors of NIS: ARF4 and VCP. ARF4 binds to NIS and increases its localisation at the plasma membrane (PM), whilst VCP targets NIS for proteasomal degradation. To address the mechanism by which ARF4 enhances NIS PM localisation, we sub-cloned the ARF4 cDNA into dsRed and mCherry vectors and carried out advanced microscopy, including dual-view inverted selective plane illumination microscope (diSPIM) lightsheet imaging. Preliminary data show that the rate of real-time vesicular trafficking of NIS to the plasma membrane is much more rapid than in previously reported studies, indicating that the movement of this critical symporter is unexpectedly dynamic. We are currently mapping the effect of ARF4 co-expression on the trafficking of wild type NIS, as well as VAPK mutant that we have identified, and which is unable to bind ARF4. The only known protein which binds NIS and facilitates its endocytosis is pituitary–tumor transforming gene binding factor (PBF). We have therefore now developed and validated CRISPR-mediated knock outs of PBF in several cell lines, allowing us to address its impact on NIS endocytosis and function. Collectively, these cutting edge imaging studies are now increasing our understanding of the mechanisms by which NIS trafficking becomes dysregulated in thyroid cancer, and how these may be targeted to boost NIS function and reduce the iodide-refractory phenotype.

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ePoster Presentations

Adrenal and steroids

EP1

A rare erythropoietin secreting adrenal adenoma

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A 41 year old female presented to the haematologists with a coincidental finding of polycythaemia: haemoglobin 198 g/L, white blood cell count 8×10^9/L, platelets 236×10^9/L, haematocrit 0.57 L/L and red blood cell count 6.16×10^{12}/L. Six years earlier haemoglobin 151 g/L, white blood cell count 7.7×10^9/L, platelets 297×10^9/L, haematocrit 0.4 L/L and red blood cell count 4.53×10^{12}/L. She was a non-smoker taking no medications with no history of cardiovascular or respiratory diseases. Investigations: exon 12 of the JAK 2 gene and exon 9 of the CALR gene analyses were normal. Erythropoietin 15 mU/ml (5–25) was inappropriately normal for prevailing haemoglobin level. Ultrasound of abdomen suggested the presence of a right adrenal mass. CT imaging confirmed a hypodense $5.8\times5.7\times5.2$ adrenal mass with peripheral heterogeneous enhancement. Endocrine investigations: 09:00 hours cortisol 241 nmol/L and ACTH 14 ng/L,16:00 hours cortisol 88 nmol/L, ACTH 6.3 ng/L, PRA 0.5 nmol/L/hr and aldosterone 56 pmol/L. Urinary metadrenalines$\times3$ were normal as were plasma metadrenaline levels, haemoglobin 207 g/L, haematocrit 0.6 L/L, red blood cell count 6.43×10^{12}/L and erythropoietin 19 mU/ml. MIBG whole body scan was negative. Right laparoscopic adrenalectomy resulted in a fall in erythropoietin, haemoglobin and red blood cell count to initial sub-normal levels with rapid normalisation. Histopathology examination suggested the adrenal lesion to be an unusual benign adreno cortical adenoma. Adrenal adenomas, carcinomas and phaeochromocytomas are commonly listed as erythropoietin secreting tumours. A literature search, whilst identifying numerous cases of polycythaemia associated with adrenal adenoma secreting cortisol and testosterone, failed to identify a single case secreting solely erythropoietin.

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EP2

Testicular adrenal rest tumours masquerading as Leydig cell tumours in a 55-year-old man with congenital adrenal hyperplasia

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Introduction
Testicular adrenal rest tumours (TARTs) are a complication of congenital adrenal hyperplasia (CAH), stimulated by hyper-secretion of adrenocorticotropic hormone (ACTH). They are the main reason for fertility problems in men with CAH owing to compression of the seminiferous tubules, obstructive azoospermia and potentially permanent testicular damage. These lesions are benign and, in most patients present bilaterally. TARTs are treatable, but they can be misdiagnosed as Leydig cell tumours (LCTs) as the histopathological differentiation is difficult.
Clinical Case
We report a late diagnosis of non-classical 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) in a 55-year-old gentleman. He was referred to endocrinology after finding an adrenal incidentaloma on MRI. Biochemical investigations into the nature of the adrenal lesion led to a surprising diagnosis of 21-hydroxylase deficiency CAH. His past medical history included bilateral orchidectomy for benign testicular Leydig cell tumours. There are reports in the literature of TARTs being misdiagnosed as LCTs and therefore, the patient's histopathological specimens were re-examined. The diagnosis of LCTs was changed to TARTs.
Clinical lessons
It is well documented in the literature that TARTs in men with CAH are commonly mistaken for LCTs due to similarities in morphology. Recognition of this disease entity is important when evaluating testicular masses in men as early diagnosis could prevent irreversible testicular damage and infertility.
Reference
1. Claahsen-van der Grinten HL, Otten BJ, Stikkelbroeck MM, Sweep FC, *et al*. Testicular adrenal rest tumours in congenital adrenal hyperplasia. *Best Pract Res Clin Endocrinol Metal 2009*; 23: 209-220.

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EP3

An atypical case of non-classical congenital adrenal hyperplasia

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We present the case of a 28-year old woman who presented with menstrual irregularity and hirsutism since menarche at age 11. She had been diagnosed with polycystic ovarian syndrome and treated with the oral contraceptive pill for 12 years, despite BMI of 21 kg/m^2. Blood pressure was 101/66 mmHg. Baseline electrolytes showed sodium 140 mmol/L, potassium 3.6 mmol/L. Short synachthen test confirmed the biochemical diagnosis of congenital adrenal hyperplasia (CAH) [cortisol 275 nmol/L (0min), 335 nmol/L (30 min), 371 nmol/L (60 min) and 17-hydroxyprogesterone of 32.5 nmol/L (0 min), 173.5 nmol/L (30 min), 201.2 nmol/L (60 min)]. Long synachthen test revealed cortisol of 356 nmol/L (0 min), 389 nmol/L (30 min), 488 nmol/L (60 min), 534 nmol/L (240 min), 586 nmol/L (360 min), 815 nmol/L (440 min), 279 nmol/L (2880 min). Prolonged oral glucose tolerance test was performed, as she complained of hypoglycaemia-like symptoms, confirming hypoglycaemia at 3 hours post-glucose load (glucose 2.1 mmol/L) with appropriate spontaneous recovery (glucose 4.1 mmol/L at 300 min). Genetic testing confirmed non-classical CAH due to 21-hydroxylase deficiency. She was heterozygous for c.89C and c.841G with normal CYP21A2 copy number. She started Dexamethasone 0.25 mg daily and responded well. Androstenedione levels decreased to 11.4 nmol/L. She still complains of fatigue in early evening and a cortisol day curve is scheduled to investigate need for a second dose of dexamethasone. Non-classic CYP21A2 deficiency is one of the most common autosomal recessive diseases. Despite general correlations, the CYP21A2 deficiency phenotype does not always correlate precisely with the genotype, suggesting that other genes influence the clinical manifestations. Women with late-onset form may be compound heterozygotes (classic mutation and a variant allele) or heterozygotes with two variant alleles, allowing for 20–60% of normal enzymatic activity. Women who are compound heterozygotes for two different CYP21A2 mutations usually have the phenotype associated with the less severe of the two genetic defects.

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EP4

Adrenal lymphoma: unusual presentation with unilateral mass and hypoadrenalism

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Background
Adrenal lymphomas are rare and often present with hypoadrenalism in the context of bilateral adrenal masses. We report a patient with unilateral adrenal mass and hypoadrenalism at presentation before evolving rapidly to bilateral masses proven to be a large B cell lymphoma. We discuss mechanisms of hypoadrenalism in adrenal lymphoma.
Case history
A 79 year gentleman with no signifanct past medical history admitted with a 6 week history of being generally unwell, dizzy and fatigued. Physical examination revealed low Blood pressure with postural drop and investigations revealed mild hyponatremia (131), hyperkalemia (6.3) and hypercalcemia (2.73). Random cortisol returned low at 117 mmol/l and failed to respond to synacthen 250 mcg with peak cortisol of 136 mmol/l. CT scan showed a Right sided large $12\times10\times8$ cm suprarenal mass with central necrosis suspicious for primary adrenal cancer and the opposite adrenal looked normal. He was started on replacement hydrocortisone and his blood pressure improved. A subsequent FDG/PET showed disseminated uptake including in both adrenals (with the previously normal left adrenal now grown to $\times$ cm) and widespread lymphadenopathy. With normal plasma metanephrines, a CT guided biopsy of right adrenal was organised and showed diffuse large B cell lymphoma. He was started on RCHOP chemotherapy. A repeat CT scan after the 4th cycle of chemotherapy showed complete resolution of lympdenopathy and left adrenal mass and shrinkage of right adrenal to $11\times7\times3$ cm. He remains well on replacement hydrocortisone and fludrocortisone.
Discussion
Hypoadrenalism in the context of adrenal masses is often related to near total ($>90\%$) destruction of adrenal cortex. Our patients presentation with hypoadrenalism and unilateral mass is unusual although the opposite adrenal rapidly grew subsequently and responded to chemotherapy for B cell lymphoma. We discuss other possible mechanisms that may explain this unusual presentation.

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EP5

What lies beneath? Herbal medications can lead to adrenal insufficiency

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A 62-year-old Asian British female presented with increasing tiredness. She had multiple co-morbidities and was prescribed steroid inhalers for suspected asthma. Her type 2 diabetes mellitus, previously well controlled on metformin, had worsened over a short period of time (48 to 85 mmol/mol). On examination, she was obese (weight 82 kg, BMI 43 kg/m^2), hypertensive (155/78 mmHg); rest of the examination was unremarkable. The blood test revealed undetectable cortisol and ACTH (<28 mmol/l, <5.0 ng/l). Renin, electrolytes, and thyroid function were normal. She failed to mount a response to a short Synacthen® test. A diagnosis of secondary adrenal insufficiency, likely secondary to long-term steroid inhaler and recurrent short courses of oral steroids for asthma exacerbations was made. The patient was commenced on Hydrocortisone 10mg, 5mg and 5mg regimen. Following lung function testing and respiratory team review, mild asthma was confirmed. The Seretide® inhaler was discontinued. Advice to consider less systemically-absorbed steroid inhaler, such as ciclesonide, if she were to become symptomatic. Despite discontinuation of steroid inhalers, the patient continued to fail responding to the short Synacthen® test. Upon further detailed history, the patient admitted taking a herbal remedy for chronic knee pain. Toxicology screening of the herbal remedy showed the presence of dexamethasone, ciprofloxacin, paracetamol, diclofenac, ibuprofen, and cimetidine. The patient was advised to discontinue the herbal remedy. Secondary adrenal insufficiency in our patient was probably due to the herbal medication containing dexamethasone, explaining persistent adrenal suppression despite discontinuation of all prescribed steroids. This may have also contributed to obesity, hypertension and suboptimal control of diabetes mellitus, previously well controlled on metformin. In conclusion, a comprehensive drug history including herbal and over-the-counter remedies should be elucidated, investigating potential presence of steroids in the latter when patients persist to have secondary adrenal insufficiency despite off-prescribed steroid medications.

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EP6

How reliable are regular menses as a guide to endocrine health?

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Background
Birth control is widely encouraged to prevent unwanted pregnancies and around two-third of women use contraception. Prescribed contraceptives may result in amenorrhoea or withdrawal bleeds which can mask the initial symptoms of many endocrine disorders delaying diagnosis and treatment.
Case Summary
A 43-year old Filipino female nurse was referred for headache, uncontrolled hypertension, weight gain, hirsutism and acne with raised serum testosterone level. She had a 6-year history of secondary amenorrhoea following the birth of her child, being on a contraceptive implant initially and then an intra-uterine device (IUD). Clinically she appeared androgenised and cushingoid. Biochemical tests revealed raised serum testosterone level of 6.8 nmol/L (0.4–2.1) with Free Androgen Index of 47.9% (07–12.5), DHEA 19.7 umol/L (1.6–7.8), FSH level 5.3 IU/L, LH level 1.8 IU/L, serum Prolactin level 189 IU/L(59–620), DHA sulphate 22.6 μmol/L (0.7–12.5) and normal 17OH Progesterone 2.6 nmol/L. Overnight Dexamethasone suppression test showed failure of cortisol suppression and 24 hour urinary cortisol was 3× the upper limit of normal. CT abdomen revealed a 12×10 cm adrenal mass with invasion of renal and adrenal veins into IVC, right adrenal atrophy, liver and lungs nodules. FDG PET scan confirmed liver and lung metastasis with bone metastasis in L4. Results were consistent with metastatic adrenal carcinoma. Following MDT discussion, she underwent surgery including nephrectomy and radiotherapy to L4. She required mesenteric artery embolisation for bleeding from liver metastasis.
Discussion
Change in menstruation may be the earliest symptom in many endocrine disorders and the continuous use of contraceptives can mask abnormalities by either false reassurance from withdrawal bleeds in women with prolactinomas, for example, or expected amenorrhoea from implants or IUDs as in this case. Should we change the guidance on contraceptives and consider interval break from their contraceptives or is the risk of unwanted pregnancy too great?

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EP7

Pheochromocytoma mimicking sepsis

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Patient is a seventy year old Egyptian female with past medical history of coronary artery disease, systolic heart failure, chronic kidney disease stage 3, and a benign pheochromocytoma previously worked up at a neighboring hospital, who was admitted for dyspnea and subjective fever intermittently for the past two weeks. Chest x-ray revealed bilateral pulmonary infiltrates. She was treated for community acquired pneumonia. Four days after admission patient has worsening respiratory distress with fever, leukocytosis, tachypnea and was intubated and transferred to ICU. Pan cultures obtained on admission returned negative and her symptoms resolved two days later. Patient's antibiotics were de-escalated and patient was then discharged home. It was thought that her sepsis was likely secondary to pneumonia resulting in acute hypoxic respiratory failure. Patient returned four days later and was readmitted directly to the ICU for worsening dyspnea with a temperature of 102.0, leukocytosis of 27.4, heart rate of 149, respiratory rate of 30, with a blood pressure of 172/90 and pulse oximetry of 83%. Chest x-ray revealed new bilateral infiltrates from previous admission. Patient was intubated and treated with Zosyn, vancomycin, and gentamycin. Cultures again were obtained and again returned negative. It was then thought after researching similar cases that the patient's pheochromocytoma could be leading to a "pseudo" septic picture. It was then determined that patient's septic symptoms were likely due to pheochromocytoma as patient's blood pressure would coincide with febrile episodes and dyspnea. Patient was placed on prazosin and blood pressure normalized during admission without return of fever. Pheochromocytoma should be considered as part of the differential diagnosis in the setting of recurrent dyspnea and sepsis when more common causes have been ruled out. It is also important to do this early as to prevent unnecessary antibiotic use and to prevent antibiotic resistance.

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EP8

Metastatic adrenocortical carcinoma: A Case Report

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Background
Adrenocortical carcinomas (ACC) are rare malignant tumours with an incidence of 1 to 2 per million per year.
Case Report
A 70 year old lady was admitted with a one month history of new onset hypertension, hypergylcaemia, hirsutism and generalised weakness. On examination she was cushingoid with facial plethora, severe hirsutism, central obesity and severe proximal myopathy. A CT trunk showed a large, lobulated, inhomogeneous, solid left adrenal mass 8×5 cm in size with enlarged local and paraortal lymph nodes. Pulmonary metastases were noted.
Biochemistry revealed the following results:
serum random cortisol: 1209 nmol/L, (145–619 nmol/L)
ACTH <5-pg/mL (10–48)
total testosterone: 46 nmol/L (ND-1.49 nmol/L)
oestradiol: 507 pmol/L (ND-118 nmol/L)
progesterone: 5.15 nmol/L (ND-3.2 nmol/L)
OH prog: 21.6 ng/mL (0.13–0.6 ng/mL)
androstenedione 19.4 ng/mL (0.35–2.49 ng/mL)
DHEAS: 23.3 umol/L (0.95–11.67 umol/L)
Plasma cathecolamines, metanephrines and aldosterone renin ratio were normal (in the setting of normokalaemia).
A few days after she complained of severe abdominal pain and was diagnosed with sigmoid bowel perforation needing emergency laparotomy. Following this she developed severe hypokalaemia of 1.94 mmol/L (3.5–5 mmol/L) which was

resistent to oral potassium supplements and aldosterone antagonists. She became dependent on continuous intravenous potassium replacement. Her post operative course was complicated by abdominal wound dehiscence. Wound healing was unsuccessful despite treatment with multiple antibiotic therapy. Poor mobility led to a right femoral vein thrombosis. She was deemed unfit for chemotherapy and passed away a few weeks later.

Discussion

This case highlights the rapid and aggressive nature of ACC. Our patient presented with a mixed Cushing's and virilization syndrome. She suffered the complications of hypercortisolism as evidenced by sigmoid bowel perforation, poor wound healing and hypercoaaguability. The excess cortisol resulted in a mineralocorticoid effect causing recurrent profound hypokalaemia.

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EP9

Delayed diagnosis of Addison's disease and Autoimmune Polyglandular Syndrome Type 2 due to misinterpretation of short synacthen test

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Background

We present a case in which a diagnosis of Addison's disease was missed due to misinterpretation of short synacthen test (SST). This patient was also found to have Polyglandular Syndrome Type 2 (APS-2) after further tests were performed.

Clinical case

A normally fit and well 28-year-old Caucasian man presented to hospital with a few days history of general malaise and a syncopal episode. On admission, patient was hypotensive and tachycardic. Admission bloods showed hyponatraemia, hypokalaemia, acute kidney injury and raised inflammatory markers. The diagnosis of Addisons's disease was suspected. Patient was given hyperkalaemia treatment, intravenous fluids, broad spectrum intravenous antibiotics and intravenous hydrocortisone. Patient markedly improved over the next few hours. On the day after, SST was performed without holding off patient's morning dose of hydrocortisone. Therefore, his SST results showed good response. This was misinterpreted as ruling out adrenal deficiency. He was hence discharged without hydrocortisone replacement. Two weeks later, patient was re-admitted to hospital with similar presentation. SST was repeated before patient's morning dose of hydrocortisone. This time, it demonstrated flat response. This finally confirmed patient's diagnosis of Addison's disease. Patient was started on oral hydrocortisone and fludrocortisone. As patient's TFT and TPO antibodies results showed evidence of autoimmune hypothyroidism, he was also started on thyroxine a week after discharge. Patient was followed up in clinic six weeks later and had remained well. Further blood tests were performed to screen for other conditions associated with APS-2. Patient was also found to have probable underlying pernicious anaemia.

Conclusion

It is important to correctly perform and interpret SST results to prevent missing the diagnosis of Addison's crisis in clinical practice. As Addison's disease can co-exist with other autoimmune conditions, screening for other autoimmune disorders should be performed to enable early identification of any other underlying conditions.

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EP10

Unusual size presents with unusual presentation

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Introduction

Pheochromocytoma is a rare tumor originating from the embryonic neural crest and secreting high levels of catecholamines. The average pheochromocytoma size is 7 cm in the previous publications (1). Sometimes these tumors may be bigger. In this abstract, a case of pheochromocytoma with a huge size presented with unusual presentation.

Case study

Fifty-six year-lady presented with an incidental finding of suprarenal mass 14.5 cm after an investigation for recurrent non-specific abdominal pain. Her CT abdominal scan showed large right suprarenal mass. Further exploration of her history; she denied all symptoms of pheochromocytoma. She has no symptoms of a headache, palpitations, sweating, tremors, dyspnea, anxiety or other symptoms related to pheochromocytoma. Her urine metanephrines showed persistently elevated normetanephrine of 9.5 and 9.73 umol/24 hrs urine (normal is less than 3 umol/24 hrs urine collection). All her other baseline blood results are normal including bone profile and glucose. After the biochemical diagnosis of pheochromocytoma, the patient was referred to a tertiary centre where all the other workup is done. After review of online English literature and as far as we know, this case is the twelfth largest pheochromocytoma reported in the English literature (2) and the largest published in the UK.

Summary and conclusion

- Most giant pheochromocytomas do not present with classic symptoms.
- Pheochromocytoma may reach huge sizes without causing any symptoms (1).
- No clear correlation between the size of a tumour and the catecholamines level.

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EP11

Glucagon Stimulation test (GST) is superior to Short Synacthen test (SST) in diagnosing Adrenal insufficiency

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Introduction

Short synacthan test is a first line endocrine test for diagnosing adrenal insufficiency except in situations like Pituitary surgery or Pituitary apoplexy within the last 2 weeks when this may give a false positive result and this is well known in literature. Here we discuss lesser reported clinical situations seen in two of our patients having good adrenal response to SST with only GST identifying adrenal insufficiency.

Case Report

Two patients who were seen in Endocrine out patients clinic. Patient A has symptoms of hypogonadism and feeling generally tired all the time. Morning cortisol was low with slightly raised prolactin levels but other anterior pituitary hormones and MRI pituitary were normal. SST showed low 0 min cortisol but satisfactory 30 minute response. Because of low 0 min cortisol and ongoing symptoms of tiredness, GST was performed which confirmed adrenal insufficiency. Patient B presented with hyponatraemia. Her Anterior pituitary test were all normal except low morning cortisol. Her MRI Pituitary showed Pituitary Macroadenoma. CT thorax, abd, pelvis was normal. SST showed good 30 minute response. She was symptomatic with low sodium, therefore GST was performed, which confirmed adrenal insufficiency

Discussion

The cause of adrenal insufficiency in both these cases were inadequate release of ACTH from the Anterior Pituitary gland when challenged with GST. Potential mechanisms involving the satisfactory 30 minute cortisol with SST are likely these patients may be in the initial phase of pan hypopituitarism and were secreting ACTH just enough to meet the daily requirement but not enough to stimulate adrenals during the time of stress or illness.

Conclusion

These cases highlights the importance of GST in detecting adrenal insufficiency under stress. Interpreting SST on the basis of 30mins cortisol response alone may mask borderline adrenal insufficiency as SST does not test the whole pituitary adrenal axis.

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EP12

Loperamide induced hypoadrenalism presenting as recurrent hypoglycaemia in a patient with type 1 diabetes

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A 32 year old female presented with recurrent episodes of severe hypoglycaemia. Type 1 diabetes had been diagnosed 10 years earlier and she had undergone subtotal colectomy/ileostomy 20 months earlier for

chronic diarrhoea. Histology suggestive of eosinophilic colitis. High stoma output (>4 litres per 24 hours) was causing stomal incontinence with disruption of normal lifestyle. Treatment with combinations of loperamide, codeine, omeprazole and octreotide were ineffective. Examination revealed dehydration, sinus tachycardia 120 beats per minute and blood pressure 100/60 mmHg. Investigations confirmed AKI and metabolic acidosis: sodium 125 mmol/L, potassium 4.9 mmol/L, urea 28 mmol/L, creatinine 248 μmol/L, pH 7.25, bicarbonate 9.6 mmol/L, glucose 3.4 mmol/L, ketones 1.1. mmol/L and cortisol 714 nmol/L. The latter was not available to the admitting team who administered IV fluids plus hydrocortisone to cover possible adrenal suppression secondary to previous glucocorticoid treatment, with rapid correction of both AKI and metabolic acidosis. Further investigations revealed 09:00 hours cortisol 52 nmol/L and ACTH 8.9 ng/L. It was ascertained that morphine sulphate 10mg po was administered 6 hours prior to these investigations suggesting opiate induced hypoadrenalism. 09:00 hours cortisol 394 nmol/L and ACTH 65.6 ng/L off opiates. Pituitary function, PRA and aldosterone levels were normal. A cortisol level of 39 nmol/L coincidental with a blood glucose of 1 mmol/L was recorded on treatment with loperamide 8 mg tds. Treatment with high dose loperamide (14, 16, 32 and 16 mg daily) reduced stoma output to <1 litre/24 hours but resulted in cortisol levels of 32-68 nmol/L and ACTH 1.8-3.0 nmg/L on day profiles. Hydrocortisone at replacement doses was therefore commenced with dramatic improvement in her quality of life and resolution of hypoglycaemic episodes.

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EP13

A rare cause of unexpected bilateral adrenal gland abnormalities

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Adrenal gland anomalies are common incidental findings when imaging tests are performed for other reasons, but are usually unilateral. We present a case where bilaterally abnormal adrenal glands held the key to a rare diagnosis. A 79 year old female ex-smoker with a background of Type 2 Diabetes Mellitus and hypertension presented to our emergency department with a four month history of falls and progressive decline in mobility. Examination revealed evidence of weight loss, with grade 3/5 power and hyporeflexia in both lower limbs. She was hyponatraemic (sodium 117 mmol/L), attributed to taking bendroflumethiazide and amitriptyline, and anaemic with a detectable paraprotein. Early morning cortisol was within acceptable limits (665 nmol/L). Spinal imaging revealed degenerative disc disease, a small lung nodule and bilateral adrenal enlargement (5 cm). Nerve conduction studies confirmed a large fibre sensorimotor axonal abnormality. Suspecting metastatic bronchial malignancy, the patient eventually underwent adrenal biopsy which gave the diagnosis of Primary Adrenal Lymphoma (of diffuse large B cell type). After a short trial of chemotherapy she unfortunately deteriorated and died within 6 weeks of diagnosis. Primary adrenal lymphoma is a very rare form of extranodal non-Hodgkin's disease, with <200 cases reported worldwide. It is usually bilateral, highly aggressive and associated with primary adrenal failure. Lymphoma should be considered in the differential diagnosis of adrenal lesions, particularly when bilateral.

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EP14

Cushing's syndrome due to primary bilateral macronodular adrenal hyperplasia (PBMAH) - clinical and hormonal characterisation

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Background
PBMAH is a rare cause of adrenal Cushing's syndrome, frequently due to aberrant adrenal expression of hormonal receptors.
Aim
To describe 6 patients with PBMAH.
Methods
Clinical, hormonal and imagistic evaluation.
Results
Age at diagnosis of patients (4M/2F) was 50–79 years. One asymptomatic patient was incidentally diagnosed on abdominal CT, two patients had overt Cushing's (central obesity, severe diabetes mellitus, arterial hypertension/renal insufficiency), three patients with metabolic syndrome (central obesity, diabetes mellitus/impaired fasting glucose, arterial hypertension, hyperlipidemia) were positive on biochemical CS screening. All patients had unsupressed cortisolemia after overnight and low-dose dexamethasone (2×2 mg) testing and 8AM ACTH was supressed. Urinary free cortisol (UFC) levels were elevated in one patient, while two patients with chronic kidney disease had UFC within the reference range. The adrenal CT imaging phenotype was variable in terms of number of nodules and size, with nodule diameters on between 1.5-5 cm. Two patients had secondary osteoporosis with prevalent vertebral fractures. Four patients were tested biochemically for the presence of aberrantly expressed receptors: cortisolemia responded to a mixed meal (GIP receptors) in two patients, one patient responded to triptorelin (gonadotropin receptors) and one patient responded to posture (adrenergic receptors), mixed meal and triptorelin. The two patients with overt Cushing's received Metyrapone, with one undergoing bilateral adrenalectomy; she developed a fatal septic shock after the second adrenalectomy, while the other patient awaits surgery. One patient refused adrenalectomy, the asymptomatic patient is being monitored, one patient received intramuscular triptorelin and one patient has been lost to follow-up.
Conclusions
PBMAH is frequently oligo-symptomatic, warranting biochemical screening in patients with metabolic syndrome and atypical Cushing's. Bilateral adrenalectomy is curative. Management depends on the severity of Cushing's and availability of medical therapy (requiring biochemical aberrant adrenal receptor profiling). Patients subjected to conservative management adrenalectomy need longterm follow-up.

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EP15

Intermittent primary aldosteronism – another hurdle in the Conn's story?

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Background
Primary aldosteronism (PA) accounts for 5–10% of all patients with hypertension, and an even greater proportion of those with refractory hypertension. Accurate assessment of PA is important both for rationalisation of medical therapy and to identify those patients with unilateral disease who may benefit from surgery. Single timepoint testing may miss patients with intermittent ('cyclical/periodic') disease, a phenomenon seen in other endocrine hypersecretory syndromes, but not commonly recognised in PA.
Methods
Retrospective analysis of all patients diagnosed with PA in our centre (2013–2018) identified those who had discordant confirmatory tests for PA, with an initial suppressed saline infusion test (SIT) followed by a result consistent with PA. Clinical (including BP and potential confounding medications) and biochemical (serum potassium, plasma renin, plasma aldosterone) data were then reviewed for these patients.
Results
Three patients, for whom clinical suspicion of PA was high, demonstrated normal aldosterone suppression on an initial SIT with subsequent non-suppressed second SIT confirming PA. Confounding medications were excluded as reasons for the discrepancy. All three had marked variability in aldosterone levels with time, while renin remained <10 mU/L. The aldosterone:renin ratio (ARR) was also variably suggestive of PA with time. Blood pressure variability did not correlate with aldosterone levels and was not predictive for a positive ARR or SIT result.
Conclusion
Intermittent PA should be recognised as a clinical entity. This may lead to false negative exclusion of PA in some patients and resultant failure to offer appropriate management. We suggest that patients with a high pre-test probability for PA (e.g. young onset or refractory hypertension, unprovoked hypokalaemia, adrenal adenoma visible), but with negative initial testing, should be followed with serial ARR measurements and subsequent careful timing of confirmatory or lateralisation tests to maximise the chances of being in an active PA phase.

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EP16

Two cases of Addison's disease in pregnancy

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Addison's disease rarely newly presents during pregnancy. We highlight two cases diagnosed within 3 months. A 41-year-old with mild depression on Sertraline, presented at 11-weeks' gestation with an 8-week history of fatigue, weight loss, dizziness and vomiting. Persistent hyponatraemia was noted (Na 122–127 mmol/l). Random cortisols were 298–428 nmol/l. Sertraline withdrawal and fluid restriction at another centre did not improve her hyponatraemia, the use of synacthen was deemed contraindicated. On transfer to our service, she had difficulty standing (lying BP 88/53). SST response at 60min showed cortisol 466 nmol/l (trimesteral SST 60-min pass cut-offs are 700, 800 and 900 nmol/l (*Lebbe 2013*)), ACTH 67.8 (7.2–63.3) and renin 16. Adrenal antibodies were negative. Subclinical hypothyroidism (positive TPO antibodies) was also noted. Marked clinical improvement was seen following in-patient resuscitation. She has subsequently been clinically and biochemically stable on hydrocortisone, fludrocortisone and levothyroxine. Whilst reassessment is planned post-partum, permanent adrenal insufficiency is likely. She has required significant psychological and pharmacological support for her diagnosis acceptance during pregnancy. Separately, a 36-year-old was referred to Bristol Dental Hospital at 8-weeks' gestation with a sublingual lesion and noted to have buccal pigmentation. Her only symptom was fatigue and she had been receiving compliments for her 'winter tan' for months. Her random cortisol was 146 nmol/l. An SST confirmed adrenal insufficiency (60 min cortisol 125 nmol/l), ACTH 1515 and renin 6.9. She is currently progressing well through pregnancy on treatment. These cases highlight the need for a high degree of clinical suspicion to diagnose Addison's in pregnancy. Trimesteral morning levels <300, <450, <600 nmol/l should alert a possibility of adrenal insufficiency (*Lebbe 2013*). Synacthen can be used safely but there is a need to appreciate trimester specific cut-offs (increasing CBG driving higher total cortisol levels in pregnancy).

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EP17

An unusual presentation of Cushing's syndrome

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A 50 year old man was admitted in September 2017 with left sided thoracic pain. A chest radiograph revealed a left-sided hilar mass. CT of thorax demonstrated a large, left-sided, anterior mediastinal mass with associated lymphadenopathy and sclerotic bone metastases. A CT-guided biopsy was performed and pathology was consistent with carcinoid tumour. The patient was referred to clinical oncology. An NM octreotide scan confirmed a left-sided avid lesion within the thorax. Gut hormone profile was normal. The patient was commenced on octreotide acetate injections. A follow-up CT scan was performed and the patient commenced on temozolamide as there was evidence of disease progression. The patient was re-admitted three months following the initiation of octreotide therapy with polyuria, polydipsia and hyperglycaemia consistent with diabetes mellitus. This was managed with twice daily insulin and metformin. Despite lacking symptoms of Cushing's the cortisol following overnight dexamethasone suppression test was 1878 nmol/l (ref. range <50 nmol/l). ACTH levels were 258 mU/l (ref. range <20 mU/l) and urinary cortisol was >2000 nmol/l. The presumed diagnosis was of ectopic ACTH secretion from the known carcinoid tumour. The patient was re-admitted 2 weeks later with hypokalaemia, marked proximal mypoathy and oedema consistent with cortisol excess. He was commenced on metyrapone at an initial dose of 250 mg, twice daily which was uptitrated; once the cortisol level was less than 400 nmol/l he was commenced on hydrocortisone 20 mg morning 10 mg afternoon. A sample of serial cortisol levels have been tabulated. He continues on octreotide injections, temozolamide, metyrapone and hydrocortisone, alongside twice-daily insulin and metformin.

	19/3	21/3	27/3
Cortisol (nmol/l, morning level)	1758	740	550
Cortisol (nmol/l, evening level)	n/a	781	361*
Metyrapone Dose (total daily, mg)	500	750	1250

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EP18

Transient hypocortisolaemia in an HIV positive patient

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We present a case of a 53 year-old lady with HIV, who was referred to the endocrine service with a random cortisol of <20 nmol/l. She complained of fatigue, appetite loss and 13 kg weight loss. She had a history of brain histoplasmosis, which had been successfully treated >5 years previously. At that time she required a short course of steroid therapy acutely. Short synachthen test revealed inadequate response (cortisol at 0 min: 378 nmol/l, 30 min: 481 nmol/l, 60 min: 488 nmol/l. At the time she was on Ritonavir. CD4 count was 222 cells/microlitre but viral load was undetectable. All other endocrine axes were intact. She was commenced on low dose prednisolone 3 mg and adequate replacement was confirmed with a prednisolone curve. She was also changed to Raltegravir. The patient reported feeling stronger on steroid replacement therapy, regained her appetite and started to regain the lost weight. Adrenal and pituitary MRI revealed no pathology. Serial synacthen tests showed inadequate peak responses and she has continued on steroid replacement. However, when her CD4 count incremented to 667 cells/microlitre, a long synacthen test was performed and that showed a baseline cortisol of 232 nmol/l with a peak cortisol of 834 nmol/l, implying steady recovery of her axis. We plan to withdraw steroid therapy and monitor. The mechanism by which HIV might affect endocrine function involves mostly immunomodulatory effects of cytokines. Impaired adrenal reserve is a common finding in HIV-infected patients. Changes in cortisol diurnal rhythm have been reported in HIV patients, along with changes in ACTH stimulation according to CD4 count and viral load in the phase of their disease. The diagnosis of adrenal insufficiency in the setting of HIV infection may be challenging because many of these patients have nonspecific symptoms such as fatigue, weight loss, nausea and vomiting, resembling those of adrenal insufficiency.

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EP19

A case of challenging post-operative management in adrenal Cushing's syndrome

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25% of Cushing's syndrome cases are caused by cortisol producing tumours of the adrenal glands. Adrenalectomy is standard treatment followed by glucocorticoid replacement therapy until the hypothalamic-pituitary-adrenal axis recovers. We present a challenging case of adrenal insufficiency after unilateral adrenalectomy for Cushing's syndrome. A 38 year-old woman was referred with hyperlipidaemia and uncontrolled hypertension diagnosed 4 years previously. Examination revealed Cushingoid features and a review of previous tests performed abroad revealed likely Cushing's. Overnight dexamethasone suppression testing showed a cortisol of 429 nmol/l and an undetectable baseline ACTH. CT imaging confirmed a 3 cm left adrenal mass. A laparoscopic left adrenalectomy was performed. Post-operatively 10 mg thrice daily of hydrocortisone was commenced with a view to wean. On attempts to taper the dose the patient developed severe proximal myalgia, which persisted for 10 months post-operatively. A rheumatological screen was negative. A hydrocortisone day curve showed cortisols of <20 nmol/l (0 min), 319 nmol/l (120 min), 263 nmol/l (240 min) and 299 nmol/l (360 min). She also developed severe anxiety, despite resolution of her hypercortisolaemia. She required referral to psychological services. 12 months post-adrenalectomy her symptoms improved so the hydrocortisone was reduced to 10/5/5 mg. Short synacthen testing confirmed no HPA axis recovery and after 22 months she remains on hydrocortisone replacement. Cortisol producing tumours are known to suppress the HPA axis, forming the basis of steroid replacement postoperatively. Replacement can be highly variable, but a review published by Di Dalmazi *et al*. indicated that the average time to recovery of adrenal function post unilateral adrenalectomy for these tumours was 11 months. Our patient had overt Cushing's for over 4 years prior to surgery which may explain the failure to recover her axis and her clinical symptoms on attempts to reduce her steroids. Additionally, some studies have reported an exacerbation of psychiatric symptoms with cortisol decrease.

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Bone and Calcium

EP20

Case of resistant hypocalcaemia secondary to iatrogenic hypoparathyroidism, treated successfully with teriparatide

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Inappropriately low circulating PTH levels following thyroid surgery, is the most common cause of iatrogenic hypocalcaemia. Standard treatment of hypoparathyroidism has comprised vitamin D analogue and calcium supplementation. However some patients remain hypocalcaemic despite use of maximal titrated and tolerated therapy. Teriparatide is recombinant formulation of endogenous PTH, containing 34 amino acid sequence which is identical to the N-terminal portion of this hormone. We report a case of severe hypocalcaemia secondary to hypoparathyroidism treated successfully with teriparatide. A 65 year old female was admitted to King's College Hospital in September 2016 with right upper limb weakness and numbness. She reported nausea, vomiting and diarrhoea. Her past medical history included total thyroidectomy for goitre with subsequent hypothyroidism and iatrogenic hypoparathyroidism. Medications included intramuscular ergocalceferol 600 000 units monthly, calcit 2 gm bd and alfacalcidol 9 mcg total. Biochemistry revealed a corrected calcium 1.67 mmol/l and magnesium 0.69 mmol/l. ECG demonstrated sinus rhythm with a normal QTc interval. She received intravenous calcium infusions with significant symptomatic improvement. Over the course of the subsequent 18 months, despite escalating doses of calcium and vitamin D supplementation, she presented to hospital trusts on multiple occasions with recurrent, symptomatic, severe hypocalcaemia. Requirements escalated to weekly IV calcium infusions. An individual funding request (IFR) was submitted for teriparatide which was initiated in March 2018. Serum calcium normalised 7 weeks after drug initiation in conjunction with alfacalcidol 4 mcg morning and 3 mcg evening with cholecalciferol 6400 units once daily. Since commencing teriparatide, administration of intravenous calcium has not been required.

Conclusion

Teriparatide therapy is not routinely recommended for the management of hypocalcaemia secondary to hypoparathyroidism but should be considered for cases resistant to high dose calcium and vitamin D supplementation. Avoidance of frequent hospital admissions is both cost effective and improves patient quality of life.

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EP21

Acute hypocalcaemic crisis precipitated by a single unit of blood transfusion

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A 33 year-old-lady presented to the emergency department with acute abdominal pain and per vaginal bleeding. Her last menstrual period was six weeks prior to admission. She had a positive urine pregnancy test and a trans-vaginal ultrasound confirming an ectopic tubal pregnancy. She underwent an emergency laparoscopic right salpingectomy under general anaesthesia with blood loss intra-operatively of 300 ml. One day post-op, her haemoglobin dropped from 129 g/l to 86 g/l. She received 1unit of blood, transfused over 2 hours. Post-blood transfusion, she reported tingling over her hands and perioral area, with acute carpopedal spasm. She had no personal or family history of calcium disorders. She was hypocalcaemic with an adjusted serum calcium 2.07 mmol/l (2.2–2.6) and ionised calcium 1.01 mmol/l (1.13.1.32), phosphate 0.27 mmol/l (0.8–1.5), magnesium 0.91 mmol/l (0.7–1.0) and PTH 4.3 pmol/l (1.6–7.2). Her arterial blood gas showed: pH 7.64, PCO2 2.4kPa, HCO3 17 mmol/l and raised lactate of 4.9 mmol/l, consistent with a respiratory alkalosis superimposed on an underlying metabolic acidosis. She was treated with IV calcium gluconate, IV magnesium and phosphate; after two-cycles of this therapy her symptoms resolved with her adjusted calcium normalised to 2.20 mmol/l and phosphate to 1.25 mmol/l. Hypocalcaemia following large volume transfusions is well-reported. This is driven by large amounts of citrate in transfusions binding calcium. This tends not to occur with low volumes of blood due to prompt removal of citrate by the liver. This case is novel in that only a single unit of blood precipitated the hypocalcaemia, due to a superimposed respiratory alkalosis lowering ionised calcium. We highlight that certain patients (rapid transfusions, alkaloses) are at increased risk of hypocalcaemia following even low volume blood transfusions. Therefore it may be beneficial to monitor serum calcium with a low threshold for ionised calcium to ensure prompt detection of this phenomenon.

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EP22

Fibroblast Growth Factor 23 (FGF23) is a useful biomarker in the investigation of incidental hypophosphataemia

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A 77 year old female was referred to endocrinology with an incidental finding of hypophosphataemia (0.26 mmol/l) on routine bloods. She described a slight unsteadiness on her feet, but denied bone pain or overt muscle weakness. Past medical history included Type 2 Diabetes Mellitus, a left humeral fragility fracture and the subsequent diagnosis of osteoporosis 2 years previously. At presentation the corrected calcium was slightly elevated (2.64 mmol/l), which normalised when repeated, with suppression of parathyroid hormone (0.8 pmol/l) and adequate 25-hydroxyvitamin D concentrations (71 nmol/l). Renal function was normal and no paraproteins were detected. Phosphate levels were suboptimal for approximately 3 years, however, had been normal prior to this. FGF23 was found to be significantly elevated (186 RU/ml; normal range <100). An octeotide scan was undertaken demonstrating the presence of a moderately octreotide avid heterogenous soft tissue mass lesion within the right thigh. A successive MRI confirmed the presence of a $7.2\times3.8\times6$ cm well-defined infiltrative enhancing mesenchymal tumour of the right adductor musculature. Tumour induced osteomalacia is a rare paraneoplastic disorder characterised by hypophosphataemia due to decreased renal tubular reabsorption of phosphate as a result of tumour FGF23 overproduction. The majority of tumours responsible for this condition are phosphaturic mesenchymal tumours of the mixed connective tissue variant. These tumours are often small, slow growing, occur in diverse locations and are largely benign, however, can metastasise. Other tumours associated include osteosarcomas and advanced metastatic cancers of the colon and prostate. Chronic hypophosphataemia impairs bone mineralisation and can result in significant proximal myopathy, however, patients are often asymptomatic and phosphate depletion is identified incidentally. Consequently, FGF23 is a useful biomarker in the diagnosis of tumour induced osteomalacia, which if resected can be curative.

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EP23

A case of severe hyperparathyroidism in pregnancy

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Primary hyperparathyroidism is a fairly common endocrine problem affecting women twice as common as men. The first case of primary hyperparathyroidism in pregnancy was reported in 1931. We present a case of a 29 years old lady who was referred to the endocrine clinic from inpatient admission for her high corrected calcium (Corr Ca) levels (3.27 mmol/mol) and high Parathyroid Hormone (PTH) levels (58.9 pmol/l), while she was 12 weeks pregnant. Her past medical history was significant for previous still birth at 25 weeks and depression. Her first serum calcium levels were done by her GP six months after she delivered a dead fetus at 25 weeks gestation. She complained of persistent tiredness and increased thirst, but denied polyuria. She also had ill-defined abdominal pain, and complained of low mood for which she was on Citalopram. Investigations done in endocrine clinic showed Corr Ca: 3.42 mmol/mol, PTH: 54.4 pmol/l and 25 OH Vitamin D level of 27.1 nmol/l. Free T4, IGF-1 and serum cortisol were all in normal range. LH (0.65 IU/l) and FSH (<0.05 IU/l) were keeping in view with the pregnant state. Parathyroid Ultrasound did not reveal any adenoma. 24 hour urinary calcium was 12.4 mmol/24 hours. She was referred to a tertiary center for urgent parathyroidectomy. After parathyroidectemy her PTH normalized to 4.42 pmol/L and Corr Ca to 2.58 mmol/mol. She progressed well with her pregnancy after parathyoiroidectectomy and delivered a healthy baby girl at full term. Serum calcium could be considered as a routine investigation in pregnancy, as appropriate treatment of primary hyperparathyroidism could result in avoidance of high incidence of fetal and maternal complications associated with the condition. Hyperparathyroidism should be suspected in females who present with depression.

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EP24

An unusual case of primary hyperparathyroidism in a patient with concomitant familial hypocalciuric hypercalcaemia

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a benign condition characterized by asymptomatic hypercalcemia secondary to hypocalciuria. Affected patients have variable parathyroid hormone levels. It is caused by a loss-of-function mutation in the calcium-sensing receptor (*CASR*) gene. The occurrence of both FHH and primary hyperparathyroidism (PHPT) in the same patient has rarely been described. We report an interesting case.
Case
A 71-year-old lady was reviewed because of severe hypercalcaemia. This was discovered during routine screening because of a family history of FHH and the presence of the *CASR* gene mutation. She was asymptomatic. She had no relevant past medical history and was not taking any medication.
Investigation and management
Blood results indicated mild chronic kidney disease and normal vitamin D levels, raised serum calcium (3.24 mmol/l), low serum phosphate (0.67 mmol/l) and a slightly raised parathyroid hormone (PTH: 11.9 pmol/l). Her 24-hour urinary calcium was inappropriately low at 2.2 mmol/24hr, confirming hypocalciuria. Genetic testing confirmed the presence of the *CASR* gene mutation [c.2444A > G, p.(Lys815Arg)]. However, the disproportionately high serum calcium level prompted further investigation. Her bone density scan showed osteopenia. An ultrasound and parathyroid MIBI scan detected a right lower pole parathyroid adenoma. After informed discussion she underwent parathyroidectomy (histology confirmed a parathyroid adenoma). Postoperatively her calcium fell down to 2.51 mmol/l and then rose to 2.78 mmol/l. PTH fell to 0.8 pmol/l then rose to 7.4pmol/L. Current serum calcium levels remains at 2.72 mmol/l with a calcium-creatinine clearance of 0.005, indicating continued mild hypercalcaemia of FHH.
Conclusion
The coexistence of FHH and PHPT should be considered in patients with hypercalcemia, hypophosphatemia, mildly elevated parathyroid hormone levels and inappropriate hypocalciuria. Although surgical intervention may not resolve the hypercalcemia completely, it will alleviate the symptoms and prevent potential complications of the hypercalcaemia secondary to PHPT.

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EP25

A rare ophthalmic condition associated with primary hyperparathyroidism (Scleralchoroidal Calcification)

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Introduction
Sclerochoroidal calcification is an uncommon condition that classically manifests as multiple discrete yellow placoid lesions, often discovered as an incidental finding. It is ordinarily believed to be idiopathic, but is also associated with primary hyperparathyroidism. It is important that these patients are identified because of the systemic implications and treatable nature of these disorders.
Case
82 years old patient with history of Primary Hyperparathyroidism and Osteoporosis was referred by the optometrist to the ophthalmology department after noticing raised pale lesions in his both fundi on a routine eye test. The patient was asymptomatic. The appearance is classical of Scleralchorodial Calcification related to hypercalcaemia caused by primary hyperparathyroidism. His corrected calcium was 2.83 mmol/l (2.20–2.60), Parathyroid hormone was 13.9 pmol/l (1.1–6.9), and PO4 was 0.66 mmol/l (0.8–1.5), Vitamin D was normal at 77.3 nmol/l (50–175), Creatinine 78 umol/l (60–105), EGFR 83 units (90–120) .His urinary calcium creatinine ratio was 0.2. His ultrasound B-scan of both eyes show multiple hyper echoic deposits in the posterior ocular coats, persisting at low gain, and causing significant shadowing, consistent with calcium deposits.The lesions appear to be posterior to the muscle insertions.
Conclusion
Collaboration between different specialties (in this case between Endocrinology and Ophthalmology) is required in managing patients. Identifying these lesions promptly helps with the management of underlying systematic disorders involving abnormal calcium – phosphorus metabolism or renal tubular hypokalemic metabolic alkalosis syndromes. As an Endocrinologist, it is important to look for such associations and undertake thorough clinical examination, including fundoscopy, followed by prompt Ophthalmology referral. Our patient was already under Endocrine clinic follow up for conservative treatment of Primary Hyperparathyroidism. Despite several cases of Sclerochoroidal calcification reported in the literature it remains poorly recognized and can be misdiagnosed as a malignant tumor resulting in unwarranted intervention.

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EP26

A case report of severe recurrent hypercalcaemia due to Milk Alkali syndrome and immobilisation

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Milk Alkali syndrome (MAS), a rare cause of hypercalcaemia, is reversible and caused by the ingestion of large amounts of calcium (Ca) and absorbable alkali. We report a case of MAS in a 37 year old female, admitted with Ca of 3.44 (2.15–2.62 nmol/l). Presenting complaints include 6 months history of worsening fatigue, thirst, polyuria, abdominal pain and a complex background of bipolar disorder, fibromyalgia, spina bifida, lumbar spine fusion and extremely limited mobility. She was taking over-the-counter (OTC) Vitamin D (400 IU)/day. Initial investigations: normal ECG, urea:11.2 (2.5–7.8mmol/l), Creatinine:197 (45–84 μmol/l), eFGR: 25ml/min, appropriately suppressed PTH < 1.2 (1.1–4.7 pmol/l) and Vitamin D 58 (50–250 nmol/l). Immunoglobulin electrophoresis: high total Protein 82 (60–80 g/l), IgG 18.80 (7–16 g/l), negative urinary Bence Jones Proteins and LDH. She was treated with i.v normal saline and was discharged with Ca 2.80 mmol/l and improved AKI. CT Thorax Abdomen Pelvis revealed no abnormal findings. However, she was re-admitted within 3 days with symptom recurrence and Ca of 3.01 mmol/l. She was treated with i.v normal saline and Pamidronate. Haematology review ruled out a haematological cause. Further careful history taking revealed patient's chronic intake of ∼2 pints milk/day plus OTC antacids. We believe that her hypercalcaemia was multifactorial in origin. Her habitual milk intake contributed to ∼1200 mg/day Ca plus ∼300 mg of OTC Ca supplements contributed to the MAS. Her hypercalcaemia was further exacerbated by immobility. She discontinued her excessive milk and antacids intake. Her Ca has been normal since. Our case report emphasises the importance of good history taking in establishing the diagnosis of MAS which is considered uncommon. MAS can cause severe hypercalcaemia warranting hospital admission.

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EP27

PTH elevation post-parathyroid carcinoma resection – metabolic phenomenon or evidence of disease spread? a case study and literature review

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We set out to describe a case of persistent PTH elevation post parathyroid carcinoma resection and assess its significance via literature review. A 71 year old lady presented with abdominal pain and weight loss. Blood tests revealed calcium of 3.42 mmol/l and PTH of 47.8 pmol/l. Ultrasound neck and SESTAMIBI scan suggested right lower parathyroid adenoma. She underwent right inferior parathyroidectomy however histology revealed parathyroid carcinoma with incomplete excision necessitating a right hemi-thyroidectomy and neck dissection. Post-operatively, PTH remained elevated between 13.1 and 33 pmol/l. Calcium level has been normal throughout and she remains asymptomatic. Vitamin D ranged between 25 and 62 nmol/l. MRI neck, SESTAMIBI and whole-body PET scans have shown no evidence of residual/recurrent disease and she remains under close follow-up. Literature reviews have previously revealed that persistent PTH rise after removal of parathyroid adenoma without evidence of recurrent disease is a common metabolic phenomenon. We undertook a literature review searching pubmed/medline using keywords 'PTH elevation' and 'parathyroid carcinoma' in the English Language up until 2018. We identified the most common cause of raised PTH post resection of parathyroid carcinoma is residual/recurrent disease. There were four cases whereby no evidence of residual or recurrent disease was found, 2 of which had a normal calcium level. The need for multiple imaging modalities and invasive investigations in the cases with confirmed recurrence/residual disease shows the diagnostic challenge this scenario presents and the need to keep a high index of suspicion. We hypothesise

there may be a similar metabolic phenomenon post parathyroid carcinoma resection resulting in normocalcaemic persistant PTH elevation. However unlike following parathyroid adenoma resection this is a rare entity and rise in PTH post carcinoma resection is much more likely to reflect residual/recurrent disease.

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EP28

A case of miliary pulmonary tuberculosis complicated by refractory hypercalcaemia following vitamin D replacement

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A 54-year-old man was admitted to hospital with a new diagnosis of Miliary Pulmonary Tuberculosis (TB). Early in admission he developed septic shock with multiorgan failure requiring organ support and anti-TB medications. Recovery was complicated by persistently low Glasgow coma score (GCS), noradrenaline dependency and limb threatening microvascular injury. At day-25 he was apyrexial but remained hypotensive and drowsy with no evidence of sepsis or hypoadrenalism. Over the next 48 hours, he showed signs of rapid recovery as alertness normalised and blood pressure improved; noradrenaline was withdrawn, allowing him to leave bed and engage in active rehabilitation. He was found to be mildly hypocalcaemic and severely vitamin D deficient. Vitamin D replacement was commenced with a weekly Colecaliferol (40,000 units) regime. Unexpectedly, recovery was severely setback during Vitamin D replacement which unmasked refractory symptomatic hypercalcaemia. This case raises three important points:

1) Current Vitamin D replacement guidance advocates the use of loading doses Vitamin D. This case highlights the risks of Vitamin D loading doses which should be avoided or used with caution in selected cases.

2) It seems prudent to stratify critically ill patients with granulomatous disease into a closely monitored group with cautious vitamin D replacement and close monitoring of calcium, phosphate, parathyroid hormone and Vitamin D levels.

3) While vitamin D-mediated hypercalcaemia in sarcoidosis is well described this case suggests that clinicians should be aware of the same phenomenon occurring in TB patients which has only been described in rare case reports.

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EP29

Hypervitaminosis D in a woman: a diagnostic conundrum!

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A 48 year-old lady was referred to Endocrinology clinic in November 2016 with symptoms of tiredness and lethargy for two months. Routine bloods were unremarkable, apart from an incidental finding of raised Vitamin D:258 nmol/l(NR: 50–150). She had depression and was otherwise fit & well. She was on Citalopram and combined oral contraceptive pill (Microgynon). She denied any excessive sun exposure. She didn't drink any milk, only drank orange juice. She took multivitamins in 2016, but stopped it in summer time. Examination was unremarkable. Investigations revealed normal full blood count, bone, kiney, liver function, inflammatory markers, thyroid, parathyroid hormones, Viamin B12, Folate, Ferritin, HbA1c, angiotensin converting enzyme, lipid profile and renal ultrasound. Urine calcium excretion was 2.4mmol/24h (NR:2.5–7.5). Dual-Energy-X-ray-Absorptiometry (DEXA) showed moderately low spine density with moderate fracture risk. Vitamin D remained persistently high from 220–258 nmol/l from June 2016 to March 2017. Hypervitaminosis D secondary to oestrogen-containing-contraceptive-pill was suspected; we changed Microgynon (ethinylestradiol with levonorgestrel) to progesterone only pill (Desogestrel) in March 2017. Repeat Vitamin D in October 2017 was normal(134 nmol/l). Recent Vitamin D was also normal(104 nmol/l) in April 2018. The majority of hypervitaminosis D cases in literature are related to prescribing or manufacturing errors and increased use of over the counter multivitamins, rarely leading to vitamin D toxicity. One of the known culprits is the oestrogen-containing-contraceptive-pill. An American study in 2016 (1662 women) showed 20% increase in vitamin D levels in women using oestrogen-containing-contraception-pill. Although there is a clear link, the biological pathway behind this association is not well understood; possibly, changes in the metabolism of vitamin D in women taking oestrogen-containing-contraception-pill and rarely leading to toxic levels, unlike our patient who reached toxic levels and subsequently reverted back to normal vitamin D levels after discontinuing the oestrogen pill.

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EP30

Atypical presentation of familial hypocalciuric hypercalcaemia (FHH1)-would you recognise it?

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Introduction

Hypercalcaemia is a commonly encountered biochemical abnormality. The most common causes of hypercalcaemia are primary hyperparathyroidism and malignancy. Familial Hypocalciuric Hypercalcaemia (FHH) is a rare cause of hypercalcaemia.

Case

We present a 53-year-old female, who was referred to the endocrinology clinic for further investigation of a persistent hypercalcaemia associated with low-to-normal parathyroid hormone level (1.5pmol/l). She suffered from chronic anergia, generalised myalgia and recurrent renal stones. There was a significant family history; her father, brother, sister and grandson were also known to have hypercalcaemia. Prior to her endocrinology referral, she was managed by the urology team for recurrent renal stones for several years. She was extensively investigated for secondary causes of hypercalcaemia, including malignancy. The patient had a myeloma screen; a CT scan of her thorax, abdomen and pelvis; and serum ACE levels (14.2 nmol/L). There were no positive findings. Ultrasound scans of her parathyroid and thyroid glands were suggestive of an atypical and equivocal right inferior parathyroid adenoma. A sestamibi scan was conducted, which showed appearances were most likely due to adenomatous hyperplasia of the parathyroid rather than a solitary adenoma. Finally, after genetic testing came back positive, a diagnosis for FHH type 1 was made.

Discussion

FHH is a rare cause of hypercalcaemia and is almost always asymptomatic. It should be suspected in any patients with a strong family history of hypercalcaemia. This is an exceptional case where the patient, who has had FHH confirmed after genetic testing, has been symptomatic with recurrent renal stones and osteopenia.

Conclusion

Patients with FHH are known to be asymptomatic. We have demonstrated a unique case of symptomatic FHH, with associated end-organ damage. The possibility of dual pathology should be explored. Thus the case has been referred to a tertiary centre for further investigation.

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EP31

Multiple vertebral fragility fractures following pregnancy

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We present the case of a 35-year-old woman who was well until pregnancy 4y previously in Israel. Her antenatal course was uncomplicated. She breastfed postpartum and a few months into this she experienced acute back pain on reaching for a nappy. MRI demonstrated six vertebral fractures. DEXA scan confirmed osteoporosis (lumbar T-score −4.3, hip T-score −3.3). She received a single dose of denosumab. She moved to the UK 2y later and was referred to our Endocrine Bone Clinic. Repeat DEXA scan showed improving bone mineral density (BMD, lumbar T-score −3.6), with raised Bone-ALP (23.7iu/l, NR6.5-14.9) and normal uNTx (18 nmolBCE/mmolCr, NR5-65), suggesting ongoing new bone formation. Osteoporosis risk factors were identified as previous low BMI, ex-smoker, previous vitamin D deficiency, previous SSRI exposure, family history of osteoporosis and breastfeeding 18 months postpartum. Additional secondary causes were excluded. Given her young age and improving BMD, we have currently advised calcium, vitamin D and exercise, as any anti-resorptive therapy may stunt her continued recovery. Teriparatide is an option to consider if improvement plateaus. It is likely that her pre-pregnancy BMD was suboptimal given the additional risk factors above. Therefore, this case highlights pregnancy/lactation-induced BMD deterioration adding to this risk and resulting

in multiple fractures. Calcium homeostasis is significantly altered during pregnancy and lactation. Current data suggest small BMD increases at cortical but decreases at trabecular sites like the spine. Subsequent lactation requires a large calcium provision to the baby, which is provided predominantly from maternal bone. In addition, hyperprolactintaemia-induced oestrogen suppression results in further bone loss. Combined, lactation can induce up to 10% BMD loss. This case illustrates the serious consequences of bone loss during pregnancy and lactation especially when starting from a suboptimal density, highlighting the need to consider cautioning patients with reduced bone density regarding future lactation.

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EP32

A curious case of hypercalcaemia associated with proximal renal tubular acidosis

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An 88-year-old Caucasian man with hypertension, single functioning kidney, vitamin D insufficiency and transurethral resection of the prostate was admitted with worsening confusion. On admission, he had acute on chronic renal impairment (Urea- 17.2 mmol/l (range: 2.5–7.5 mmol/l), Creatinine- 163 μmol/l (range: 60–120 μmol/l), eGFR- 35 (Baseline- 60 ml/min/1.73m^2) and a normal serum/corrected calcium (2.51 mmol/l (range- 2.2–2.6mmol/l). He was commenced on IV fluids and was also started on high dose Vitamin D. Routine investigations did subsequently showed severe hypercalcaemia which was confirmed on repeat testing (corrected calcium 3.01 mmol/l and ionised calcium 1.888 mmol/l). On review, the patient had ongoing symptoms of constipation for several days but had normal calcium levels during this period until the incidental diagnosis. Clinical examination was unremarkable. Blood gas analysis revealed hyperchloremic metabolic acidosis (pH-,bicarbonate 16.6 mmol/l,chloride 15.1 mmol/l. Investigations for common causes of hypercalcaemia were negative (Parathyroid hormone 1.1pmol/l, vitamin D- 69.1 nmol/l, Immunoglobulin (Ig) G- 12.55, IgM- 0.80, IgA- 5.07, Magnesium- 0.86 mmol/l, Phosphate-0.64 mmol/l, Alkaline phosphatase- 134 IU/l). Following discussion with the renal team, a diagnosis of proximal renal tubular metabolic acidosis was made. He was treated with intravenous bicarbonate and fluid therapy. Over the next few days, his hypercalcaemia resolved as his metabolic acidosis improved. Although there are a number of causes for acute hypercalcaemia, we could not establish a definitive cause in this patient. To our knowledge, this is the first case of idiopathic hypercalcaemia associated with renal tubular acidosis. We observed a temporal association between onset of metabolic acidosis and hypercalcaemia and its subsequent resolution following correction of acidosis leading us to speculate that the hypercalcemia was due to decreased calcium excretion from the proximal tubule.

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EP33

Directly observed therapy in a patient with refractory hypocalcaemia

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We report a 45-year-old man who developed acquired primary hypoparathyroidism based on a low serum adjusted calcium level and low parathyroid hormone level. His past medical history included recurrent chronic anaemia requiring multiple transfusions since 2011. He was an ex- intravenous drug user, and suffered from chronic bilateral venous leg ulcers, and liver cirrhosis following Hepatitis C infection. Despite using doses of up to 8 mcg Calcitriol daily, his calcium levels fell recurrently and he required repeated intravenous calcium infusions. Vitamin D levels were replete, as were Magnesium levels corrected as best possible (> 0.50 mol/l) using supplements and Amiloride (24 hour urine magnesium was 0.93 mmol/L). He was not on a proton pump inhibitor. Finally, Teriparatide 40mcg was added to a combination of Calcitriol 2.5 μg, calcium carbonate 10 mg, Adcal D$_3$, colecaciferol 800 units, magnesium aspartate 13 g, and Amiloride 20 mg daily. Yet, recurrent hypocalcaemia continued to occur requiring Infusions almost twice weekly. With regards to the recurrent chronic anaemia, he has been extensively investigated by haematology and gastroenterology colleagues, with no cause found. However, his Ferritin levels averaged around 30 ng/ml, suggesting blood loss and iron deficiency as the cause. We looked into the possible theory of exposure to citrate from multiple bloods transfusions as a cause of hypocalcaemia. But an avoidance of blood transfusions for 2 weeks did not prevent hypocalcaemia. Compliance with medications was questioned repeatedly with both the patient and nurses during his prolonged admission. Directly observed therapy for all his medication was carried out. With this, we were able to maintain calcium levels above the acceptable range and the patient did not require intravenous calcium replacement for 3 months. Non-compliance with medication poses a challenge in managing chronic conditions. Supervised treatment should be considered in situations where conventional treatment does not yield results.

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EP34

An atypicalpresentation of primary hyperparathyroidism

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A 46 year old female presented to orthopaedics with a painful swelling at the base of the middle finger, which was gradually increasing in size. Ultrasound and x-ray showed a highly vascular irregular mass with bony involvement of the third metacarpal. Initial suspicions were of an enchondroma. Following an MRI scan, the orthopaedic team proceeded to biopsy the lesion. The histology suggested a giant cell tumour. Curretage of the lesion, with bone grafting was performed and further histology taken for a further opinion. This again suggested a giant cell tumour of soft tissue. Whilst awaiting further investigations, the patient described increasing pain in her left hip. Blood investigations revealed an adjusted calcium concentration of 3.29 mmol/l (reference range 2.20–2.60 mmol/l). Her parathyroid hormone level was elevated at 71.1 pmol/l (reference range 0.9–6.5 pmol/l). A suspected diagnosis of primary hyperparathyroidism with a Brown tumour therefore followed. CT delineated multiple expanded lucent bone lesions consistent with Brown tumours. Also an irregular soft tissue mass of approximately 2 cm in diameter was identified adjacent to the left inferior pole of the thyroid. A SPECT scan described an intense focus of abnormal activity at this site. DEXA confirmed the presence of significant osteoporosis. She underwent planned parathyroidectomy with pre-loading of vitamin D. There was no evidence of post-operative hypocalcaemia and she has gone on to make a good recovery. Her subsequent imaging has shown significant improvements in bone health. This case represents a now relatively rare presentation of primary hyperparathyroidism. The textbook symptomatic presentation with renal stones and bone pain is far less frequent than the more common finding of incidental hypercalcaemia- with only ~1% presenting with skeletal disease. However, atypical presentions can still occur in endocrinology and other specialities, and considering the diagnosis is key.

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EP35

PTHrP-associated hypercalcemia of pregnancy and postpartum resolved after delivery.Kamal AbouglilaDiabetes centre, University Hospital of North Durham, Durham

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Hypercalcemia is a rare pathology in pregnancy and postpartum, but an important one to recognize in the effort to reduce fetal and neonatal morbidity and mortality. We describe a case of hypercalcemia at end of pregnancy. A30 year-old woman was referred to Endocrine clinic at 36 weeks Gestations for symptomatic mild hypercalcemia (tired and lack of energy). She had previous history of acute lymphocytic leukemia treated with bone Marrow Transplant in remission for the last 6 years. She is not taken any medication to contribute for hypercalcemia including Vitamin D treatment. Biochemical assessment showed corrected

calcium 2.8 mmol/L; renal function test were normal and Liver function test normal except raised ALP (180 U/l). Vitamin D level 75 nmol/l. Parathyroid hormone was undetectable (PTH) less than 0.3 pmol/l but parathyroid hormone-related peptide (PTHrP) was elevated at 46 pg/l (NR <15 pg/l). She was treated with conservative treatment with close monitoring of her serum calcium during pregnancy and postpartum. The patient delivered a healthy and normal for gestational age female infant with normal birth weight. Serum calcium levels normalized after delivery and it took a few weeks for PTH to come back to normal range.

Conclusion

This pregnant patient presented with PTHrP-associated hypercalcemia, presumably of placental origin. Delivery resulted in prompt reduction of serum calcium levels. The release of PTHrP into maternal circulation was the most likely cause of hypercalcemia.

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EP36

Low bone mass in young patient with Crohn disease: to treat or not to treat?

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Introduction

Decreased bone mass is associated with inflammatory bowel disease (IBD), due to multiple factors, including endocrine disturbances, deficits in calcium and vitamin D, malnutrition, drugs (corticosteroids), chronic inflammation. If in older man and postmenopausal women, the treatment is well established, for young patients is not a general consensus.

Case report

We report the case of a 20-year-old, male, nonsmoker, diagnosed with Crohn disease (2010), complicated with axial spondylarthrosis. He received glucocorticoids high dose at least 2 times (>3 months). Between 2011-2017, he was lost of the follow up, as his parents decided to use non-pharmacological treatments. In 2017, he was admitted to hospital with abdominal abscess, severe denutrition (BMI $=12,3$kg/m^2), impaired weight bearing, limited range of motion of bilateral hip joints. His blood tests showed inflammation, feriprive anemia, hypoalbuminemia. We performed DXA, who showed L1-L4: BMD 0,806 g/cm^2, Z score $=-3.5$ DS, left hip: BMD 0.775 g/cm^2, Z score $=-3$. 4 DS, BMD (TBLH) $=-3$. 6 DS, TBS score L1–L4 $=1,031$. His hormonal tests revealed deficit of vitamin D (25 hidroxy vitamin D $=13,98$ ng/ml), low testosterone and IGF1, normal thyroid function. Gastroenterologist's decision was to initiate Infliximab, after parenteral nutrition, antibiotic and drainage of the abscess. The challenge was whether to initiate the anti-osteoporotic treatment or not. As the disease was not well controlled, correlated with deficit in vitamin D, we decided first to administer cholecalciferol (4000 UI/day, for 6 weeks) and then reconsider bisphosphonates. As after 6 weeks, his level of 25 hidroxi vitamin D was still low (15 ng/ml) despite daily administration, we decided to give cholecalciferol 100000 i.m; follow-up is needed.

Conclusion

Low bone density in young adults is an important complication for patients with chronic diseases, so every case is treated individualized.

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Clinical Biochemistry

EP37

Recurrent severe hypernatraemia in a young man with hydrocephalus and normal osmoregulatory function

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A 24 year old man presented with gait instability, myalgia, and cognitive decline, after a holiday in Crete; his alcohol intake exceeded 200 units/week. He had marked facial dysmorphism, with frontal bossing, and global muscle weakness. He had hypernatraemic dehydration (plasma sodium 175 mmol/l urea 16.9 mmol/l), but denied thirst. Urine concentration was 894 mOsm/kg, excluding diabetes insipidus. CK was elevated at 15,540 U/l. CT brain shown marked hydrocephalus. Rhabdomyolysis secondary to dehydration was diagnosed. He was treated with IV dextrose; when normonatraemic, his conscious level normalised and he experienced normal thirst. A reset osmostat for thirst and AVP release was suspected and he underwent 5% saline infusion. Plasma AVP rose from, 1.4 to 7.3 pmol/l, and linear regression analysis defined a normal osmotic threshold for AVP release, of 283 mOsm/kg (pAVP $=0.27$ (pOsm-283), $r=0.88$, $P=0.002$). Thirst (visual analogue scale) rose appropriately, with a normal osmotic threshold (thirst $=0.31$ (pOsm -283), $r=0.98$, $P<0.0001$). The patient therefore had normal osmoregulatory function. However, in the 30 mins following infusion, the patient only drank 400 mls water, despite normal thirst dynamics (normal water intake 700–1200 mls). There was therefore a disconnect between normal osmoregulated thirst and his abnormal drinking behaviour. Sleep studies were normal, but a multiple sleep latency test revealed severe hypersomnolence. The patient remained eunatraemic, with a fixed fluid intake of 2–3 litres daily, until ten years later, when following a flu-like illness, fluid intake fell, there was cognitive decline, and he presented with hypernatraemic dehydration (sodium 166 mmol/l) associated with rhabdomyolysis and a DVT. This is a unique case where intercurrent illness is associated with life threatening hypernatraemia, despite normal osmoregulation. Hydrocephalus has caused cognitive decline and hypersomnolence; without obligate fluid intake the patient is vulnerable to hypernatraemic dehydration.

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EP38

A case of the syndrome of inappropriate antidiuretic hormone secretion treated successfully with Tolvaptan to prevent hospital admission and delay chemotherapy treatment in patient with a small cell lung cancer. Kamal Abouglila Diabetes centre, University Hospital of North Durham, Durham

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Hyponatraemia is the most commonly recorded electrolyte abnormality occurring in 7% to 8% of elderly, ambulatory patients and 15 to 20% of hospitalized patients presenting a variety of symptoms ranging from very mild to life threatening. Correction of hyponatremia has been shown to improve the symptoms and signs associated with this condition. It is also recognized that excessively rapid correction of hyponatremia can be detrimental. During hospital admission, hyponatremia is also associated with increased length of stay and worse primary clinical outcomes. Fluid restriction remains the mainstay of treatment for moderate hyponatremia associated with SIADH. However, fluid restriction is often challenging and unpleasant for patients and when therapies such as chemotherapy for malignant disease are planned it is not a preferred option due to risk of dehydration and acute kidney injury. We describe a Case of 71 years male who presented with recurrent admission with severe hyponatremia (SIADH) due to metastatic small cell cancer which failed to response to standard treatment of SIADH including using demeclocyline therapy and as a sequence to failure of correcting hyponatremia, his chemotherapy treatment has been postponed on a few occasions. We decided to treat his hyponatremia by using Tolvaptan which is an antagonism at the V2 receptor causes a decrease in the number of aquaporin-2 channels in the renal collecting tubules, resulting in decreased water reabsorption, a net increase in free water excretion, and an increase in serum sodium concentrations. Sodium improved with a few days and he had not a further admission with similar problems and he had his chemotherapy treatment for the lung cancer.

Conclusion

This case highlights the importance of the use of Tolvaptan in patients with recurrent admission with hyponatremia and to patients who are chemotherapy postponed. It helps to reduce the length of hospital stay & avoid delaying chemotherapy.

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EP39

A case of the syndrome of inappropriate ADH secretion in the setting of pre eclampsia

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Background
Hyponatremia is a rare complication of pre eclampsia. We present a case of syndrome of inappropriate ADH secretion (SIADH) in the setting of pre eclampsia.
Case Report
A 40 year old lady known to have type 1 diabetes on insulin pump therapy presented with hypertension at 33 weeks gestation. Treatment with labetalol 100 mg bd was initiated but she was admitted at 34 weeks due to lack of BP control. Sodium levels were 136 mmol/L (135–145 mmol/L) on admission. Labetalol was increased to 300 mg tds and she was discharged after four days with a sodium level of 129 mmol/L. She was readmitted at 35 weeks with pre-eclampsia as evidenced by severe headaches, persistent hypertension(186/92 mmHg), a high uric acid (400 umol/L), low platelet count (91 × 10^9/L) and proteinuria (1557.1 mg/24 hrs). Her sodium rapidly dropped to 125 mmol/L. Urine sodium was 38 mmol/L, urine osmolality: 267 mOsm/kg, serum osmolality: 269 mOsm/kg. The patient was euvolemic with normal thyroid and adrenal function. These results were consistent with SIADH. Labour was induced but an emergency caesarean section was performed in view of signs of foetal distress. The baby's sodium level was 127 mmol/L. The mother's fluid intake was restricted to 1.25 litres/day initially and then to 2 litres/day. Within 48 hours of delivery, her sodium improved from 125 mmol/L to 133 mmol/L. Proteinuria decreased to 759.9 mg/24 hrs and platelet count and uric acid normalised.
Discussion
Pre eclampsia is associated with reduced intravascular volume which may stimulate ADH release resulting in SIADH. Foetal sodium rapidly equilibrates with maternal sodium and this can cause foetal jaundice, tachypnoea and seizures if serum sodium is < 130 mmol/L. Acute hyponatremia further increases the likelihood of seizures in pre eclampsia. Management includes fluid restriction and delivery in a timely manner.

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EP40

An interesting case of cranial diabetes insipidus

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Introduction
Diabetes Insipidus (DI) is the inability of the kidneys to concentrate urine. This is due to decreased production of Anti-diuretic Hormone (ADH) from the posterior pituitary gland (cranial DI) or decreased tubular sensitivity to ADH (nephrogenic DI) or a mixed picture.
Case
A 53-year-old male presented with several-months history of polyuria and polydipsia. He had constant thirst and had to void urine four times at night. He did not have diabetes mellitus or previous urological ailments. He is a smoker but not on any regular medication. He had no significant findings on physical examination.
Investigation and management
He had kept a 24-hour fluid input-output diary which revealed an input of 6000 ml and output 7900 ml. His serum osmolality was normal at 287 mOsm/kg with low urine osmolality of 105 mOsm/kg. A repeat test revealed a raised serum osmolality of 297 mOsm/kg with an inappropriately low urine osmolality of 143 mOsm/kg. Further test demonstrated a low serum testosterone level (5.9 nmol/L) in the presence of inappropriately normal Luteinising Hormone and Follicle Stimulating Hormone levels, suggesting hypogonadotrophic hypogonadism. His prolactin, thyroid and adrenal function tests were normal. He had a water deprivation test during which time his serum osmolality climbed to 299 mOsm/kg while his urine osmolality climbed to a maximum of 304 mOsm/kg at first then rose to 559 mOsm/kg only after a 2 mcg injection of Desmopressin. A diagnosis of diabetes insipidus was made. An ultrasound scan revealed normal kidneys. An MRI scan revealed a complex cyst arising from his hypothalamus. This awaits aspiration biopsy. He was started on Desmopressin with appreciable symptomatic improvement.
Conclusion
We present a rare combination of cranial DI and hypogonadotrophic hypogonadism secondary to a hypothalamic lesion. Other rare causes such as craniopharyngioma, lymphocytic hypophysitis and Erdheim-Chester disease make interesting differential diagnoses.

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Clinical Practice, Governance & Case Reports

EP41

Macrohormones: bigger isn't always better

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Introduction
Macrohormones are complexes of monomeric hormone molecules with IgG leading to formation of macrocomplexes. They are usually immunoreactive, but biologically inactive. The higher molecular weight results in reduced renal clearance and therefore accumulation in the blood. We present two cases of unusual macrohormones.
Case 1
A 55-year-old male had his thyroid function checked as part of investigation for chest pain, and was started on thyroxine on finding of TSH at 36 mU/L (0.35–5) with FT4 at 10 pmol/L (9–22). He developed flushing and general discomfort whilst on thyroxine, which was discontinued. Subsequent analyses showed consistently elevated TSH and low normal FT4. Since he was clinically euthyroid analytical interference was considered a potential cause of high TSH. Implementation of polyethyleneglycol (PEG) precipitation protocol gave recovery rate at 30.9%, suggestive of macro-TSH.
Case 2
A 72-year-old male, with a history of renal transplantation, recovering from recent influenza-A pneumonia, was reviewed in the Renal Clinic. Blood tests revealed PTH at 506 pmol/l (1.6–7.5), confirmed on repeat sample, with normocalcaemia and vitamin D insufficiency. His PTH had previously been between 26–48 pmol/l. His clinical presentation was inconsistent with a severely hyperparathyroid state. Treatment of serum with blocking reagents did not detect heterophilic antibodies. Analysis on two different analytical platforms gave discordant results. Another sample was subjected to PEG extraction: PTH was reduced from 297.9 to 61.38 pmol/l (recovery rate 20.6%), and decreased linearly following serial dilutions. These suggested the presence of macro-PTH, likely attributed to anti-influenza antibodies.
Conclusions
Discrepancies between clinical findings and laboratory results should raise the suspicion of analytical interference. Presence of macro-complexes is a type of interference, with PEG precipitation being a technically simple, yet efficient method to detect it.

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EP42

2 cases of Pneumocystis Jirovecii Pneumonia occurring during treatment of Cushing's Syndrome. Is there a case for prophylaxis of PJP in the treatment of severe hypercortisolism?

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Pneumocystis jirovecii pneumonia (PJP) is well recognised in HIV infected and transplant recipient populations and prophylaxis is standard practice. PJP may also occur in rarer cases of immunodeficiency. We report 2 cases of Cushing's syndrome complicated by PJP. Patient 1 was a 30 year old Indian male who presented with 2 weeks of bloody diarrhoea, abdominal pain and lethargy. He was cushingoid and investigations showed severe hypercortisolism (urinary cortisol > 266,786 nmol/24h) due to Cushing's disease. He developed hospital acquired pneumonia and was commenced on Tazocin. Metyrapone treatment was initiated to reduce his immunodeficiency. 48 hours after commencing metyrapone he developed type one respiratory failure and was admitted to intensive care. Laboratory results confirmed PJP, tuberculosis, cytomegalovirus, Influenza and streptococcal pneumonia. Following a life threatening illness, requiring prolonged antimicrobial therapy including cotrimoxazole, he was fit to proceed

to pituitary surgery, and presently remains well. Patient 2 was a 59 year old man who presented with shortness of breath and peripheral oedema. CT imaging suggested adrenal adenocarcinoma with pulmonary and hepatic metastases. Urinary cortisol was 1357 nmol/24h and Cushing's syndrome was diagnosed. Mitotane was commenced however 10 days later he was diagnosed with PJP. Cotrimoxazole was later switched to clindamycin and primaquine because of a widespread skin rash. Following this treatment dapsone was advised for PJP prophylaxis. Although he recovered from PJP he died 3 months later. PJP occurs in Cushing's syndrome with severe hypercortisolism and typically after initiation of cortisol lowering therapy, implying an effect of immune reconstitution. The mortality rate of PJP in Cushing's patients is estimated to be 60–65%. PJP prophylaxis is not recommended in current guidelines. We propose that PJP prophylaxis should be considered in patients with severe hypercortisolism.

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EP43

Multiple acyl-CoA Dehydrogenase Deficiency: a rare cause of hypoglycaemia

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We report the case of a 37-year-old woman with a 9-month history of intermittent and variable symptoms of anorexia, nausea & vomiting, muscular weakness and pain in association with recurrent hypoglycaemic episodes. The patient stated that she had episodes of myalgia with generalised weakness affecting mobility and a history of significant weight loss as a result of anorexia and nausea & vomiting. The patient had two previous hospital admissions with similar symptoms and had improved with supportive treatments. Case note review revealed extensive normal biochemical and radiological investigation. It was thought that her symptoms were psychological in nature and that the the low blood glucose readings were spurious or as a result of starvation. Investigations on re-admission to hospital revealed hypoglycaemia on two occasions with a lab glucose of 2.0 mmol/L and 3.2 mmol/L. HBA1C was 29 mmol/Mol. Urinalysis demonstrated Ketonuria $++++$. Creatine Kinase was greater than 1000 u/L. Venous Lactate was raised at 4 mmol/L. Transaminases were mildly raised and renal function was normal. On examination the patient had weakness of her limbs and had difficulty lifting her head up from her chest. A metabolic disorder was suspected owing to the combination of intermittent and variable symptoms in association with hypoglycaemia, ketonuria, raised CK and metabolic acidosis. Urine organic acid profile was performed and revealed raised 2-hydroxyglutarate levels suggestive of Multiple Acyl-CoA Dehydrogenase Deficiency (MADD). The patient was commenced on treatment with oral Riboflavin, vitamin B2, and her symptoms improved as did the biochemical abnormalities. Genetic analysis revealed a heterozygous EFTDH mutation confirming the diagnosis. MADD is rare inherited and clinically heterogeneous disorder of fatty & amino acid oxidation and a rare cause of hypoglycaemia. As Endocrinologists special consideration must be given to potential non endocrine and unusual causes of hypoglycaemia.

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EP44

Iatrogenic Cushings secondary to inhibition of triamcinolone metabolism by cobicistat

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Background
CYP3A4 is the most prevalent cytochrome P450 (CYP) enzyme in the liver, and is used by the majority of medications for their metabolism and elimination from the body. The inhibition of CYP3A4 can result in the accumulation of drug concentrations increasing the risk for possible toxicity. We report a case of iatrogenic Cushings's syndrome secondary to impaired CYP3A4 metabolism of triamcinolone by coadministration of darunavir/cobicistat, with resultant secondary hypoadrenalism on conventional synthetic ACTH testing.
Case
A 54 year old woman presented with one week history of increasing neck and face swelling associated with fatigue. Past medical history included HIV infection. Her medication included darunavir/cobicistat with dolutegravir. 2 weeks previously she received an intracapsular injection of triamcinolone acetonide (equivalent to hydrocortisone 200mg) for hip pain. On examination she appeared Cushingoid with a round face, facial plethora and buffalo hump. Despite the clinical picture random cortisol was <40 nmol/L with 30 minute cortisol post ACTH 165 nmol/L. 24 hour urine cortisol was 85 nmol. We were unable to measure serum triamcinolone concentrations. The clinical picture was explained by exogenous steroid interference from triamcinolone. Due to persistent symptoms her antiretrovirals were temporarily changed to facilitate metabolism of triamcinolone. She required several doses of hydrocortisone to cover intercurrent illness. Recovery of endogenous HPA axis was observed 10 weeks after the initial injection.
Discussion
Iatrogenic Cushing's syndrome secondary to the antiretroviral ritonavir is well recognised. We describe a case related to an additional antiretroviral, cobicistat, which is known to be a strong inhibitor of the CYP3A4 metabolism. This case highlights the importance of taking a robust drug history and considering potential drug interactions in patients on antiretroviral treatment. This is particularly important as not all electronic medicines systems will have access to specialist prescribing records, that sit outwith standard primary care prescribing systems.

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EP45

Galactorrhea secondary to increase prolactin secretion following resection of thoracic schwannoma

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Introduction
Galactorrhea is a common symptom of raised prolactin irrespective of cause of hyperprolactinemia. Whereas pituitary prolactinoma is the commonest cause, there are many other causes of increased prolactin including chest wall injuries or chest surgery. Galactorrhea without prolactin increase has been reported as well. We describe a case of galactorrhea following thoracoscopic resection of schwannoma from apex of left hemithorax.
Clinical Case
A thirty four years old patient presented with symptoms of chest infection. X ray chest showed left basal consolidation and a small well circumscribed incidental shadow was noted on left apex, she had no symptoms relating to the apical shadow. She was treated for community acquired pneumonia. On discharge an outpatient CT scan of neck and chest was arranged. CT described a well circumscribed 2.4 cm apical mass suggesting either a vascular lesion or a neurofibroma. Subsequent MRI suggested high suspicion of a schwannoma. Three months post MRI she had a successful left thoracoscopic dissection for removal of schwannoma, histology report was in keeping with Schwannoma. Ten days following surgery she noted engorgement of left breast which was followed by bilateral galactorrhea. She had no headache or visual symptoms to suggest any pituitary lesion. She had normal mensuration following recent stoppage of oral contraceptive pill. Reproductive hormonal profile showed raised prolactin of 2090 mU/L (normal value 102–496 mU/L) and normal LH, FSH & estradiol. TFT, LFT and renal functions were normal as well. Galactorrhea and Prolactin improved gradually. Prolactin became normal after 7 weeks; mild expressive galactorrhea persisted for further few weeks.
Conclusion
This case shows galactorrhea in this patient was secondary to prolactin secretion in response to surgical stress to chest wall. The mechanism behind is neurogenic reflex which stimulates prolactin via suppression of dopamine.

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EP46

More than meets the eye - an unusual presentation of Cushing's syndrome with bilateral central retinal vein occlusion

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A 53-year old male presented to his optician with blurring of vision on the right and was diagnosed to have branch retinal vein occlusion. Over the next

6 weeks he manifested further visual impairment, initially due to right central retinal venous occlusion (CRVO) and after another 3 months left CRVO. He received intravitreal Ranibizumab injections and timolol-dorzolamide eye drops in both eyes. Soon after this, he had a hospital admission for infected submandibular gland and was noted to have persistent hypokalaemia and referred to endocrine outpatient. He complained of fatigue, 15 kg weight loss, poor sleep and memory; and had proximal muscle wasting and weakness but no striae or bruising. Investigations confirmed hypercortisolism with suppression of gonadal, thyroid and growth hormone axes. MRI revealed $8\times8\times12$ mm pituitary nodule, which along with $>50\%$ suppression of plasma cortisol after high-dose dexamethasone (baseline 861 nmol/L, 48-hour 310 nmol/L) suggested Cushing's disease. However, acute presentation with rapid weight loss and hypokalaemia raised a suspicion of ectopic ACTH overproduction and he was referred to the regional centre for CRH test with IPSS. However, his health deteriorated rapidly with further weight loss and progressive cognitive decline eventually leading to acute psychosis. He received intravenous Etomidate and on the basis of pituitary MRI scan, emergency transsphenoidal hypophysectomy was performed without IPSS. He had dramatic improvement and all axes other than the adrenal axis recovered. He had complete visual recovery in left eye but unfortunately vision in the right eye is limited to hand movements. This case was unusual because when presented with bilateral CRVO the patient did not manifest any other features of Cushing's syndrome and only 3 months later he had dramatic weight loss, muscle weakness and acute psychosis. Cushing's syndrome is a known hypercoagulable state but there is no association in literature with CRVO.

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EP47

Spindle cell oncocytoma of the adenohypophysis: a rare non-functional pituitary tumour masquerading as a macroadenoma

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Spindle Cell Oncocytoma (SCO) is a neoplasm of the adenohypophysis, often pre-operatively misdiagnosed as pituitary macroadenoma due to its rarity. First described in 2002, 28 cases have been described. It is a benign tumour manifesting in adults with no sex predilection, classified as WHO Grade I. A 71-year-old woman presented with bitemporal hemianopia, secondary hypoadrenalism, hypothyroidism and hypogonadotrophic hypogonadism. Imaging in October 2017 confirmed a $18.0\times27.0\times21.0$ mm supra-sellar mass with optic chiasm displacement, suggestive of a pituitary macroadenoma. Appropriate hormone replacement was commenced and the same month, tumour resection by an endoscopic endonasal transsphenoidal approach was achieved. The tumour appeared firm and hypervascularised and debulking was associated with unexpected haemorrhage. Post-operative bitemporal hemianopia and visual acuity improved and imaging showed good decompression of the optic chiasm with some persistent suprasellar tumour and no signs of cavernous sinus invasion. She was discharged with no neurological sequalae on appropriate hormone replacements. Rather than the expect results, however, pathology revelated a Spindle Cell Oncocytoma (SCO), showing a proliferation of spindle cells arranged in short fascicles with eosinophilic cytoplasm and eccentric nuclei containing fine granular chromatin. Immunohistochemistry showed the tumour was positive for S-100 protein, epithelial membrane antigen(EMA), thyroid transcription factor-1 (TTF-1) and vimentin, typical of SCO. Ki67 was expressed in 10% of the neoplastic cells and p53 in 4%. Considering the low-grade and long natural history of SCO, pituitary radiotherapy may be required pending imaging and neuro-ophthalmology assessment. Our case was pre-operatively misdiagnosed as a pituitary macroadenoma and highlights that although rare, SCO masquerading as a macroadenoma remains an important differential diagnosis.

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EP48

Phaeochromocyoma- but where?

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Fifty-three year old male presented to gastroenterologist with retrosternal pain and dysphagia. On gastroscopy a 2 cm soft sub-pedunculated polypoid mass in the lower oesophagus was identified and on biopsy it was confirmed as adenocarcinoma. CT scan confirmed the finding but additionally identified 20mm right adrenal "incidentaloma" with mild calcification and reassuring imaging characteristics, further supported by a low uptake on 18-FDG PET-CT. He underwent Ivor Lewis oesophagectomy without endocrine assessment. However 2 years later a repeat CT scan revealed a mild increase in the size of adrenal lesion and the patient was referred to the Endocrine team to assess its functionality. The patient was asymptomatic but the urinary free noradrenalin was persistently elevated with normal adrenaline and dopamine. Surprisingly, MIBG scan showed intense uptake within the gastric pull-up with normal uptake in the adrenal glands. Further biochemistry revealed elevated plasma and urinary normetanephrine confirming catecholamine hypersecretion. ^{68}Gallium-DOTATATE scan showed intense uptake in the right adrenal nodule and excluded DOTATATE avidity elsewhere. Right adrenalectomy was performed after appropriate alpha and beta blockade and histology confirmed phaeochromocytoma (immunohistochemistry positive with chromogranin and synaptophysin) with PASS (Phaeochromocytoma of the Adrenal gland Scoring Scale) score of two. Oesophageal uptake in MIBG scan proved to be a red herring. This case reminds us of two interesting points. Firstly, although most adrenal phaeochromocytomas secrete both norepinephrine and epinephrine, about a third exclusively produces norepinephrine and a much smaller proportion exclusively produce epinephrine. Secondly DOTATATE scan is generally found to be more sensitive and specific than MIBG scans and there is some association in literature linking false negative MIBG scans with SDHB mutations, high frequency to develop metastatic disease, extra-adrenal location and hypersecretion of normetanephrine or norepinephrine.

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EP49

A rare case of neonatal hyperinsulinemic hypoglycemia

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Background
Hyperinsulinemic hypoglycaemia refers to inappropriate secretion of insulin in the presence of low plasma glucose levels. One day old male infant 3.6kg, born to non-consanguineous parents referred for symptomatic hypoglycaemia. APGAR score was 8/10 and 9/10 at 1 and 5 minutes. There was no history of gestational diabetes mellitus in the mother. General physical examination was unremarkable. Glycemic monitoring revealed persistent hypoglycemia with low plasma glucose 43 mg/dl and 14 mg/dl, Cortisol; 690 nmol/l (171–536). His TSH: 8.53 mIU/ml (1–39), Free T4: 2.32 ng/dl (0.93–1.7), GH: >10 ng/ml, Plasma Lactate: 2.1 mmol/L (0.5–2.2) were within normal and Urine ketones negative. He responded to 10% Dextrose Water and Dextrose fortified breast milk. His glucose infusion rate (GIR) was tapered and stopped on day 4. However, hypoglycemia recurred (RPG 11 mg/dl) and glucose infusion was restarted (GIR of 1 mg/kg/minute) to maintain euglycemia. Serum insulin was inappropriately elevated at 16 mIU/L corresponding with plasma glucose 39 mg/dl and Insulin-Glucose ratio 0.41 (NR <0.25). Post glucagon stimulation test glucose level was also low at 30 mg/dl. A final diagnosis of 'Persistent Hyperinsulinemic hypoglycemia' was made. He was evaluated with 18 F- DOPA PET/CT showed diffuse DOPA uptake in pancreas. Molecular genetic investigation revealed two heterozygous mutations (*Asp854Asn* and *Arg1394cys*) in the *ABCC8* gene. He was commenced on Diazoxide 10 mg/kg/day in four divided doses (up to 30 mg/kg/day) with which he maintained euglycemia and successfully weaned off glucose infusion. He demonstrated appropriate fasting tolerance on Diazoxide before discharge and did not have any neurodevelopmental deficits.
Conclusion
This case highlights the importance of prompt diagnosis of persistent hypoglycaemia in neonates and prevent neurodevelopmental complications. Mutations in *ABCC8* and *KCNJ11*, are the most common cause.

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EP50

Bronchial carcinoid presenting as Cushing's syndrome: A challenging diagnostic conundrum

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Introduction
Localising the aetiology of Cushing's syndrome can be challenging, especially when investigations utilised are limited in their sensitivities and specificities. We present a case whereby the reliabilities of laboratory and radiological investigations are tested to their limits.
Case Presentation
A 70 year old female presented with a one year history of fatigue, weight gain and headaches. She had proximal myopathy, cheek telangiectasia and abdominal striae, suspicious for Cushing's syndrome. Past medical history includes hypothyroidism, hypercholestrolaemia, hypertension and depression. Two sets of 24hour urinary cortisol excretion screened positive with elevated cortisol levels on overnight dexamethasone suppression testing. On high dose dexamethasone suppression, her cortisol levels suppressed to less than 50 nmol/l, suggesting a pituitary ACTH-dependent aetiology. However, her MRI pituitary and inferior petrosal sinus samplings were unremarkable. CT thorax, abdomen and pelvis were also unremarkable. Thus, a MRI Ga68 DOTANAC scan was performed, initially revealing no somatostatin receptor positive lesions. Her thoracic MRI singled out a 1.2 cm left lower lobe nodule. Additionally, her whole body MIBG Iodine123 was unremarkable. A whole body FDG PET CT followed, revealing a 1.2 cm$\times$1.1 cm nodule within the left lower lobe demonstrating low activity. On a re-review of her DOTANAC scan, a small focus of trace activity was noted at a 7mm nodule in the left lung base with mild somatostatin receptor positivity corresponding to the thoracic MRI. She was referred for a video assisted thoracoscopy with left lower lobectomy. Histology revealed an 11mm cream-coloured nodule, classified as a typical ACTH-producing carcinoid tumour.
Conclusion
Limitations in investigations for Cushing's syndrome should always be taken into account when requesting tests. Small carcinoid tumours producing ACTH can elude a variety of imaging modalities and it is therefore essential consider specialist imaging such as NM Ga68 DOTANAC upon discussion with radiologists, especially when considering ectopic sources.

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EP51

Diffuse large B-cell lymphoma: An unusual cause of bilateral adrenal masses with adrenal insufficiency

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Adrenal insufficiency is not commonly associated with a finding of bilateral enlarged adrenal gland when diagnosed in late adulthood. Various cases in the literature to date seem to indicate that the combination of these two findings may be suggestive of adrenal lymphoma. Our patient was initially referred to Gastroenterology with weight loss, nausea and early satiety from where he was referred for a whole body computed-tomography (CT) scan as part of a screen for malignancy. This unexpectedly showed bilateral adrenal masses; lung nodules were also noted. Further asessment by dedicated adrenal CT scan showed no change interval increase in size with contrast washout $>$60% and relative washout of 40% consistent with multiple bilateral adenomata. Subsequent to this he presented via the emergency department with dizziness and collapse alongside his pre-existing symptoms. His biochemistry was significant for hyponatraemia (129 mmol/L) and a high-normal potassium (5.1 mmol/L). A Short Synacthen Test showed a complete failure of response with a significantly raised ACTH; his renin was also significantly elevated consistent with mineralocorticoid deficiency (post-synacthen Cortisol 69 nmol, ACTH 351 ng/L, Renin 115.2 mU/L). His adrenal autoantibodies were negative. Urine metanephrines were not elevated excluding phaeochromocytoma. His imaging was discussed at Urology MDT and an interval CT adrenal was arranged 6 months later. This demonstrated substantial progression of both adrenal lesions. An FDG positon emission tomography scan (PET) was performed on MDT advice which showed avid uptake in both glands. Urgent excisional adrenal biopsy was undertaken; the histology was consistent with diffuse large B-cell lymphoma. Despite urgent commencement of chemotherapy by Haematology the patient eventually passed away. This case highlights an unusual cause of adrenal insufficiency with adrenal masses and is consistent with similar cases in the literature. We would urge anyone investigating these findings to consider adrenal lymphoma as a differential in future.

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EP52

Idiopathic hyperhidrosis- A black hole in medicine

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Background
Hyperhidrosis is a debilitating disease that has a significant impact on quality of life. There is limited research and gudelines on the investigations and management of hyperhidrosis.
Aims
To assess if investigations and treatment of hyperhidrosis meets NICE CKS July 2013 guidelines.
Method
The term 'hyperhidrosis' was used as a keyword search on an electronic patient record. Letters were restricted to those created by the department of diabetes and endocrinology. The first 50 records were analysed for: relevant investigations completed, treatments initiated and whether treatment was effective.
Results
50 patients presented with hyperhidroisis to an endocrinology clinic over a period of 3 years and 7 months. 15 were diagnosed with secondary hyperhidrosis (30%) and 34 (68%) with idiopathic hyperhidrosis. 66% of patients referred with hyperhidrosis were female and 34% male. 74% of patients diagnosed with idiopathic hyperhidrosis were female. No patient had all investigations completed. 80%–100% had: Full blood count, Urea & electrolytes, Liver function tests, Thyroid function tests, Glucose/hba1c. 50–80% had: urinary catecholamines, FSH/LH/testosterone and a CRP. 22% had a chest radiograph. 0 patients were tested for HIV or infectious diseases. Aluminium chloride was trialled in 10% of patients and was ineffective, oxybutynin in 48% and effective in 33%, glycopyrolate in 4% and effective in 50%, propantholine in 2% and effective in 100%. Surgical intervention was not offered to any patient. 59% of patients were discharged to their GP following assessment. 10% were referred to dermatology.
Conclusion
0.01% of all endocrinology referrals are due to hyperhidrosis. The pick up rate for secondary hyperhidrosis is 30%. Females are more likely to present with hyperhidrosis and receive a diagnosis of idiopathic hyperhidrosis.Investigations for hyperhidrosis are haphazard and variably completed despite the need to exclude secondary causes.Treatment for hyperhidrosis is poor and ineffective.

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EP53

Case Report: The experience of using Etomidate in the management of severe Cushing's disease and MRSA bacteraemia in a district general hospital in the United Kingdom

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Background
The management of Cushing's disease can be challenging especially when patients can present with sepsis and severely immunocompromised with limited oral medications to achieve cortisol control. We review a case of Cushing's disease and the medical management of Cushing's disease.
Case Report
A 54 year old female presented with symptomatic hyperglycaemia with truncal obesity, proximal muscle weakness, right posterior thorax haematoma and hypertension. Her glycated haemoglobin was 115 mmol/mol, consistent with newly diagnosed Type II diabetes mellitus. She had refractory hypokalaemia and elevated cortisol levels on overnight, low and high dose dexamethasone suppression tests. Pituitary magnetic resonance imaging revealed a 16X 16X 18 mm hypoenhancing lesion on the right pituitary gland with stalk deviation consistent with Cushing's disease secondary to a pituitary macroadenoma. This was complicated by severe cellulitis from her infected haematoma. Treatment for Cushing's syndrome was initiated with Metyrapone with cortisol levels improving to nadir of 900 nmol/L. A week later, she developed hospital-acquired pneumonia and acute respiratory distress syndrome with hypoxia requiring intubation and ventilation in the intensive care unit. Due to suboptimal

administration of Metyrapone capsules and under-dosing of crushed Ketoconazole tablets through a nasogastric tube, her cortisol levels rose to a peak of 3319 nmol/l. The alternative option of a bilateral adrenalectomy was unsafe given the degree of metabolic decompensation and severe sepsis. Therefore, parental Etomidate was trialled to achieve target cortisol levels of between 600–800 nmol/L. The accumulation of 11b-deoxycortisol interfered with the laboratory assay and a mass spectrometry from another tertiary hospital was utilised to accurately quantify cortisol levels instead. Once stable, she was transferred for a transsphenoidal hypophysectomy at the tertiary centre where she made a good recovery.
Conclusion
This case reviews the treatment options for Cushing's disease and recommends the use of Etomidate use in challenging cases such as this one.

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EP54

High ketones due to excess growth hormone

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Thirty-eight years gentleman presented with DKA as the first presentation of his diabetes. His HbA1c was 12%. On exam, he showed features of Acromegaly and normal BMI. His Growth hormone and IGF-1 were very high in confirming the diagnosis of Acromegaly. His Anti GAD and Anti Islet cell antibodies are negative. MRI dedicated pituitary showed pituitary macroadenoma. Treatment of his DKA was difficult. He was discharged on insulin. Later, the patient was seen in the endocrine clinic. Insulin dose was reduced gradually till completely stopped due to recurrent hypos. He also mentioned marked improvement of his Acromegaly symptoms. GTT showed appropriate Growth hormone response and his maximum blood sugar was 7.5 mol/L. also his IGF-1became normal. After the disappearance of his symptoms and normalization of his blood sugar, Growth hormone and IGF 1, the patient was scheduled for another MRI pituitary which showed cystic changes and marked reduction of his pituitary adenoma size. Further, follow up, revealed persistent remission of his diabetes (his HbA1c is 5.4%) and Acromegaly.
Conclusion and Discussion
1. It is not uncommon for DKA to be the first presentation of DM. Furthermore, DKA could be the first presentation of Acromegaly as well.
2. Secondary diabetes should be considered in any new onset diabetes especially if with an atypical presentation (our patient MBI was not typical of type 2 and his age and antibodies were not typical of type 1). We recommend general physical examination and act upon the findings.
3. Pituitary adenoma showed spontaneously cystic degeneration which cured his excess growth hormone and subsequently his secondary diabetes.
4. Few reported cases in the literature of DKA after stoppage of Octreotide in Acromegaly.
5. Apart from steroid induced hyperglycemia, there are no guidelines to manage secondary diabetes. There is a need for guidelines for diabetes management in Acromegaly.

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EP55

Hypogonadism and acute hepatitis caused by ingestion of epistane (EAST®) for body-building purposes

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Background
Self-administration of anabolic steroids among bodybuilders is an underestimated problem, often not admitted by patients.
Case presentaation
A 19 year old male (planning to study medicine!) presented with gynaecomastia, general malaise and erectile problems. Investigations revealed acute hepatitis: ALT 2125 U/L [Ref. range (RR) < 45] and hypogonadotropic hypogonadism: LH – 1.6 IU/L [RR: 1.5-9.3], testosterone 0.214 ng/mL [RR: 2.49-8.36]. Testicular ultrasound was normal. He denied excessive alcohol consumption. The patient reluctantly admitted that he was taking anabolic steroids for at least about two months: EAST® (Enhancing Athletic Sports Technology – Anabolic Technologies Cosmetics, USA), that contains 2a, 3a-epithiol-17a-methyl-17b-hydroxy-5a-androstane (known as epistane – a substance binding inter alia with androgen receptors), milk thistle – advertised as an antidote for hepatotoxic effect of epistane, N-Acetyl-L-Cysteine and Tongkat Ali (Long Jack – Malaysian Ginseng – supposedly improves libido during ingestion of epistane) as well as BULLK® – a preparation of vitamins and resveratrol – advertised as an antidote for side-effects of anabolic steroids.
Outcome
In hospital we confirmed low testosterone [0.87 ng/mL, LH 2.26 IU/L, FSH 5.95 IU/L [RR 0.7-11.1]) and liver dysfunction (ALT 252.0 IU/L, AST 113.0 IU/l [RR: 17-59]). He had normal thyroid function, prolactin (13.77 ng/mL), and morning cortisol 602 nmol/L. Viral hepatitis and autoimmune causes of hepatitis were excluded. Ultrasonography confirmed gynaecomastia without significant abdominal pathology. GnRH test revealed satisfactory testosterone response to hCG (2500u im): from 0.87ng/ml to 4.33ng/ml. A short course of clomiphene was recommended as well as an outpatient check of testosterone and liver function. The patient, however, failed to attend further follow-up appointments.
Conclusions
Our case demonstrates severe risks associated with the use of anabolic steroids (acute hepatitis/hypogonadism) compounded by patients' belief that they are taking simultaneous "antidotes" and fail to follow medical advice.

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EP56

Diabetes Insipidus in Craniopharyngioma after Ventriculoperitoneal (VP) Shunt Surgery – a case report

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Craniopharyngioma is a rare and benign type of tumour derived from squamous cell nests of the primitive Rathke's pouch of the pituitary gland. Commonly present in childhood, it is also found in adults in their 50s and 60s. People may initially present with vision disturbance, usually bitemporal inferior quadrantanopia, progressing to bitemporal hemianopsia as the tumour grows and compresses on the optic chiasm. Although a slow-growing tumour, both the disorder and therapy associated complex neuroendocrine symptoms, especially salt disorders, can bring considerable challenges to subsequent care. A 64-year-old man with a known heterogeneous craniopharyngioma measuring 2.9 cm (transverse) $\times$3.45 cm (craniocaudal) $\times$3.15 cm (anteroposterior), was referred to A&E by his GP, 15 months after VP shunt procedure for hydrocephalus. At the time of admission, there has been a six months' history of persistent and worsening hypernatremia. Clinically euvolaemic, he also presented with polydipsia, increased confusion and irritability on the background of gradual cognitive decline. The tumour has also rendered him partially blind and incontinent. Despite difficulty in monitoring fluid balance accurately due to patient's inability to keep the catheter in situ, polyuria was evident. Paired urine and serum osmolality test confirmed cranial diabetes insipidus. Hypernatremia responded well to desmopressin (DDAVP) therapy and long-term desmopressin is required to maintain a stable electrolyte balance. Cranial diabetes insipidus has been reported in multiple literature to be significantly more prevalent in those managed with surgery. This case illustrates that although the tumour itself was not resected, associated intracranial intervention in the area may also result a similar picture. From clinical practise point of view, all clinicians should raise the index of suspicion of cranial diabetes insipidus in hypernatremia patients with known craniopharyngioma. Recognition of diabetes insipidus is critical to institution of appropriate therapy and prevention of life-threatening electrolyte disturbances.

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EP57

A rare case of hirsutism

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We present a rare case of a 50 years old lady who presented with new onset hirsutism and hoarseness of voice since 2 years. Investigations showed high serum testosterone, androstendione and free androgen index. All other systemic and endocrinology evaluation for hirsutism did not reveal any abnormality. CT scan of her abdomen showed a right ovarian mass which was confirmed as a Sertoli-Leydig cell tumour (stage Ia) on surgical staging and completely cured

after bilateral salpingo-oophorectomy. Sertoli-Leydig cell tumours are a rare type of sex cord-stromal neoplasms constituting less than 0.5% of ovarian neoplasms. Over two-third of the patients are under the age of 40 years with mean age at diagnosis being 25 years. These tumours include pure Sertoli or pure Leydig cell tumours, however majority of them are mixed Sertoli-Leydig cell tumours also known as androblastomas. These tumours are generally considered as low-grade malignant tumours; however, they can be benign. About one third of these tumours may have hormonally active testicular structures in them, which produce androgens resulting in secondary amenorrhoea, irregular menstrual bleeding and virilisation. Due to extremely low incidence, evidence about the clinicopathological behaviour, prognostic factors and optimal management of these neoplasms is limited. Approach for the evaluation and diagnosis of causes of hirsutism and virilisation in middle aged females and relevant review of literature about Sertoli-Leydig cell tumours will be presented.

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EP58

Diabetic foot disease complicated by spondylodiscitis and spinal epidural abscess – a case report

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A 57-year-old woman with poorly controlled type 2 diabetes (HbA1c 148 mmol/mol) presented acutely with lower back pain, in the absence of trauma. Her WHO performance status score was 2. 18 months earlier she had developed a left fifth toe ulcer, resulting in left forefoot amputation six months later which had not healed. She had also developed a neuropathic ulcer in her right hallux, complicated by osteomyelitis. Despite excellent peripheral vasculature, conservative therapy with antibiotics had failed to achieve healing. She defaulted from the diabetic foot service and concordance with antibiotic therapy was not optimal. On admission, she was septic with acute renal failure and profound metabolic acidosis. Her residual amputation wound site revealed soft tissue infection. Examination demonstrated lumbar vertebral tenderness, bilateral lower limb weakness and absent reflexes. She required inotropic support in the high dependency unit. Chest X-ray and urine cultures were negative. Blood cultures grew group β-haemolytic streptococcus. Spine MRI confirmed L3/L4 and L4/L5 discitis, with adjacent vertebral end-plate oedema. Additionally, she had a posterior epidural collection with canal compression extending from T12 to L4. She was managed conservatively with Meropenem, as neurosurgical intervention was deemed to carry significant mortality risk. Despite prolonged antibiotic therapy, she died in hospital three months later. Spondylodiscitis with epidural abscess can result from haematogenous seeding and diabetic foot disease can be the primary focus of infection. It presents clinically with back pain – fever or neurological signs can be present or absent. The most common microorganism implicated in spondylodiscitis is Staphylococcus aureus but Streptococci are also common. Here, the only likely primary focus identified clinically was her infected diabetes foot ulcer. Clinician awareness for early diagnosis and management of spondylodicsitis, following haematological seeding from diabetic foot disease, is crucial to improve clinical outcomes.

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EP59

The chameleon – primary hyperparathyroidism: Still a diagnostic challenge

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Introduction
Primary hyperparathyroidism is a common endocrine disorder. Symptoms at onset are often non-specific, thus the diagnosis tends to be overlooked.
Objective
To highlight varying modes of presentation in primary hyperparathyroidism, the need for early recognition and treatment to prevent complications.
Case Presentation
A 51-year old woman presented with complaints of back and lower limb pains of 7-year duration. She also has paresthesia in both feet and polyuria. She has history of compressive myelopathy and nephrolithiasis 3 and 6 years ago respectively. She had spine surgery and lithotripsy done in the Middle East, without pain resolution. Patient was eventually referred to the Endocrinologist following biopsy findings of extensive osteoclastic bone resorption. Elevated blood pressure was found on examination. Investigations–serum calcium 3.72 mmol/l (2.10–2.55), parathyroid hormone 1941 pg/ml (15–65), low Vitamin D 11 ng/ml, parathyroid nodule on Magnetic Resonance Imaging and nephrolithiasis on ultrasound scan. Dual Energy X-ray absorptiometry showed T-score of -12. Diagnosis of primary hyperparathyroidism complicated by severe osteoporosis and nephrolithiasis was made. She is presently on Tabs Alendronate, with clinical improvement, and being planned for parathyroidectomy.
Discussion
Primary hyperparathyroidism is a disorder characterized by overproduction of parathyroid hormone resulting in abnormal calcium homeostasis. Parathyroid adenomas are the most common cause, as in this patient. Most patients are asymptomatic, others present with a myriad of symptoms. Nephrolithiasis, osteoporosis are common complications, identified as separate entities in this patient. Diagnosis is based on elevated serum parathyroid ± calcium. Definitive treatment is surgery. Without clear indications for surgery, regular monitoring for, and treatment of complications should be done.
Conclusion
Holistic evaluation of patients' clinical clues and symptoms facilitates early diagnosis. This limits complications, improving outcomes and quality of life in patients.

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EP60

A case report of hereditary hemorrhagic telangiectasia and primary hyperparathyroidism

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Introduction
The diagnosis of hereditary hemorrhagic telangiectasia (HHT) is definite if 3 of the following criteria are present, possible or suspected if 2 are present and unlikely if fewer than 2 are present:

- Epistaxis.
- Telangiectasias.
- Visceral lesions: gastrointestinal, pulmonary, hepatic, cerebral and spinal).
- Family history: a first-degree relative with HHT.

Case presentation
She is 81 years lady, well-known case of HHT. She was found to have hypercalcemia on a routine checkup. Her hypercalcemia was proved to be caused by primary hyperparathyroidism. Patient's blood tests showed hypercalcemia (serum levels of corrected calcium was 2.8 mmol/l), hypophosphatemia (phosphorus of 0.75 mmol/l respectively), high levels of parathyroid hormone (16 pmol/l) and hypercalciuria. However, she did not have any symptoms of hypercalcemia. Total proteins and albumin levels were normal as well as her vitamin D, thyroid hormones and other electrolytes were also normal. A neck ultrasound was performed, showing no notable pathologies.
Conclusion and discussion
Here we present a case of primary hyperparathyroidism in a patient of HHT. No definite association between HHT and endocrinal disorder was confirmed before. However, a case report described the occurrence of hypoparathyroidism and HHT (1). Another case of Hashimoto thyroiditis and HHT was reported in 2006 (2).
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EP61

A case of pituitary macroadenoma in a 38-year-old Nigerian woman

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Introduction
Pituitary adenomas are not uncommon presentations in our clinical practice but the challenge with management becomes more daunting as the size of the tumour gets bigger as seen in this woman we present herein with a macroadenoma. The combination of factors militating against accessing the best of health care available is unconnected with the usual problems affecting health care delivery in Sub-Saharan Africa, including out-of-pocket payments for health services and unavailability of prescribed drugs.
Case presentation
A 38-year-old lady presented to the endocrine clinic of our hospital 2 years ago with a 4-year history of irregular menses and 1-year history of both right sided headaches and blurring of vision. There is associated galactorrhea, weight gain and loss of libido. The CNS examination is remarkable for a right homonymous hemianopia. Examination of the cardiovascular, chest, abdomen and thyroid glands are not remarkable. She was referred from a neurosurgeon on account of pituitary macroadenoma after cranial CT confirmation because she declined surgery, however, was already commenced on 0.5 mg weekly of carbagoline. At presentation she has a normalized serum prolactin level (16 ng/ml) as compared to a baseline of 96 ng/ml. The free T3, free T4, TSH, LH, FSH were within reference range. A repeat cranial CT was ordered which revealed a further increase in the size of the mass to 35.9*28.3*25.5 mm compared to the initial CT. Carbagoline was increased further to 1 mg weekly and noticeable changes in symptoms include: return of menses, less frequency of headaches and improved vision on the right eye. However, another cranial CT to recheck the tumor size could not be done due to lack of funds.
Conclusion
She has been on and off carbagoline in the past year because of lack of funds though appears clinically stable.

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EP62

A review of appropriate Endocrine referrals in a District General Hospital

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Over the last few years, there has been an increase in the demand on the National Health Service, with patients presenting to hospital with multiple co-morbidities and increasingly complex needs. The type of endocrine referrals received can vary both in complexity and also between clinicians. The Royal College of physician has published a 'Referring wisely' report in June 2017 which aims to improve and streamline the quality of referrals received in each speciality. Two streams of referrals were identified for each speciality, specifically looking at five referrals which were felt to have required special attention as identified from the referring speciality and five conditions that should have been within the knowledge of any physician and therefore, referrals should be avoided. We retrospectively analysed the inpatient referrals and matched this to the RCP criteria for referrals to review if this had been appropriate. During a three month period, it was noted that 32 patients were referred for an inpatient review. 41% ($n=13$) of referrals were in the recommended category of the RCP report. In the recommended referral group, 4 patients had hyponatraemia, 2 for thyrotoxicosis, 3 for adrenal insufficiency, 1 for Incidentaloma mass, 1 for hypocalcaemia and 1 for amenorrhoea/ hypogonadism. 31% of patients ($n=10$) were in the avoidable referral group, with hypercalcaemia accounting for all of these cases. 9 patients were found to be unclassified in the RCP report accounting for 34%. This included 1 patient for suspected Diabetes Insipidus, 1 for pituitary insufficiency, 1 for suspected Insulinoma, 3 for hypernatraemia, 1 for weight loss, 1 for subclinical hyperthyroidism and 1 for osteoporosis. This reflects the variety of workload that an endocrine department in a district general hospital can encounter in a three month period.

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Diabetes & cadiovascular

EP63

Multiple insulin allergies in a patient with diabetes

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We present a 52-year-old female with a 26-year history of type-2 diabetes mellitus who has been difficult to treat owing to the development of multiple insulin allergies. She initially developed local hyperpigmentation and itchy swellings at the injection sites of her Humulin I in 2016, with similar symptoms occurring when she was switched to NovoRapid. Additionally, she developed one severe, systemic reaction to Humulin I. All insulin treatment was stopped, and she was left solely on oral agents. The patient was referred to an allergy specialist: specific IgE to insulin was found to be raised at 3.39 kUA/l, and intradermal testing was positive to nearly all insulins tested. The only negative intradermal test was to Hypurin Bovine Lente, the only insulin not to contain the excipient metacresol. It is therefore likely that her allergy is actually to metacresol as opposed to insulin per se, but she has not yet been challenged with metacresol alone. To optimise her diabetes control, and known diabetic complications of retinopathy and neuropathic feet, she was started on a regimen of Hypurin Bovine Lente; HbA1c reduced from 121 mmol/mol to 73 mmol/mol over the course of five months. Unfortunately, Hypurin Bovine Pente will not be available in the United Kingdom for much longer. Patients with diabetes requiring insulin who have an insulin allergy are rare, but there are multiple reported cases. In contrast to our case, allergy is usually to bovine or porcine insulins and thus its incidence has decreased since the advent of human insulins. There is no obviously superior management option, and a patient-specific approach is needed. Successful managements reported in case literature vary from specific immunotherapy, to desensitisation regimes and continuous subcutaneous insulin infusion. We plan to challenge our patient with Insuman Infusat and refer her for potential bariatric surgery.

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EP64

Pneumomediastinum in diabetic ketoacidosis: an ominous sign?

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A 22-year-old male presented to the Emergency Department with nausea and vomiting. He reported thirst, polyuria, reduced appetite and weight loss. He did not have pre-existing medical conditions and did not take regular medications. On examination, he appeared pale and clammy. He was apyrexial, tachycardic and tachypnoeic with normal blood pressure and oxygen saturation. His chest was clear and abdomen generally tender. A venous blood gas revealed pH 6.94, base excess −29 mmol/l, bicarbonate 3.2 mmol/l and glucose 27 mmol/l. His capillary blood ketone concentration was 4.9 mmol/l. Diabetic Ketoacidosis (DKA), secondary to undiagnosed type 1 diabetes, was diagnosed. He was treated with fluid resuscitation and insulin infusion. As clinical and metabolic statuses improved, Radiology alerted the medical team about the presence of subcutaneous emphysema and pneumomediastinum on chest radiograph. Vomiting-induced subcutaneous emphysema and pneumomediastinum raised suspicion of spontaneous oesophageal perforation. The patient was started on antimicrobials, antifungals and high-dose proton-pump inhibitors, transferred to a tertiary referral gastro-oesophageal centre and scheduled for urgent feeding tube insertion. However, CT scan with oral contrast showed the absence of pleural effusions and contrast extravasation. After discussion, the Surgical and Endocrinology teams agreed on conservative management: the patient remained NBM until an unremarkable contrast swallow on day 5. He was discharged with outpatient follow-up. Spontaneous pneumomediastinum occurs due to increased intra-alveolar pressure and alveolar rupture (Hamann's syndrome): it is a benign, self-limiting condition. In DKA, it may arise from vomiting and Kussmaul breathing. Treatment is conservative, and it is important to differentiate it from oesophageal rupture (Boerhaave's syndrome).

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EP65

Treating salt before sugar

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Introduction
Diabetes Ketoacidosis, DKA, is a serious condition with significant morbidity and mortality. Most DKA patients are potassium deficient, but present with hyperkalaemia due to severe acidosis and insulin deficiency. Hypokalaemia at presentation of DKA is extremely uncommon.
Clinical case
A 25 year old man was admitted with severe DKA as a first presentation of diabetes. His venous pH was 6.97, bicarbonate 3.0 mmol/l, potassium 3.4 mmol/l. He was treated with intravenous fluids supplemented with potassium chloride (10 mmol/h), a fixed rate insulin infusion (10 Units/h) and oral potassium supplements. Over the next 8 h, his acidosis failed to improve (serum bicarbonate 2 mmol/l). Despite full replacement, his serum potassium levels dropped to 1.7 mmol/l and he developed new ECG changes, with profound ST depression and QT prolongation to 504 ms. The patient was transferred to the Intensive Care Unit and commenced on 20 mmol/h intravenous potassium chloride. Given the life-threatening ECG changes, insulin was omitted for the next 8 hours until serum potassium level was above 3 mmol/l. Thereafter, insulin treatment was recommenced and the patient required a consistent potassium replacement at a rate of 60 mmol/h to ensure serum potassium $\geq$4 mmol for 48 hours. This was delivered under cardiac monitoring via central vein. He developed transient polyuria with high potassium urinary losses. His condition gradually improved and after 3 days he made a full recovery.
Summary
We present a case of life-threatening hypokalaemia during management of severe DKA which required a delay in insulin treatment for 8 hours. Insulin therapy causes an intracellular shift in potassium which worsens hypokalaemia. In severe, refractory cases, it may be necessary to withhold insulin therapy until hypokalaemia is corrected. Intensive management is crucial, as hypokalaemia remains the main contributor to DKA associated mortality.

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Neoplasia, cancer & late effects

EP66

Rapid onset hirsuitism in a post menopausal woman with an ovarian cyst

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Sertoli-Leydig cell tumours are rare comprising 0.2–1.2% of all primary ovarian cancers. Virilisation is seen in 30–50% of cases. Heterologous Sertoli-Leydig cell tumours with dominant cystic component are even rarer and mainly affect females aged 20 to 30 years. A 66-year-old lady was referred to the Endocrine Department with a one year history of rapid severe hirsutism involving the limbs, abdomen, chest, face and thinning of hair on the scalp. Blood pressure of 156/89 and BMI of 34. Her testosterone was raised at 11.9 nmol/l, serum cortisol was 461 nmol/l and TSH was 9.29 mu/l. Twenty-four hour urine cortisol was normal at 80 nmol (N 0–146) and 1 mg overnight dexamethasone suppression test showed a morning serum cortisol of 24 nmol/l. CT scan of the abdomen showed normal adrenal glands but a large left ovarian cyst measuring 10 $\times$ 11 $\times$ 8 cm in size. Transvaginal ultrasound showed a large unilocular cyst measuring 12.7 $\times$ 8.3 $\times$ 9 cms with some thick septations seen. CA 125 was normal at 7 Ku/l (N 0–35). Testosterone level normalised to 0.5 nmol/l once the ovarian cyst was removed surgically and had significant improvement in hirsuitism. Initial histological analysis of the wall of the ovarian cyst was ambiguous and even after review by the Histopathology department at our tertiary centre, the two main differential diagnoses were mucinous cystadenoma with stromal luteinisation and hilar cell hyperplasia or heterologous Sertoli-Leydig cell tumour with dominant mucinous cystic component. The latter was finally the favoured diagnosis when correlated clinically.

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EP67

Erythrocytosis caused by Vandetanib treatment in metastatic medullary thyroid carcinoma: the first case report

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Erythrocytosis is classified as either primary or secondary. Polycythemia vera (PV), a myeloproliferative neoplasm, is often caused by a mutation in exon 12 of the Janus kinase 2 (JAK2) tyrosine kinase gene which phosphorylates erythropoietin receptor (EPO-R) at multiple sites. Secondary erythrocytosis mainly results in conditions with increased erythropoietin (EPO) production. We report a 21-year-old man with metastatic medullary thyroid carcinoma (MTC) at diagnosis. The total thyroidectomy with central and cervical compartment dissection was carried out by a thyroid surgeon. At the time of diagnosis, the tomography of the chest and abdomen revealed multiple nodular lesions suggestive of metastasis. We identified three measurable target lesions that meet RECIST 1.1 criteria for follow up of the tumour burden. Due to the progression of the disease, defined as at least a 20% increase in total measured tumour burden (TMTB), we started Vandetanib treatment. The patient received at Vandetanib at a dose of 300 mg/day for three months with frequent clinical evaluation for adverse effects of the treatment. Other classic side effects were dermatitis acneiform and decreased weight. We observed progressively elevated hematocrit in the examination after a week of therapy with maximum increased in 4 weeks after the beginning of treatment. Following the haematologist's advice, four sessions of bloodletting (300 ml each time) were performed over the following two months, and aspirin at a dose of 75 mg/day was administered at the same time to prevent thrombogenesis. Serum erythropoietin (EPO) level was within normal range, and molecular testing for the JAK2 V617F mutation was negative. The recent history of initiation of Vandetanib treatment may be the charged reason for the secondary erythrocytosis in our patient. This is the first report with erythrocytosis as an adverse effect during therapy with Vandetanib.

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EP68

IGF2 related non-islet cell tumour hypoglycaemia in a patient with hepatic sarcoma

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Hypoglycaemia is a common and potentially life threatening presentation to Emergency Departments across the UK.It is often a result of medications for treatment of diabetes but other differentials include rarer reactive and fasting causes.This case report describes a 69 year old man who initially presented with right upper quadrant pain and weight loss which then lead to a diagnosis of inoperable hepatic sarcoma. He later presented with hypoglycaemia and Whipples triad in the context of no circulating oral hypoglycaemic agent and fasting biochemistry that was not supportive of the role of insulin in the genesis of the hypoglycaemia: insulin $<$1.0IU/l, c-peptide $<$0.1 nmol/l and glucose 2.0 mmol/l. Short synacthen test was normal. IGF2: IGF1 ratio was 14.7, supporting evidence of 'Big' IGF2 over production. IGF2 excess in the context of hypoglycaemia and known malignancy confirmed a diagnosis of non-islet cell tumour hypoglycaemia. In this case, the patient's tumour had grown extensively by time of diagnosis and was inoperable due to both size and location in the caudate lobe of the liver. His case was further complicated by admissions with Moraxella and E.coli bacteraemia; likely stemming from the tumour as no other was source found on imaging. Despite initial treatment with once daily steroids he had multiple near-fatal hypoglycaemic episodes requiring inpatient monitoring. Growth hormone treatment was felt to be contra-indicated due to concern over tumour growth. Ultimately, a regime of twice daily steroids at supra-physiological dose and regular carbohydrate intake was used to maintain glycaemic and symptomatic control. Although rare, the exact incidence of non-islet cell tumours causing hypoglycaemia is unknown and they are often diagnosed late. Treatment options are limited, however if surgical resection is possible, hypoglycaemia can be fully resolved. There is limited evidence base for other therapeutic options such as glucocorticoids, recombinant growth hormone and glucagon.

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EP69

An unusual case of hypoglycaemia

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A 79-year-old female patient, with a background history of hypertension and ischaemic heart disease was brought by ambulance to hospital with near collapse episode associated with capillary blood glucose (CBG) of 2.1 mmol/l. Her regular medications include Ramipril, clopidogrel and atorvastatin. She had no history of diabetes. While inpatient, it was observed that majority of low capillary blood glucose readings (CBG) were late night or early mornings. At venous glucose of 1.9 mmol/l, C peptide was found to be <94 pmol/l and serum insulin <10 pmol/l pointing towards non-islet cell hypoglycaemia. She has normal hypothalamic pituitary adrenal (HPA) axis. Further investigations revealed insulin like growth factor-2 (IGF-2) value of 79.5 nmol/l with Serum insulin like growth factor-1 (IGF-1)- 3.6 nmol/l (4.4–21.8) and serum insulin like growth factor binding proteins (IGFBP3) of 2.2 mg/l (2.0-5.5). IGF-2: IGF-1 ratio was significantly high at 22.1 suggesting diagnosis of insulin like growth factor 2 (IGF-2) driven non islet cell hypoglycaemia. CT abdomen and pelvis with contrast showed an 18 cm lobulated inhomogeneous pelvic mass with multiple liver masses. There was filling defect within the inferior vena cava extending into the left common iliac vein in keeping with venous thrombosis. Subsequent tissue biopsy confirmed a diagnosis of gastro-intestinal stromal tumour with paraneoplastic IGF2 driven hypoglycaemia. Hypoglycaemia treated initially with prednisolone showed little improvement. Later she was switched to dexamethasone with good response. Unfortunately patient developed retroperitoneal bleed secondary to treatment dose enoxaparin for inferior vena cava thrombosis and passed away within 8 weeks of her diagnosis. Non islet cell tumour hypoglycaemia (NICTH) is a rare but serious complication of malignancy characterised by tumoral overproduction of incompletely processed IGF-2, which results in stimulation of insulin receptors and increased glucose utilization.

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EP70

MEN 2A – a rare syndrome with variable intrafamilial gene expressivity, case presentation

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MEN2A is an autosomal dominant inherited syndrome, caused by a gain of function germline mutation in the RET proto-oncogene, with multiglandular tumoral development. Although the presence of MTC is very high and 50% of patients present with pheochromocytoma, the penetrance of hyperparathyroidism is estimated to be between 9 and 34%. The clinical presentation of the syndrome varies widely even in members of the same family, because of the difference of gene penetration (1). In 5% of cases, hyperparathyroidism may be the first manifestation. We present a patient with MEN2A, yet to be confirmed as a family case. MT, 53 yo woman, presented in our clinic in 2017 for medical evaluation. She was known with pheochromocytoma diagnosed at the age of 31, Graves disease with multinodular goiter, and operated breast cancer at 48 yo. She had normal urinary and plasma MN and NMN values, normal calcium, phosphate and PTH levels, and high calcitonin value (81 pg/ml). In the presence of a high risk thyroid nodule on ultrasound, total thyroidectomy was performed and MTC was confirmed. Recently, genetically testing revealed the presence of RET 11 Cys634Trp mutation and MEN2A was confirmed. Her sister, BC 49 yo, known with multiple melanomas, was subsequently evaluated and primary hyperparathyroidism due to parathyroid adenoma was diagnosed in the presence of repeated high calcium (10.7/10.61/10.8 mg/dl), high normal PTH (62 pg/ml) and normal 25-OH-vitamin D levels. MTC and pheocromocytoma were excluded and genetic testing result is in pending. What is the correct diagnosis for the second case? Does this patient with a solitary parathyroid adenoma have MEN2A syndrome or is it just a sporadic disease, in a family with different associated malignancies (breast cancer, malignant melanomas), where the RET mutation was confirmed in her sister?

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Neuroendocrinology and pituitary

EP71

Internal carotid artery haemorrhage in a patient with a radiotherapy treated pituitary macroadenoma with sphenoid extension and osteonecrosis

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Pituitary macroadenomas often extend to the suprasellar region, however rarely they can extend inferiorly and include erosion into the sphenoid bone, presenting unique challenges. We present a 74-year-old female who received pituitary radiotherapy in 1995 for a pituitary macroadenoma with sphenoid extension. She initially presented in 1994 with secondary amenorrhoea and hyperprolactinaemia (30,000 mu/l). She could not tolerate MRI and subsequent CT showed a pituitary macroadenoma with destruction of the sellar floor to the sphenoid sinus. She was managed for a macroprolactinoma with bromocriptine. One year later prolactin was reduced (670 mu/l) however CT showed no change in size to the lesion eroding into the sphenoid sinus. There was no visual compromise and surgery was felt not to be indicated but she received external beam radiation in 1995 to reduce further growth. Thereafter, she remained well with modest prolactin levels and normal vision. A more recent CT in 2017 showed no residual pituitary mass but ongoing destruction of the sellar floor extending into the sphenoid sinus. In 2018, she presented with severe epistaxis with haemorrhage requiring operative management. Intra-operatively, bleeding from the right sphenoid sinus ostium was documented. Subsequent CT angiography described the bony defect in the right sphenoid sinus with exposure of the right internal carotid artery with features of recent haemorrhage, the likely site of epistaxis. We postulate that this is a long-term complication from bony erosion from the initial pituitary disease exacerbated by subsequent pituitary radiotherapy causing osteonecrosis and artery exposure. Internal carotid artery haemorrhage has previously been described in the context of osteoradionecrosis of the skull base secondary to radiotherapy for nasopharyngeal cancers, although has not been previously described with pituitary radiotherapy. Given the significant comorbidity this patient has been treated conservatively and counselled on the risk of possible life threatening haemorrhage.

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EP72

Carcinoid heart disease as the presentation of ovarian neuroendocrine tumour (NET) in the absence of liver metastases

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Ovarian neuroendocrine tumours are rare ($<$ 2% gynaecological tumours) and first described in 1939 by Stewart et al. The occurrence of carcinoid heart disease alongside this is anecdotal. We present a previously fit 66 year old female, with a 6 month history of shortness of breath and ankle oedema. Echocardiogram revealed severe fixed tricuspid regurgitation, pulmonary valve disease, dilated right heart chambers and preserved left ventricular function. Carcinoid heart disease was suspected and she was referred to our neuroendocrine tumour clinic. She gave a seven year history of facial flushing and diarrhoea. Examination revealed a fixed violaceous facial flush, injected red eyes and evidence of right heart failure. The liver was pulsatile and a large pelvic mass was palpable. Investigations revealed chromogranin A of 242 nmol/l (0–6) and 5-hydroxyindolacetic acid (5HIAA) at 857 umol/24 hrs. CT and MRI showed a large solid/cystic 15 cm mass arising from the right ovary, avid on Octreoscan. No lesions were noted in the bowel or liver. Her carcinoid syndrome was controlled with octreotide 50 mg thrice daily subcutaneously with cross over to Lanreotide 120 mg deep sc injection every 28 days. Right heart failure was managed with bumetanide 1 mg daily. After careful review in the Neuroendocrine MDT including gynaecology, cardiology, anaesthetic and HPB surgical review; joint procedure with the neuroendocrine surgical team and gynaecologist was performed. She underwent an uneventful oophorectomy under octreotide cover. Histology revealed an ovarian insular carcinoid tumour with lymphovascular space invasion, ENETS grade 1 (KI 67 $<$1%). Her 24hr urinary 5HIAA normalized to 17 umol/24 hrs. Ovarian carcinoid presenting with carcinoid heart disease and syndrome is very rare and needs to be considered in elderly females who present with right heart valve disease. This case highlights the need MDT discussion in patients with NET.

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EP73

Acute psychosis related pituitary haemorrhage

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Background
Pituitary haemorrhage or infarction into a pituitary tumour is well reported unlike isolated Pituitary haemorrhage due to traumatic injury of a normal gland.
Case report
A previously healthy 44-year-old man presented following two episodes of seizures following a closed head injury. He reported transient extreme thirst, polyuria and headache at the outset, which had resolved by the time of admission. His Glasgow Coma scale was 14/15 and his clinical examination showed frontal bruising to his head but was otherwise normal with no focal signs. One week prior to admission he had been diagnosed with Acute Psychosis requiring restraint and admission to a Mental Health unit. MR Imaging of his brain revealed high T1 signal within the pituitary gland suggestive of an isolated pituitary heamorrhage. Short Synacthen test; baseline 205 nmol/l and 408 (30') (Abott assay N 30 mins $>$ 450 nmol/l). The rest of his pituitary hormone profile was within normal limits. Infective and other infalmmatory causes were excluded by normal CSF findings. The patient made satisfactory progress with appropriate management of his acute psychosis and maintaenance hydrocortisone replacement.
Discussion
Due to the anatomical location of the pituitary gland as well as the long hypophyseal portal vessels, the pituitary is vulnerable to direct mechanical trauma (1).
Pituitary adenomas are more prone to blled than a normal pituitary gland, due to diferences in blood supply (2).
Trauma related Pituitary haemorrhage requires a high index of suspicion to enablr accurate diagnostic work up and corection of hormone deficiences to ensure a satisfactory recovery (1).
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EP74

A rare case of prolactin secreting pituitary carcinoma with extra-cranial metastasis

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We present a case of 71-year-old gentleman who presented with bitemporal hemianopia in 2008 with pituitary apoplexy compressing the optic chiasm. Prolactin was 55287MU/l, with deficiency of all other anterior pituitary hormones. He underwent transphenoidal adenectomy (TSA). Prolactin was 35633MU/l post-operatively and cabergoline was commenced. Histology was consistent with a lactotroph adenoma with MiB-1 index of 3–5%. Visual fields recovered and prolactin was normal until 2013. He re-presented with new visual field defect and the prolactin of 32558MU/l in 2014, with no response to escalation of cabergoline. He underwent debulking surgery in February 2015 and September 2015 due to progression; histology showed elevated MiB-1 (20–30%). The post operative MRI scan in December 2015 confirmed rapid regrowth of the tumour and further TSA and radiotherapy were performed. His prolactin was stable until September 2017. Slow rise in prolactin was seen initially with no change in pituitary MRI findings. Between March and May 2018 the rate of rise of the Prolactin was accelerated and reached 65807MU/l. MRI in May 2018 demonstrated two large extra-axial intra-dural enhancing masses at the level of C1-C2 junction with risk of neuronal compression. The patient underwent resection of the right intradural extramedullary lesion. Histology demonstrated a metastatic deposit with raised MiB-1 (10–20%), confirming lactotroph carcinoma. Post operatively the prolactin level to 50460MU/l. MRI spine and PET CT scan is planned to investigate for distant metastasis and possible resection of the left intradural extramedullary lesion will be performed if no other metastases are identified and possible temozolomide therapy. This case highlights the changing course of an aggressive lactotroph lesion with resistance to dopamine agonist therapy and subsequent development of metastatic disease. Lactotroph lesions with high MIB-1 and unusual course harbour malignant potential and warrant close follow up.

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EP75

Unusual cause of meningioma

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Case
60 year old transfemale had normal delivery, milestones and puberty. She developed gynaecomastia aged 14, associated obesity which resolved. As an adult she had reduced facial and body hair and reduced sexual function prior to hormone therapy but normal self-reported genitalia. She has female role from age of 24. She never had any children and was commenced female hormones 36 years ago. These were Premarin and Cyproterone Acetate which were continued post genital reconstructive surgery. No complications post operatively and her sexual function returned to normal. She had good breast development (c cup). She presented in early 2017 with rapid deteriorating visual acuity in the right eye. Investigations revealed three meningiomas – olfactory groove, left paraoptic, right sphenoid wing. All of these were Oestrogen receptor negative. She had neurosurgical intervention which confirmed no involvement of the pituitary gland. She had good improvement to vision. Post operatively Oestrogen and Cyproterone acetate was stopped. Post-operative pituitary profile off Oestrogen therapy confirmed
IGF-1 47.8 nmol/l
TSH 1.36 mU/l
Free T4 15.6 pmol/l
LH 18.4 IU/l
FSH 24.7 IU/l
Oestradiol $<$92 pmol/l
Testosterone 0.6 nmol/l
SHBG 84 nmol/l
Prolactin 151 mU/l
Discussion
There have been 11 cases reported in the literature of meningioma in transfemales using Oestrogen with Cyproterone acetate. All so far have been associated with long term cyproterone acetate use and either oestradiol, or ethinyl oestradiol use. This is the first report of a meningioma caused by long term premarin and cyproterone acetate. This case illustrates the importance of withdrawing antiandrogen therapy post genital surgery in transwomen. It also suggests the causative factor in meningioma formation is the cyproterone acetate not the oestrogen type used. Clinician should be aware of this as a possible complication of long term antiandrogen therapy in transfemales.

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EP76

Hyponatraemia associated with autoimmune limbic encephalitis

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Introduction
Limbic encephalitis is characterised by seizures, changes in personality and memory impairment. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with autoimmune limbic encephalitis is rare. We present an interesting case.
Case
A 57-year-old gentleman presented with seizures and a cardiac arrest. He had a past history of excess alcohol intake and had been taking excess alcohol prior to this event. Physical examination was unremarkable. His serum sodium was slightly low. He was treated for alcohol-related seizures, counselled concerning his alcohol intake and discharged to his general practitioner for serum sodium monitoring. He was readmitted twice thereafter with further seizures, visual hallucinations and chronic hyponatraemia. Further history revealed that he had experienced behavioural changes and memory impairment a few weeks prior to his initial presentation.

Investigations and management
Initial investigation revealed chronic hyponatraemia (127 mmol/L), hypo-osmolality (264 mOsm/Kg), raised urinary sodium (82 mmol/L) and inappropriately raised urine osmolality (498 mOsm/Kg): all suggestive of SIADH. His renal, thyroid and adrenal function tests were normal. A CT scan (chest-abdomen-pelvis) revealed no underlying cancer and paraneoplastic antibody screen was negative. However, his leucine-rich glioma inactivated-1 (LGI1) antibody screen was positive. MRI brain scan demonstrated hyper-intensity and left hippocampus swelling on fluid-attenuated inversion recovery (FLAIR) images. These features were suggestive of autoimmune limbic encephalitis. He was commenced on fluid restriction for hyponatraemia, Levetiracetam for seizures and oral prednisolone for encephalitis. However, slow improvement prompted the need for intravenous Methylprednisolone and five plasma-exchange sessions. His sodium levels normalised accompanied by significant improvement in cognition and confusion. He remains on a maintenance dose of prednisolone.
Discussion
Autoimmune limbic encephalitis is reportedly more common than once thought and should be suspected in patients presenting with unexplained neurological symptoms and seizures. Urgent specialist referral for immunomodulatory therapy is required to reduce morbidity and mortality.

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EP77

Asynchronous delayed Growth Hormone co-secretion in a patient with a macroprolactinoma whilst on dopamine agonist therapy

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We present a case of a 48 year old male who presented originally with a 8mm prolactinoma. He presented with a reduced libido for 6 months, and lethargy and retro-orbital headaches for the previous 18–24 months. He had no visual disturbance. Initial investigations revealed hyperprolactinaemia with a level of over 4000 iu/L and a normal IGF1 of 184 iu/L in the presence of a pituitary macroadenoma (8 x 11mm). He responded well to Cabergoline with a noticeable improvement in all his symptoms in conjunction with fall in the prolactin levels to the reference range and reduction in size of macroadenoma. After 3 years (2009), he started describing increasing tiredness, which was associated with an increase in his IGF1 from normal to 2-3x upper reference range On direct questioning he admitted to have difficulty in getting his rings on and skin thickening. Prolonged growth hormone-oral glucose tolerance testing showed non-suppression of his growth hormone consistent with Acromegaly. He was initially mamanged conservatively, but due to persisting symptoms and a consistently raised IGF1, he was treated with pituitary surgery. Post-surgery was associated with a normalisation in Prolactn and IGF1. Histology confirmed co-secretion of Prolactin and GH. Whilst it is well recognised that co-secretion of prolactin and growth hormone can occur in significant number of patients with macroadenomas, it is usually synchronous. Asynchronous secretion is less common (<2%) and should be monitored and considered with any symptom changes and/ or with an annual assessment of IGF1/ Prolactin. It is also more unusual to see growth hormone secretion whilst on treatment with dopamine agonist medications due to the frequently found sensitivity of GH in co-secreting prolactinomas.

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EP78

Gigantism due to two different causes in the same family – *AIP* mutation-positive acromegaly and Marfan syndrome

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Germline aryl hydrocarbon receptor-interacting protein (*AIP*) mutations are responsible for 30% of pituitary gigantism cases. However, pathological accelerated growth and/or tall stature can be unrelated to the growth hormone (GH) axis, and may occur in isolation or as part of a syndrome, such as in Klinefelter, Marfan or Sotos syndromes. We report a five-generation kindred with two brothers with pituitary gigantism due to *AIP* mutation-positive GH-secreting pituitary adenomas and their first-cousin coincidently also having gigantism due to Marfan syndrome. The proband, presented with accelerated growth (at the age of 10, height SDS + 2.1) and was diagnosed with pituitary gigantism due to a pituitary adenoma co-expressing GH and prolactin. Following surgery, octreotide LAR was ineffective and he was started on pegvisomant. His brother presented few years later at the age of 16 with accelerated growth (height = 201 cm, SDS + 3.9), and was operated on two occasions for somatolactotropinoma. Genetic testing identified a truncating R304* mutation in the *AIP* gene in these two affected brothers, as well as in eight unaffected family members, who are currently under surveillance. A deceased uncle had acromegaly based on photographs. In the same kindred we identified a tall first-cousin (height 208 cm) due to Marfan syndrome. Clinical and biochemical exclusion of GH-related pituitary gigantism is usually straightforward; however, some conditions may present with acromegaloid features, or tall stature. In this family, the diagnosis of the two brothers with pituitary gigantism may have been hindered by the presence of extreme tall stature in the family (due to Marfan syndrome). Overlapping features between GH excess and other conditions could present challenging issues for patients and their families as well as for their general practitioners.

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EP79

Atypical presentation of Pituitary Apoplexy with fevers and gradual onset of headaches -Would you miss it?

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Introduction
Pituitary apoplexy is both an endocrine and a neurosurgical emergency, and can typically present with sudden onset of headaches, impaired level of consciousness, fever, visual disturbances, nausea or vomiting. Apoplexy ensues when pre-existing pituitary tumour presumably outgrows its blood supply leading to ischaemia, necrosis and haemorrhage or infarction.
Case
A 31-year-old man presented to the hospital with 3 months' history of gradual onset of headaches. He was found to be pyrexial at presentation (39 C). He also complained of progressive worsening of his left and right eye vision. He developed complete ptosis of his right eye 3 days prior to admission. His other background problems include long-standing gynaecomastia and low libido, and inflammatory bowel disease. Examination findings revealed no light perception on the left eye, 6/21 vision on the right eye, right partial third nerve palsy with ptosis and asymmetry pupil. His Glasgow Coma Scale (GCS) was 15/15. The blood test showed WCC 14.9 10*9/L and CRP 331 mg/L. TSH 0.99 mU/L, FT4 6.8 pmol/L, FT3 1.7 pmol/L, cortisol 427 nmol/L, LH 1.4 iu/L, FSH 1.5 iu/L, prolactin 3597 miu/L, testosterone 1.2 nmol/L, IGF-1 139 ng/ml. His MRI pituitary revealed macroadenoma with suprasellar extension with central necrosis and pus in the sphenoid and ethmoid sinus. He was treated with iv antibiotics and had image-guided endoscopic transsphenoidal drainage of sphenoid and ethmoid pus. His vision improved postoperatively. Immunohistochemical staining for pituitary was positive for prolactin.
Discussion
Pituitary apoplexy remains a potentially life-threatening condition. Its presentation may vary from relatively benign to a catastrophic presentation with neurological deficits. The presentation with gradual onset of headaches and gradual deterioration of vision and clinical features of sepsis is atypical and may lead to delayed diagnosis. Involvement of neurosurgical and endocrine team is vital for the right treatment of the patient.

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EP80

A difficult case of Cushing's disease with unexplained hypertension and rapid metabolic decompensation

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A 26 year old man of Angolan descent presented to the endocrine clinic with poorly controlled hypertension (systolic blood pressure >200 mmHg). He had been treated with Amlodipine for almost six years, and more recently the addition

of Irbesatan and Indapamide had not led to adequate blood pressure control. His hypertension was diagnosed at age 19 and progressive features of Cushing's disease had remained unnoticed, with truncal striae, easy bruising, myopathy, puffiness around the face and lower leg swelling. In the previous year he had had a skin graft to his right leg following a football injury, which prompted his referral. Investigations showed failure of cortisol suppression on a low dose dexamethasone suppression test (time = 48 hours, cortisol 1107 nmol/l) and magnetic resonance (MRI) imaging demonstrated a right-sided pituitary macroadenoma of 13 mm. Urgent petrosal venous sampling was scheduled, but he acutely decompensated in the interim after being admitted with newly diagnosed diabetes mellitus, a hyperosmolar hyperglycaemic state (HHS) and multiple cranial nerve dysfunction, including facial nerve palsy. Brainstem MRI imaging was unremarkable and the working diagnosis was imminent pontine myelinolysis secondary to osmotic change. He was treated appropriately for the HHS and recovered fully. Hypercortisolaemia was treated with Ketocanozole and he went on to have urgent transphenoidal pituitary surgery. Histology confirmed tumour cells expressing ACTH with P-53 overexpressed at 2% and the Ki-67 index high at 5%. Cushing's post-operative work-up showed he was not biochemically cured and an interval MRI showed residual tissue extending into the right cavernous sinus. Further treatment options are being considered including a second transsphenoidal procedure and/or stereotactic radiotherapy. This rare case demonstrates two interesting presentations; firstly, a rapid decompensation of Cushing's disease resulting in HHS, and secondly a rising osmolality in HHS causing cranial nerve dysfunction.

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EP81

Secondary resistance to Cabergoline-pitfalls and challenges of managing macroprolactinoma with high dose dopamine agonist therapy

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Dopamine agonists (DA) are first line therapy for Prolactinoma which normalises prolactin(PRL) level in 80% of cases at a median weekly dose of 1 mg. An accepted criterion of pharmacological resistance to DA is failure to normalize PRL levels. We report a case of aggressive macroprolactinoma that required 7 mg of Cabergoline to reduce prolactin despite radiological evidence of tumour shrinkage. A 42 year old male presented with a bitemporal field defect. Imaging confirmed an invasive macroprolactinoma. Investigations showed elevated PRL level of 91,760 mU/L and hypogonadotropic hypogonadism (FSH-3.3 u/L, LH-2.5 u/L; testosterone- 6.2 nmol/L). The patient was started on 500 mcg of Cabergoline/week and the dose was titrated to 1 mg/week. After 6 months there was marked reduction in the size of the tumour which was accompanied by a fall in prolactin to 10,6050 mU/L. Thereafter, prolactin level remained static and the dose of Cabergoline was progressively titrated to a maximum of 7mg weekly. Repeat MRI scan showed complete shrinkage of macroprolactinoma. Prolactin remained persistently elevated at 1,826 mU/l. This dose was associated with adverse effects and the dose of cabergoline was reduced gradually to a maintenance dose of 500 mcg weekly. Prolactin remains slightly elevated at 2037 mU/l but is stable with no associated increase in tumour size. This case highlights marked secondary resistance to Cabergoline following an initial favourable response. Secondary resistance to DA occurs rarely but this case demonstrates that effective tumour shrinkage can be obtained with higher doses of cabergoline with careful monitoring of adverse effects. Once tumour shrinkage has been achieved the dose of cabergoline should be reduced to the lowest effect dose that maintains a stable prolactin level. Complete normalisation of prolactin may not be feasible or indicated in the majority of cases.

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EP82

Acromegaly due to a mixed growth hormone secreting adenoma-gangliocytoma - a rare cause of GH excess

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Adeno-gangliocytomas are rare tumours of the pituitary gland with less than 40 cases described worldwide. Due to the rarity of these tumours, treatment modalities largely follow that of conventional therapies for common pituitary lesions. Case reports on these tumours offer insight into their presentation and the effectiveness of treatment which helps guide future management. A 64-year-old man was admitted for stone fragmentation and ureteric stent insertion. During anaesthetic recovery he developed sudden onset severe frontal headache with nausea, photophobia and visual field disturbance. Urgent cranial CT scanning showed pituitary apoplexy. Subsequent pituitary MRI scan confirmed a pituitary macroadenoma with evidence of tumoral haemorrhage. On examination he had classical clinical features of acromegaly including prognathism, interdental separation, large hands and macroglossia. Investigations showed raised GH (5.32 mcg/l) and IGF-1 (103.8 nmol/l) with non-suppression of GH levels during an OGTT. Thyroid and gonadal axes were normal. Pituitary apoplexy was managed with Dexamethasone in the acute phase. Endoscopic trans-sphenoidal pituitary surgery was undertaken electively. At operation a hard fibrous tumour was noted and decompression of the macroadenoma was undertaken. Resection was incomplete due to the fibrous nature of the tumour and risk to surrounding structures. Histology of the excised tumour showed a composite lesion of neoplastic cells expressing GH and ganglion cells, confirming the diagnosis of a GH secreting adenoma-gangliocytoma. Post-operative assessment showed evidence of residual GH hypersecretion. Adjuvant treatment with pituitary radiotherapy is being planned along with somatostatin analogue therapy in the interim. The histogenesis of mixed pituitary adenoma-gangliocytomas is unclear. These tumors are difficult to distinguish from pituitary adenomas on neuroimaging. Treatment is along conventional lines with pituitary surgery followed by radiotherapy and somatostatin analogue therapy. It is unclear as to whether the clinical course of these tumors is different to conventional GH secreting pituitary adenomas.

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EP83

A disappearing act in the pituitary fossa with recovery from panhypopituitarism

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A 36-year-old, previously healthy, man presented with several weeks' history of gradually worsening headache. He attended A&E after he was woken by sudden worsening of the headache, associated with vomiting and pre-syncopal symptoms. Investigations revealed severe hyponatraemia - serum Na 109 mmol/L. He was also severely hypocortisolaemic – serum cortisol (random) 16 nmol/L, ACTH 19 ng/L. Cranial imaging revealed a 17 mm suprasellar, complex cystic pituitary lesion compressing the optic apparatus; there was no calcification within the mass. He was treated with intravenous saline and glucocorticoids. Serum Na initially improved to 129mmol/L and he felt better. However, after four days, he complained of headache with nausea and his serum sodium declined again. He was clinically euvolaemic and repeat biochemical assessment confirmed a persistent state of antidiuresis despite replacement of glucocorticoids - serum Na 116, urine osmolality 726 mOsm/kg, urine Na 62 mmol/L. He was then treated with fluid restriction, while continuing glucocorticoids, and serum sodium gradually returned to the normal range. He had panhypopituitarism, without polyuria, – serum free T4 6.1 pmol/L (10.5–24.5), TSH 0.68 mU/L, testosterone 0.8 nmol/l (8–29). He commenced appropriate hormone replacement. Serum prolactin was not elevated (101mU/L) and the neurosurgical team planned transsphenoidal debulking; however, repeat pituitary imaging, six weeks later, demonstrated substantial shrinkage of the lesion, now confined to the sella. Six months after presentation, the lesion had regressed further and dynamic endocrine testing, including insulin tolerance test, demonstrated almost complete recovery of pituitary function – he remained partially deficient in growth hormone only. Spontaneous recovery of panhypopituitarism is uncommon in patients with a pituitary mass. This case highlights the complexity of the diagnosis and management of severe, symptomatic hyponatraemia, in patients with a newly discovered sellar lesion.

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EP84

A clinically functioning gonadotroph adenoma presenting with abdominal pain, bilateral multi-cystic ovaries and fibromatosis

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Introduction
We present the case of a clinically functioning gonadotroph adenoma in a pre-menopausal woman with abdominal pain, bilateral multi-cystic ovaries and fibromatosis. To our knowledge, this is the first case of fibromatosis associated with a functioning gonadotroph adenoma.
Case
A 36 year old female presented on three occasions with acute abdominal pain. She was previously well and had two normal pregnancies. On the first admission, she underwent bilateral cystectomy for large benign follicular cysts. On the second admission she required a right oophorectomy and salpingectomy for ovarian torsion and left ovarian cyst aspiration. On her third presentation she required resection of a 4×1.7 cm rectus abdominis muscle mass. Histology confirmed fibromatosis (desmoid tumour). On review in the endocrine clinic, she reported persistent abdominal pain, slightly less regular periods, no galactorrhoea and no headaches. Examination was unremarkable. Endocrine investigations showed an elevated oestradiol, FSH at the upper limit of normal and a suppressed LH. Prolactin was mildly elevated. All other pituitary function tests were normal. Pituitary MRI revealed a 1.5 cm pituitary macroadenoma, with no evidence of chiasmatic compression. A diagnosis of an FSH secreting pituitary adenoma was made and she underwent transphenoidal hypophysectomy. Histology confirmed a pituitary adenoma with FSH immunopositivity in keeping with gonadotroph cell adenoma. Post operatively, her abdominal pain resolved and she resumed a normal menstrual cycle. Her oestradiol, FSH and LH levels normalised. Pelvic ultrasound showed two normal follicles 2–3 cm in size. Post-operative MRI at three months showed removal of the majority of the pituitary adenoma with a small residuum within the right cavernous sinus.
Discussion
Gonadotroph adenomas are usually clinically non-functioning, but rarely can cause clinical symptoms. This case highlights the importance of considering the diagnosis of a functioning gonadotroph adenoma in patients presenting with recurrent, large follicular cysts and fibromatosis.

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EP85

The many faces of hypoglycaemia–Would you recognise all of them?

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Introduction
Hypoglycaemia is an endocrine and medical emergency. It is usually due to the excessive dose of insulin or oral anti-diabetic agents. Although rare, hypoglycaemia can be a tumour–induced. Some of the other causes include renal and liver failure, hormonal deficiency, antibodies to insulin, infection, starvation, spontaneous hypoglycaemia and reactive hypoglycaemia.
Case report
A 70-year-old man presented with 6 months' history of recurrent collapses; progressively worse over the last 3 months. He required frequent hospital admissions with 'funny turns' and seizures. He denied palpitations or chest pain. He was hypoglycemic during every admission with glucose levels <2 mmol/L, requiring treatment with i.m glucagon and iv dextrose. The blood test results showed glucose 3.1 mmol/L (< 2 mmol/L previous admissions), C-peptide <94 pmol/L, low insulin level (1 pmol/L), GH 0.38 mcg/L, ketones (beta-hydroxybutyrate) <0.05 mmo/L, IGF-1 29.2 nmol/L (1.5–35), and IGF-2 134.5 nmol/L. IGF2:IGF-1 4.5 (<10); not hypoglycaemic at that time(glucose 5.5 mmol/L. SST (cortisol 255,719). Urine sulphonylurea screen was negative. CXR- chronic right-sided pleural effusion and lung mass. His background includes right-sided pleural effusion, IHD, heart failure, hypertension and right-sided lung tumour diagnosed in 2010. His medications include aspirin, atorvastatin, candesartan, furosemide, omeprazole, paracetamol and eplerenone. He was treated with steroids and given growth hormone. He underwent radiotherapy for the right lung mass and subsequently, his hypoglycaemia resolved.
Discussion
Tumour-induced hypoglycaemia is a rare paraneoplastic process. This can be divided into an insulin-secreting tumour, due to a tumour related infiltration of the liver or adrenal glands, and tumours producing substances interfering with glucose metabolism such as IGF-1 and tumours that produce partially processed precursors of IGF-2 ("big IGF-2").
Conclusion
Tumour-induced hypoglycaemia should be considered in the differential diagnosis in patients with active malignancy or past medical history of malignancy presenting with hypoglycaemia.

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EP86

Sheehan's syndrome in a man

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Background
The blood supply of the pituitary gland comes via a portal circulation from the hypothalamus. During pregnancy, the anterior pituitary gland enlarges but the blood supply cannot increase, as it is derived from a capillary plexus. The pituitary is thus vulnerable to arterial pressure changes and infarction secondary to hypotension. We describe a case of a male patient with large pituitary adenoma who developed Sheehan's like syndrome due to adenoma infarction secondary to postoperative hypotension, confirming that the mechanism of Sheehan's syndrome is a combination of critical pituitary ischaemia because of its unique blood supply, and relatively mild hypotension, which is not otherwise life threatening.
Case
An 84 year-old male was found to have bilateral hemianopia. Subsequent MRI imaging confirmed a large (non-functioning) pituitary macroadenoma associated with chiasmal compression and hormonal evidence of partial hypopituitarism. The patient was offered a TSS, but he chose a conservative approach. A follow up pituitary MRI showed an increase in the height of the lesion with increase in chiasmal compression and surgery was again offered to the patient. He agreed to be done after another major shoulder surgery (in another institution), which was a priority for him. In the immediate postoperative period (orthopedic surgery), he vomited 25 times with hypotension and severe visual restriction and required intensive support to maintain his blood pressure. Weeks later, he noticed dramatic improvement in his vision. Post surgery, the prolactin level dropped from peak level of 1095 to 48 milliunit/L (60–300), suggesting lactotroph infarction. Repeated pituitary MRI showed dramatic reduction in the height of the pituitary macroadenoma due to an infarction. This correlated with the improvement in VF.
Conclusion
The pituitary is vulnerable to infarction either in the presence of a tumour or at the end of pregnancy, both times of pituitary enlargement.

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EP87

Weight-related hypothalamic dysfunction: a memorable case

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Background
The effect of weight loss on hypothalamic function is complex and not fully understood. There is interplay between neuropeptides (leptin, ghrelin) and hypothalamus with the postulated aim of energy conservation and prevention of pregnancy during unfavourable conditions. We present a memorable case.
Case
A 35-yr-old lady presented with secondary amenorrhoea of 17 years duration. She attained menarche at age 13. At age 16 her periods became scanty and stopped. She had been on the contraceptive pill for 3 years. She never exercised excessively but lost a stone in weight during examination stress as a teenager. She had normal secondary sexual features, weight: 47.9 kg and height: 1.55 m (BMI 19.9).
Investigation and management
After stopping the contraceptive pill her endocrine profile revealed hypogonadotrophic hypogonadism (Oestradiol <37 pmol/L, Luteinising Hormone: 2U/L, Follicle Stimulating Hormone: 5U/L) and mild central hypothyroidism [Thyroid Stimulating Hormone (TSH): 1.35 mU/L, Free thyroxine (FT_4): 10.1 pmol/L]. Bone density scan revealed spinal osteopenia (T-score −2.4) and MRI scan revealed normal pituitary. Because of ongoing tiredness, she had a trial of Levothyroxine 50 mcg daily. Her TSH level fell to 0.02 mU/L while her FT_4 rose above normal (23.8 pmol/L). Upon advice we gradually withdrew the Levothyroxine. Her TSH rose to 0.1 mU/L and FT_4 fell to 18.0 pmol/L on 25 mcg/day of Levothyroxine, and further stabilised (TSH 0.47 mU/L, FT_4 9.6 pmol/L), six weeks after stopping Levothyroxine. She declined oestrogen

replacement because of side-effects but continued calcium-vitamin D supplements. Weight-loss-related hypothalamic dysfunction was discussed. Her weight is currently 50.4 kg and her thyroid function remains stable.
Conclusion
This case highlights the interplay between weight loss and hypothalamic function. The resultant endocrine abnormalities, especially thyroid, could be protective mechanisms and may revert to normal with weight gain. Hasty hormone replacement therapy could make things worse.

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Reproduction

EP88

An Unusual but Important Cause of Hyperandrogenism in Women

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A 61 year-old woman presented with a two year history of facial hirsutism and frontal balding. She did not report voice change or acne. Menarche was at age 14 with regular menses until a hysterectomy (with ovarian preservation) for menorrhagia aged 29. She had a past medical history of T2DM and gastric bypass surgery. She was not on androgenic medication. Examination revealed clinical hyperandrogenism with androgenic alopecia and hirsutism (FG score 20) but no cliteromegaly. There were no clinical features of Cushings or other endocrine disease. Secondary sexual characteristics and remaining examination were normal. Blood tests revealed marked biochemical hyperandrogenism; testosterone 4.7 nmol/l(0–2), androstenedione 1.6 nmol/l(0–9), DHEAS 0.8 umol/l(0.4–4.7), oestrogen <70 pmol/l with gonadotrophins in the postmenopausal range. Prolactin, AFP, and hCG were normal. Testosterone was non-suppressible on LDDST. MRI adrenals and US ovaries were unremarkable with normal-size ovaries. She was initially diagnosed with ovarian hyperthecosis and commenced on monthly LHRH-analogue therapy. However on LHRH-analogue therapy, her testosterone levels, although now lower were still raised (2.3–3.8 nmol/l). Given the rapidity of the hirsutism, the normal-sized ovaries on US, and the failure to suppress adequately with LHRH-analogues, the diagnosis was questioned. Subsequent MRI offered superior resolution for ovarian pathology and revealed a 1 cm left ovarian mass. She subsequently underwent laparoscopic bilateral salpingo-oophorectomy and the histopathology identified an ovarian Leydig cell tumour. Six months post-surgery her testosterone remains undetectable off LHRH-analogues, with gradual improvement of her hirsutism and stabilisation of her alopecia. Leydig cell tumours make up $<0.5\%$ of ovarian tumours with over a third presenting with overt clinical hyperandrogenism. This case also demonstrates the need to question a previous diagnosis (ovarian hyperthecosis) when features are inconsistent, and to determine appropriate management based on the entire clinical picture and not imaging alone.

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EP89

From Antipsychotic-related Hyperprolactinemia to Klinefelter Syndrome: Taking the Patient as a Whole

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A 59 year old man was referred to our endocrine service for persistently elevated prolactin levels. He did not report any headache, visual disturbance or galactorrhoea. He was diagnosed with schizophrenia in 1994 and was tried on different antiphychotic drugs until established on a combination of Amisulpride and Clozapine 11 years later. For the past years, his prolactin levels had been elevated ranging from 1477 to 1972 milliunit/L [60–300]. Further history revealed that he had been found to have mild normocytic normochromic anaemia for which no cause had been identified. On direct questioning, the patient reported erectile dysfunction and loss of morning erections. He had not been sexually active since 1993. In addition, he had a history of un-provoked deep venous thrombosis and pulmonary embolism, hyperlipidaemia and diabetes mellitus type 2. Physical examination showed a pale and tall man with central obesity and scanty body and facial hair. There was no gynaecomastia on breast examination. Testicular examination was not performed initially. Blood results showed a prolactin level of 1199 milliunit/L [60–300] negative for macroprolactin, total testosterone of 1.7 nmol/L [10–30], LH of 11.5 IU/L [2–12] and FSH of 28.6 IU/L [1.7–8]. A diagnosis of primary hypogonadism was made and chromosome analysis revealed 47,XXY consistent with Klinefelter syndrome. Transdermal testosterone replacement was commenced and both testosterone and haemoglobin fully normalised. This case illustrates several points. Firstly, the diagnosis of Klinefelter syndrome may be missed due to very variable phenotypical presentations. Secondly, testosterone deficiency can be a cause of unexplained anaemia. Thirdly, patients with Klinefelter syndrome can develop different co-morbidities later in life that are unrelated to testosterone deficiency. These include pulmonary diseases, thromboembolic disease, cancers and diabetes mellitus. Also, the risk of psychosis, autism and ADHD appears to be increased in patients with Klinefelter syndrome.

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EP90

A rare case of primary hypogonadism and partial hypopituitarism in klinefelter syndrome

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Klinefelter syndrome is the most common genetic cause of primary hypogonadism in men. Upto 80% have karyotype 47 XXY. It can present with a wide range of phenotypical and biochemical abnormalities. It is also known to be associated with certain autoimmune diseases. We describe a rare case of Klinefelter syndrome with partial hypopituitarism and suggest screening with full pituitary profile plus dynamics tests at first presentation if clinical suspicion is high. A 36 year old male was having infertility work up and incidetally found to have micro orchidism. Subsequent biochemical assays show mildly raised FSH, LH and normal testosterone level and azoospermia on semen analysis. There were no symptoms of adrenal insufficiency initially but 9 am cortisol was low at 108 nmol/L. Prolatin, TSH and IGF1 were with normal limits but Synacthen test was slightly suboptimal with cortisol level of 429 nmol/L at 30 minutes and 487 nmol/L at 60 minutes. However patient was symptomatic hence Insulin stress test was performed which mounted a suboptimal cortisol response with a peak of 370 mmol/L (normal >450 mmol/L) despite adequate and symptomatic hypoglycemia of 1.6 mmol/L indicative of ACTH deficiency. Growth hormone deficiency was revealed with a peak response of 0.16 mmol/L (normal >6.6 mmol/L). Karotyping confirmed diagnosis of Klinefelter Syndrome along with Growth hormone and ACTH deficiency. Patient was initiated on adequate replacement therapy with Growth Hormone and Hydrocortisone with good response and referred to fertility clinic. Klinefelter syndrome with partial hypopituitarism is rarely been described in the literature. It is unclear how these conditions could be linked to each other and more studies and case reports will be needed to establish a link. We recommend performing panel of pituitary profile and subsequent dynamic testing in symptomatic patients with new diagnosis of Klinefelter Syndrome.

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EP91

An unusual case of hirsutism, baldness and ovarian leiomyoma

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A 60-year-old woman presented to the endocrine clinic with significant hirsutism and male-pattern baldness, progressive since the menopause 5 years earlier. She was otherwise fit and well. Testing revealed an elevated serum testosterone of 14.2 nmol/L. A CT scan revealed a large malignant 19 cm mass arising from the left adnexa, a large fibroid uterus and 2 small masses in the left kidney. Other abdominal organs were normal with no visible ascites. With the presumption of malignancy, she underwent a staging laparotomy under the gynaecology oncology team, which included a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Histology confirmed multiple intra-mural uterine leiomyomas and a benign ovarian leiomyoma confined to the capsule of different morphology. Her

symptoms of hirsutism resolved within 5 months of surgery with significant head hair re-growth. A repeat testosterone was returned to normal (0.3 nmol/L). Ovarian leiomyomas are rare constituting $<1\%$ of benign ovarian tumours. The majority co-exist with uterine leiomyomas. Leiomyomas constitute smooth muscle overgrowth and are not usually related to androgen production. There have only been sporadic reports of virilisation and ovarian leiomyomas in the literature. Androgen production in conjunction with ovarian leiomyoma, is considered secondary to thecal cell irritation by tumour growth. This case serves to remind that androgenic symptoms in the postmenopausal woman may be related to ovarian tumours and should be considered in the differential diagnosis. Surgical treatment is highly successful, returning most women to their norm. Incidentally, the renal masses in this case may reflect a wider case of leiomyomatous disease.

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EP92

A rare case of bilateral testicular epidermoid cysts in a patient with Klinefelter's syndrome

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Introduction
Klinefelter's syndrome (KFS) is associated with an increased risk of certain malignancies; including leukemia, breast cancer and mediastinal germ cell tumours. Testicular tumours are uncommon. Epidermoid cysts are benign tumours of hair-growing areas. Testicular epidermoid cysts are very rare and account for 1–2% of all testicular tumours. We report a rare case of bilateral epidermoid cysts in a patient with Klinefelter's syndrome.
Case
A 30-year-old man diagnosed with Klinefelter's syndrome in childhood was referred to the endocrine outpatient clinic to initiate testosterone replacement in view of worsening symptoms of tiredness and erectile dysfunction. On physical examination he had gynecomastia and both his testes were very hard with irregular surfaces.
Investigation and management
His laboratory tests showed elevated Luteinising Hormone and Follicle Stimulating Hormone levels and a very low testosterone level (2.7 nmol/L) consistent with primary gonadal failure. An ultrasound scan of his testes demonstrated bilateral solid testicular masses with no blood flow seen within the lesions. There was very little identifiable normal testicular tissue seen within the right testis (the right testicular mass measured 34 mm$\times$27 mm$\times$23 mm and the left testicular mass measured 9 mm$\times$5 mm). A CT scan of his chest, abdomen and pelvis, along with serum alpha-fetoprotein and beta-human chorionic gonadotrophin levels were all normal. He went on to have a right orchiectomy. The histology revealed features characteristic of an epidermoid cyst. The left testis remained unchanged over three years of ultrasound surveillance. The patient was put on testosterone replacement.
Discussion
There are very few cases of testicular epidermoid cyst reported in the literature and even fewer cases are bilateral or found in patients with Klinefelter's syndrome. The decision between surgical or conservative management is controversial because of the differential diagnosis, the possibility of diagnostic errors and the issues of fertility.

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EP93

The challenge of diagnosing 5-alpha-reductase deficiency post gonadectomy

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A 35 year old woman was referred to Endocrinology after imaging investigating unexplained pyrexia demonstrated an absent uterus. She was of Pakistani origin and was born phenotypically female with reported normal female genitalia. During late teenage years she experienced virilisation with deepening voice, increased pubic and axillary hair and clitoromegaly. She had absent breast development. Her parents were first cousins and siblings were unaffected. Investigations in Pakistan demonstrated a high testosterone and 'small ovaries and uterus'. She underwent removal of a possible testicle to her right labia majora and a 'rudimentary uterus'. Following surgery she did not receive ongoing medical care. She had a socially difficult adolescence, and moved to the United Kingdom aged 28. At presentation to Endocrinology she had a blind-ending vagina, clitoromegaly, and minimal breast tissue. Hormonal evaluation reflected primary hypogonadism. Chromosomal analysis demonstrated an 46 XY karyotype. Urinary steroid profile indicated 5-alpha-reductase deficiency with reduced androsterone at 194 ug/24h (mean 1526 ug/24h) and increased aetiocholanolone at 3124 ug/24h (mean 1308 ug/24h). Analysis of the SRD5A2 gene revealed a homozygous point mutation for c.698+1G>T at the exon 4/intron 4 boundary. Result Normal range (male) Testosterone (nmol/L) 1.5 8.4–28.7 SHBG (nmol/L) 77.4 13–71 Oestrodiol (pmol/L)

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EP94

Pubertal arrest and hypoplastic reproductive organs in a 22-year-old female with a prolactinoma

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Case
We report the case of a 22-year-old lady with pubertal arrest from a prolactinoma. She was diagnosed with a prolactinoma elsewhere at age 16 years when she presented with headaches, visual field defects and primary amenorrhea. She attained pubarche and telarche at ages 11 and 14 respectively. Pituitary MRI showed a 22 mm pituitary mass. Initial tests 6 years ago showed high prolactin, secondary hypothyroidism, low IGF-1 and gonadotropins. Cabergoline and levothyroxine were prescribed which she used for a year then stopped when headaches resolved. She did not go for follow-up because of financial constraints. She presented at our facility with recurrence of headaches and persistent primary amenorrhea. She had no visual field defects or galactorrhea. Normal female secondary sexual characteristics were present. Hormonal profile showed marked hyperprolactinemia and persistent pan-hypopituitarism. Growth hormone assay and repeat pituitary MRI were not done due to financial constraints. Pelvic sonography showed hypoplastic uterus and ovaries. She was re-commenced on cabergoline, hydrocortisone and levothyroxine. Repeat hormonal profile after 6 months showed normalization of prolactin and thyroid function. Estrogen however remained low despite normal progesterone and gonadotropins. She remained amenorrheic as at 8 months after recommencing treatment.
Discussion
The prolonged under-stimulation of the ovaries by the gonadotrophins and the persistent hyperprolactinemia likely contributed to the underdevelopment of the ovaries and uterus. It is uncertain if she will attain menstruation and fertility, considering the prolonged course through the critical adolescence period. It is important to promptly evaluate, educate and treat persons with hypoprolactinemia-related pubertal disorders to prevent persistent dysfunction of the pituitary-gonadal axis.

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EP95

Localisation Challenges in Postmenopausal Hyperandrogenism

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A 48 years old lady with BMI of 46kg/m^2 was postmenopausal since age 45. Due to abdominal discomfort she had an abdominal CT, which incidentally identified bilateral adrenal adenoma (9 mm on right, 18 mm on left, with fat content). This

resulted in Endocrinology referral and a history of gradually worsening hirsuitism was uncovered. Her hyperandrogenism was confirmed biochemically with markedly elevated testosterone at 6.5 nmol/l (0.0–1.8), leading to a search for adrenal and ovarian source. However, her adrenal androgens were normal: Androstenedione 3.3 nmol/l (0.9–4.8), DHEAS 0.9 μmol/l (0.7–7.8), and 17-OH progesterone 3.4 nmol/l (0.0–5.0). FSH and LH were of post-menopausal levels. Thyroid function test, ACTH, 9am Cortisol, prolactin and CA125 were normal. Her body habitus limited ultrasound and MRI-abdomen-pelvis was performed. Again, adenomatous adrenals with signal-drop were identified. Interestingly, the ovaries were reported to have normal appearance with small follicles. A delineation between adrenal and ovarian aetiology was unclear at this stage while patient preference and body habitus limited the option for specific venous sampling. An overnight dexamethasone suppression test had led to cortisol suppression to 38 nmol/l excluding Cushing's syndrome, while testosterone remained non-suppressed at 5.8 nmol/l, suggesting an ovarian androgen source. Following this, a trial of GnRH analogue (subcutaneous Leuprorelin 3.75 mg monthly) had led to suppression and normalisation of testosterone (0.6 nmol/l) after 2 months, consistent with ovarian hyperandrogenism. However, she found GnRH analogue intolerable due to flushing, precluding its adoption as long-term therapeutic measure. Laparoscopic bilateral oophorectomy then resulted in persistent normalisation of post-op testosterone level (0.6 nmol/L at 2 month), further affirming the ovarian source. Contrary to the MRI findings, her ovaries were found to be significantly large (17 and 23 cm^3) for a postmenopausal lady, who typically has mean ovarian volume of 1.3–3.7 cm^3. Therefore, a diagnosis of hyperthecosis was entertained.

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EP96

Unusual Cause of Severe Hyponatraemia

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Introduction
Testosterone replacement therapy is the standard treatment for hypogonadism. However, there are also serious side effects which clinicians should be aware of. Here we present a case of unusual side effect related to testosterone therapy.
Case history
A 90 year-old gentleman attended A&E with gradually worsening confusion and dyspnoea. His breathing had deteriorated in the last week with marked decrease in exercise tolerance. Investigations for multiple osteoporotic vertebral fractures, four months ago led to the diagnosis of hypergonadotrophic hypogonadism (Testosterone 4.8 nmol/l, LH: 30.5 U/l, FSH: 20.9 U/l). 18 days before admission, he was commenced on 20 mg Tostran 2% gel. Past medical history, included GORD and mildly impaired LV systolic function. He was not on any treatment for impaired LV function. On clinical assessment, he was found to have signs of decompensated heart failure.
Investigations
Na: 113 mmol/l (was 132 mmol/l before testosterone treatment), rest of U&E, LFT and TFT were normal. Plasma osmolality: 240 mosm/kg, Urinary Na: $<$20 mmol/l, Urine Osmolality: 335 mosm/kg, Cortisol: 405 nmol/l, Testosterone level 17.2 nmol/l. CXR: ill-defined airspace opacification within both lower zones with cardiomegaly.
Management
Hypervolaemic Hyponatraemia secondary to heart failure was diagnosed. 1L fluid restriction and IV diuretics (for 6 days) had failed to improve sodium level. However 48 hours after discontinuation of testosterone, heart failure symptoms and signs had improved dramatically and sodium concentration increased by 11 mmol/l.
Discussion
Testosterone can cause fluid retention and could exacerbate incipient heart failure. Endocrine society recommends against testosterone therapy in men with uncontrolled heart failure. Some studies have however revealed that testosterone improves exercise capacity in hypogonadal men with heart failure.
Conclusion
Careful risk and benefit assessment should be conducted before commencing testosterone replacement in elderly patients with heart failure.

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Thyroid

EP97

The Use of Salvage Radiotherapy and Radioactive Iodine in a Case of Recurrent Metastatic Papillary Thyroid Cancer: A Case Report

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Background
Thyroid carcinoma consists of just 1% of all malignancies but is the commonest malignant endocrine tumour. Papillary thyroid carcinoma is the most common form of thyroid carcinoma consisting of 80% of all cases. There are very few case reports in the literature of papillary thyroid cancers presenting with distant to the pelvic organs. Distant metastases are noted in 1–3% of patients with thyroid cancer at initial diagnosis.
Clinical case
A 69-year-old woman was diagnosed with metastatic papillary thyroid carcinoma, having presented with post-menopausal vaginal bleeding. She had a total thyroidectomy with histology showing papillary thyroid carcinoma pT3N1b with maximum tumour diameter of 70 mm. She then underwent a Total Abdominal Hysterectomy (TAH) and Bilateral salpingo-oophorectomy (BSO). The resected histology showed metastatic papillary thyroid adenocarcinoma in the uterus measuring 2.9 cm $\times$ 2.4 cm. Finally, the patient was then treated with radioactive iodine (RAI). No evidence of disease was detected during follow up, until 2 years later, the patient re-presented with further episodes of vaginal bleeding. On internal pelvic examination, a vaginal polyp was visualized and a biopsy showed metastatic papillary thyroid carcinoma. Subsequent CT Thorax Abdomen Pelvis (TAP) showed a vaginal vault lesion, left adnexal mass (4.4 cm $\times$ 4 cm) as well as right paratracheal lymph nodes (the biggest measuring 1.4 cm). The patient received 50.4Gy in 28 fractions of EBRT followed by 5500 MBq of RAI. Her post-therapy whole body iodine uptake scan showed no iodine-avid metastases with no residual functioning thyroid tissue. Her post-therapy PET scan showed complete remission of her disease recurrence following the EBRT and RAI.
Conclusion
Papillary thyroid carcinoma presenting initially with distant pelvic metastases makes this case rare. However, the complete remission of the disease recurrence with the use of EBRT and RAI makes this case truly remarkable.

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EP98

Alternatives to surgery for patients with stridor secondary to multinodular goitres?

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An 88 year old female presented with gradually worsening stridor and dysphagia. Her past medical history was complex and included included ischaemic heart disease and atrial fibrillation treated with warfarin. She had been initially referred for enlargement of her lonstanding goitre 6 years ago (2012) with investigations demonstrating a suppressed TSH and a normal FNA cytology. Respiratory function tests did not show any significant extra thoracic compression, but her CT scan confirmed a large goitre with retrosternal extension, tracheal deviation and narrowing (see image). Although surgery was considered, in view of her multiple medical comorbidities, she underwent radioiodine treatment as she had been relatively asymptomatic. There was limited improvement in the goitre size but her thyroid function normalised. In 2017, she re-presented with a gradual increase in the size of her goitre associated with new onset stridor and dysphagia. In view of her comorbidities, anti coagulation, and the risks of surgery, she had tracheal stenting which successfully improved her symptoms. Diffusely enlarged thyroid glands can cause compressive symptoms involving the trachea, oesophagus and recurrent laryngeal nerve. These symptoms are usually treated with surgical removal of all or part of goitre which not only requires high level of expertise but may also lead to significant complications. In elderly patients with multiple comorbidities, tracheal stenting could be considered as a useful alternative to surgery or radio-iodine.

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EP99

When locoregional recurrences (LRR) in papillary thyroid carcinoma (PTC) can be repeatedly eliminated by ultrasound-guided percutaneous ethanol ablation (UPEA) and appropriate use of dermatologic surgery, cervical skin metastases (SM) in low risk PTC (LRPTC) can be associated with an excellent long-term prognosis

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Background
UPEA for LRR in PTC was introduced in 1993 (JCEM 96:2717, 2011). It is not appreciated that such non-invasive ablations can often be repeated over decades (Surgery 154:1448, 2013). Skin metastases (SM) from thyroid carcinoma are typically associated with disseminated disease; average survival after SM diagnosis is 19 months (JAAD 36:531, 1997). Our case provides insights into managing LRR and SM in LRPTC.
Clinical case
In 2004, an open biopsy of a lateral neck mass in a 48-year old man revealed neck nodal metastasis (NNM) due to PTC. He had a near-total thyroidectomy and node dissection, confirming a right lobar 8 mm primary and two ipsilateral NNM; MACIS score was 4.08 and pTNM (8^{th} edition) stage I. During 2004, he received two doses of ^{131}I for neck uptake (cumulative dose 12,506 MBq). In 2007, he underwent right multi-compartmental dissection for NNM. In 2008, serum thyroglobulin on T4-suppression was 4.8 ng/ml and US-guided biopsy confirmed a right level III NNM. He was referred to our institution for consideration of UPEA. During his initial evaluation, two sites of LRR were treated with UPEA and subsequently disappeared. During 2010–16, he developed another six NNM, also treated with UPEA, resulting in disappearance of all ablated lesions. In 2016, an SM in right neck was removed by dermatologic surgery. Following this, two further SM were excised with negative margins, one after Mohs surgery. He is now disease-free at 14.4 postoperative years.
Conclusions
Despite three neck surgeries and 12,506 MBq of ^{131}I, this man with LRPTC, during postoperative years 4–14, developed eight separate sites of LRR and three sites of SM. All eleven sites were treated with minimally invasive outpatient procedures. In contrast to earlier reports, this patient is likely to survive long beyond his present 14 postoperative years.

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EP100

Spontaneous Ovarian Hyperstimulation Syndrome in Pregnancy: A Rare Presentation of Hypothyroidism

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Clinical Case
A 27 year-old primigravida was referred for gynaecology assessment after her 12 week booking ultrasound scan showed a multiloculated cystic mass in the Pouch of Douglas. She reported fatigue, dry skin and constipation for several months. She had no past medical history and took no regular medications. She had conceived naturally, and her periods were previously regular. There was a family history of hypothyroidism in her sister. She emigrated from India 3 years earlier with her husband.
Investigations and management
Pelvic MRI at 14 weeks' gestation revealed bilateral multicystic ovarian masses (measuring 9.2×5.6 cm and 7.8×5.1 cm). Ca125 was mildly elevated, a non-specific finding in pregnancy. A serial MRI, performed at 20 weeks' gestation, showed enlargement of both masses (14.4×6.4 cm and 15.6×7.5 cm), suggestive of spontaneous ovarian hyperstimulation syndrome. Thyroid function tests were performed and revealed severe primary hypothyroidism (free T4 <5, NR 9-21 pmol/L; TSH >200, NR 0.35–5 mU/L]. Anti-TPO antibodies were strongly positive (1597.1, NR <6 U/mL). TSH receptor antibodies were in the normal range (1.1, NR 0.0–1.9 U/L). Following assessment at the endocrine antenatal clinic, levothyroxine 100mcg daily was commenced. The patient returned to India for the remainder of her pregnancy, therefore her remaining clinical course is unknown.
Discussion
Rapidly enlarging ovarian cysts are a rare consequence of severe hypothyroidism and represent a form of spontaneous ovarian hyperstimulation syndrome. This has been reported previously in the context of pregnancy. The mechanisms of cyst enlargement include TSH stimulation of ovarian FSH receptors, and, in some cases, activating mutations of the FSH receptor. Cyst shrinkage and resolution is reported with successful treatment of hypothyroidism. The impact of untreated maternal hypothyroidism on fetal development is not well defined however impaired neurocognitive development has been reported in offspring.

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EP101

Relapse of Graves' Disease and Severe Thyroid Eye Disease following Total Thyroidectomy

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Total thyroidectomy is one of the definitive treatments for Graves' disease. This case describes the rare recurrence of thyroid eye disease (TED) and thyrotoxicosis due to thyroid remnant tissue. We present a 58 year old lady with Graves' disease first seen in 2005 with positive TSH receptor antibodies (TSHRab) level of 2.5 U/l. She had a large multinodular goiter at presentation and this continued to grow with retrosternal extension and subsequent tracheal deviation. She underwent total thyroidectomy in 2014. At this point she had mild TED treated with lubricant eye drops. She had stable thyroid functions on levothyroxine (125 micrograms od). Two years later she developed sudden thyrotoxicosis and her thyroxine replacement was stopped. Her thyrotoxicosis persisted and she developed worsening TED needing opthalmology input. Her TSHRab levels were now high at 26.4 U/l. Technetium (Tc) thyroid uptake scan demonstrated mediastinal thyroid remnant low in the thoracic cavity. Her thyroid remnant would have required thoracotomy for removal. She was commenced on Carbimazole titration therapy with coninued ophthalmology input. Her latest thyroid functions are normal on Carbimazole with stable eye disease. She is now considering radioactive iodine tharapy under steroid cover as definitive therapy for her Graves' disease. This case describes the importance of considering thyroid remnant tissue in recurrent. TED and Graves' disease post thyroidectomy.

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EP102

A case of severe Graves's ophthalmopathy

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Grave's orbitopathy typically presents with symptoms of proptosis and diplopia. It is an autoimmune condition of retro-orbital tissues. We present a case in which the management of orbitopathy has been complex and required escalation to immunosuppression and consideration of biological agents. A 34-year-old female presented with 2 weeks of diplopia. She had normal visual acuity with no past medical or family history. She never smoked. Thyroid eye disease was diagnosed, she was started on selenium and commenced on pulsed methylprednisolone. At the time thyroid function showed TSH <0.01 U/ml, FT4 >65 ng/dl, FT3 45 ng/dl. TSH receptor antibodies were positive at 2.9 unit/ml (NR <0.4). She was commenced on Carbimazole 60mg and responded very quickly. 10 weeks into into her pulsed methylprednisolone course and despite biochemical euthyroidism she developed worsening visual acuity and colour vision and required bilateral orbital decompression. Post-operatively she was commenced on oral prednisolone 50 mg daily and mycophenolate, which was uptitrated to 1.5 g twice daily. Colour vision has recovered but she has restrictive strabismus in the left eye with visual acuity of 6/18 pinhole (6/9 unaided) and acuity in the right eye 6/18 pinhole (6/12 unaided). Prednisolone has not been weaned beyond 30 mg daily as the patient develops worsening diplopia at every such attempt. She remains biochemically euthyroid on block and replace regimen. Rituximab is being explored as second-line immunosuppressant. Thyroidectomy is considered; however, its role in euthyroidism with low antibody titres remains controversial. The management of Grave's orbitopathy is complex. Sometimes it is difficult to predict the course of Grave's ophthalmopathy from that of thyrotoxicosis and many of the treatments cause their own side effects. In severe cases of ophthalmopathy aggressive treatment is required for sight-saving measures. This case however highlights the importance of the multidisciplinary approach in managing severe cases to ensure early diagnosis and treatment.

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EP103

High dose levothyroxine combined with repetitive transcranial magnetic stimulation for bipolar disorder with DIO2 gene polymorphisms

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23-year-old woman presented with rapid cycling bipolar disorder (RCBPD) with alternating episodes of mixed affective states, hypomania & severe depression. Quetiapine was initiated & discontinued due to side effects. Levothyroxine was started & gradually increased to 500mcg daily. This was coupled with 6 weeks of low frequency (LF) rTMS. She was clinically euthyroid. TSH <0.01 miu/l (0.27–4.2), fT4 37.1 pmol/l (12–22), fT3 8.4 pmol/l (3.1–6.8), rT3 30 ng/dL (10–24). Genetics: heterozygote polymorphism DIO2 (rs225014; T92A). A 53-year-old woman presented with refractory RCBPD. Quetiapine was started, increased to 700 mg with no response. Levothyroxine was added and increased to 750 mcgs daily & rTMS was commenced. She was clinically euthyroid. TSH <0.01 miu/l, fT4 77.3 pmol/l, fT3 11.7 pmol/l, rT3 79 ng/dl. Genetics: heterozygote polymorphism DIO2 (rs225014; T92A). Both cases achieved sustained remission for 7 months and 9 months respectively. We describe 2 cases of RCBPD with SNPs of DIO2, resistant to standard treatments who achieved sustained remission using HDL. This combination, we believe, has not been described before. Previous data highlights safety and effectiveness of supra-physiological doses of Levothyroxine in promoting remission. Heterozygote polymorphism DIO2 gene is associated 1.6-fold risk of bipolar disorder. Both patients had this and elevated fT4:fT3 ratio. Low circulating T4 weakens effectiveness of DIO2's ability to generate T3 in the brain. We speculate high dose Levothyroxine helps to overcome this relative deficiency while robust inactivating deiodinases in the periphery help to protect from systemic thyrotoxicosis. RCBPD is a dangerous condition and has a 1: 6.5 mortality rate. Standard treatments are ineffective. We venture that HDL overcomes relative thyroid deficiency in patients with RCBPD while robust inactivating deiodinases in the periphery protect from systemic thyrotoxicosis. DIO2 is found in the brain. We speculate that RCBPD is a predominantly thyroid condition.

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EP104

Myxoedema coma – importance of early recognition!

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A 70-year-old lady, with a background of primary hypothyroidism presented to the Emergency department with a 1 day history of confusion and drowsiness. On examination her HR was 58 bpm, temperature 28 degrees celsius. She was resuscitated with warm fluids and bair hugger, whilst also given broad spectrum intravenous antibiotics. Her blood results showed an AKI with creatinine of 213 and was treated for a NSTEMI with a troponin on admission of 1770, rising to 2190. ECG showed prolonged QTc with 1st degree heart block. Her thyroid function tests on admission showed TSH 236.98, free T4 6.1, free T3 2.7. Thyroid peroxidase antibodies were strongly positive. Short Synacthen test was normal. A diagnosis of myxoedema coma was made and she was treated with IV Liothyronine and oral thyroxine and IV hydrocortisone. Due to severe obtundation, she required ITU admission with ventilatory and inotropic support. The dose of liothyroinine was carefully titrated, in view of risk of causing further ischaemia in view of presentation with NSTEMI. She made a good recovery, with TSH 1.07 and free T4 24.4 on discharge. She was discharged on oral Levothyroxine 175 micrograms, with education on the importance of good medication adherence. Myxoedema is an important life threatening manifestation of hypothyroidism, which can result in fluid retention, negative inotropism and chronotropism with cardiogenic shock, stupor and coma. In severe cases, the overall mortality is 25–60%. Prompt recognition and effective management of such patients is key to improving prognosis.

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EP105

Recovery of thyroid function after 26 years post thyroidectomy for Graves' disease with evidence of active remnants

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A 56 years old lady was referred to our endocrine service for further management of levothyroxine replacement. She was diagnosed with Graves' disease 26 years ago and underwent thyroidectomy as definite treatment. Post-operatively, she was commenced on 100mcg of levothyroxine and continued to have regular follow up with her GP. It was noted that her levothyroxine dose had to be reduced to 50 mcg daily over a period of 10 years due to persistently suppressed TSH levels with free T4 levels within the normal range. In January 2015, her thyroid function showed a picture suggestive of over-replacement with TSH <0.01 (0.3–4.2) milliunit/l, free T3 of 6.3 (2.5–5.7) pmol/l and free T4 of 24 (9–23) pmol/l. Therefore, her thyroxin dose was further decreased to 50 mcg on alternate days by her GP. In November 2016, she was seen in our endocrine clinic while on the above levothyroxine regimen. She didn't report any symptoms related to thyrotoxicosis or over-replacement. Repeat thyroid function sowed TSH of 0.01 (0.3–4.2) milliunit/l, free T3 of 4.3 (2.5–5.7) pmol/l, free T4 of 14.5 (9–23) pmol/l and a positive TSH receptor antibody level of 2.9 (<0.4) unit/ml. Levothyroxine was withheld and she underwent a thyroid ultrasound that showed three hypervascular nodules (thyroid remnants) in the thyroid bed. A technetium uptake scan was suggestive of multiple toxic nodules: two large nodules in the left with high increased tracer uptake and another smaller nodule in the right mid pole of the thyroid with low level activity. Four months after discontinuing thyroxin, the patient was clinically euthyroid with TSH of 2.25 (0.3–4.2) milliunit/l, free of T3 3.7 (2.5–5.7) pmol/l and free T4 of 10 (9–23) pmol/l. She remains under regular surveillance as she is at high risk of Graves' disease recurrence.

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EP106

A rare case of carbimazole related Rhabdomyolysis

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Introduction
There are many causes of rhabdomyolysis, with Carbimazole, the first line treatment for hyperthyroidism, being one of the rarest. Rhabdomyolysis can potentially cause significant morbidity and mortality if left untreated.
Case
A 38 year old female presented to the Emergency Department in May 2018 with a 4 day history of severe sudden onset bilateral thigh pain. Her only prior health problem was primary hyperthyroidism for which she had been receiving Carbimazole therapy (started December 2017). At diagnosis, Thyroid Stimulating Hormone (TSH) was 0.05 mU/l and T4 46.4 pmol/l. On admission, her Creatinine Kinase (CK) was found to be 32721 U/l. Common causes of rhabdomyolysis were excluded including: bacterial and viral infection, autoimmune, heatstroke, alcohol excess and trauma. Her CK gradually decreased after stopping Carbimazole and receiving intravenous fluids. She stayed in hospital for 8 days and was discharged with a CK of 383 U/l. Prior to discharge Propylthiouracil therapy was commenced as her thyroid function tests worsened (TSH <0.05 mU/l, T4 20.0 pmol/l) from being euthyroid. This was used as a bridging therapy prior to definitive surgical cure. Whilst on Propylthiouracil her CK remained low.
Discussion
Rhabdomyolysis secondary to anti-thyroid drugs (including Propylthiouracil) appears to be relatively rare, though the specific incidences have not been researched. The mechanism of Carbimazole induced Rhabdomyolysis is not fully understood. Other case reports have suggested that rapid improvement of hyperthyroidism may be a contributing factor. However, our case goes against this theory as the patient had been on Carbimazole for over 6 months and was still thyrotoxic when diagnosed with rhabdomyolysis.
Conclusion
Although not yet fully understood, this rare cause of rhabdomyolysis is important for clinicians to be aware of because of its simple yet effective management of stopping the medication.

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EP107

Neonatal thyrotoxicosis caused by persistently high levels of thyroid stimulating antibodies in autoimmune hypothyroidism

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Neonatal immune hyperthyroidism is a rare but potentially fatal condition. It occurs in 1–5% of infants born to women with Graves' disease (GD). We present

a case of neonatal thyrotoxicosis due to maternal hypothyroidism secondary to radioactive iodine treatment for Graves' disease. A new-born female at 13-days of age was readmitted due to maternal concerns. She noted the baby to be jittery, unsettled, tachycardic and tachypnoeic. The infant was born via a spontaneous vaginal delivery at 38 + 1 weeks' gestation to a gravida 1, para 1 mother. The infant's birthweight was 2750g. The mother was taking thyroxine. She was commenced on intravenous antibiotics for presumed sepsis, however despite normal inflammatory markers and cultures, the infant continued to deteriorate. The tachycardia persisted and she started vomiting so was admitted to Special Care. Thyroid function tests were done which confirmed neonatal hyperthyroidism (TSH <0.05 T4 124) due to high level of TBII (Thyrotropin binding Inhibitory Immunoglobulin) of 6.2. The mother had positive TBII of 17.8 IU/L at 32 weeks gestation during pregnancy. The baby was then commenced on carbimazole and propranolol. Clinically the symptoms resolved and as her bloods (including TFT) were improving, she was discharged on 13/4/18 with a weaning dose of carbimazole. Last TFTs were normal with TSH 2.1, T3 5.8 and T4 11. She is being regularly followed up as an outpatient and she has been fully weaned off her carbimazole.

Conclusion

This case illustrates the importance of measuring TBII during prenatal care and follow up in order to help early diagnosis of neonatal hyperthyroidism and improve neonatal outcomes. Both Obstetricians and paediatricians need to be aware of the importance of a high TBII at the end of pregnancy to predict the risk of neonatal hypothyroidism in autoimmune hypothyroidism secondary to radioiodine treatment.

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EP108

Growth failure due to severe primary hypothyroidism

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Introduction

Thyroid hormones are critical for early brain development, somatic growth, and bone and pubertal maturation. Primary hypothyroidism is a well-known cause of poor linear growth in children. This case highlights role of thyroid hormone replacement to improve final height in the setting of profound hypothyroidism.

Case

We report the case of 16 years old Caucasian girl initially evaluated for primary amenorrhea and delayed growth of 139 cm putting her below the second centile on growth chart. She has had delayed growth throughout which was considered as developmental delay however other developmental milestones were acquired appropriately. Her non-identical twin brother had height of 180 cm. Mother and father's reported height was 156 cm and 182 cm respectively. On examination she had normal external genitalia and breast Tanner stage 2. Her Body Mass Index was 20. Investigation showed profound hypothyroidism with serum TSH of over 100 miu/l (0.35–4.5 miu/l) and free T4 of 0.8 pmol/l (10.5–26 pmol/l). MRI Pituitary was normal. She was started on Levothyroxin. Her linear growth velocity immediately improved to up to 16 cm/year, and she rapidly progressed through puberty, achieving menarche 18 months after starting treatment. She was also started on Growth Hormone replacement following Insulin Tolerance Test which showed partial Growth Hormone deficiency with peak level 8 mcg/l. She gained further 4.5 cm height giving a final height 158.5 cm at the age of 18 years which is close to the calculated Mid Parental Height of 162 cm.

Conclusion

Early diagnosis and treatment is essential to achieve final height in children with severe Primary Hypothyroidism, as late diagnosis and treatment during puberty invariably results in incomplete catch up growth and attenuated final height. Our patient responded well to Levothyroxin alone with further benefit from Growth Hormone replacement.

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EP109

A curious case of paralysis

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A 32 year old Polish gentleman presented following a collapse with preserved consciousness. Preceding this he was noted to have had a rapid deterioration in mobility with worsening weakness in all four limbs. On further questioning the patient had been diagnosed with hyperthyroidism two months previously and was being treated with propylthiouracil. Positive examination findings included tachycardia with upper limb weakness with 2/5 power bilaterally and lower limbs weakness with 1/5 power. Biochemically, he was found to have a potassium result initially of 3.2 which dropped to 1.8 shortly after treatment with peripheral potassium replacement. His electrocardiogram showed sinus tachycardia and global T wave inversion. His thyroid function tests remained deranged with TSH <0.03 mU/l and T4 of 32.5 pmol/l. He was diagnosed with Thyrotoxic Periodic Paralysis and was admitted to the Intensive Care Unit for close observation and central potassium replacement. His paralysis improved with treatment and he was discharged with close follow up. Thyrotoxic Periodic Paralysis (TPP) is an uncommon acquired presentation in the context of hyperthyroidism, usually manifesting as sudden attacks of painless muscle weakness without loss of consciousness. The pathogenesis is not well understood but it has been postulated thyroid hormone increases tissue responsiveness to beta-adrenergic stimulation, which increases sodium-potassium ATPase activity on skeletal muscle membrane. This drives potassium into cells, leading to hyperpolarisation of the muscle membrane and relative inexcitability of the muscle fibres. As in this case, the acute treatment of TPP is replacement of potassium. A reduction in potassium is often observed after initial replacement therapy and rebound hyperkalaemia, a common problem occurring in those treated for TPP, should be avoided. Ultimately the return to a euthyroid state eliminates further attacks of Thyrotoxic Periodic Paralysis. This uncommon case demonstrates a disabling but readily treated condition essentially being caused by a state of hyperthyroidism.

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EP110

Use of Carbimazole in a Thyrotoxic Patient known to have Aplastic anaemia

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Introduction

Carbimazole is a first line antithyroid drug for thyrotoxicosis management in UK. Its main but rare complications include allergic reaction and risk of neutropenia. Here we discuss the lesser reported situation in which a thyrotoxic patient who is in a remission from Aplastic anaemia was treated with Carbimazole.

Case Report

Out patient was seen in Ambulatory care with symptoms of heart failure along with tachycardia. Thyroid blood test showed severe thyrotoxicosis. After discussion with Haematologist and ENT surgeons, patient was consented to have low dose Carbimazole with monitoring for any clinical or biochemical relapse of Aplastic anaemia. She became euthyroid both clinically and biochemically within 6 months of starting carbimazole without any relapse of her aplastic anaemia and was referred to surgeons for definitive treatment.

Discussion

The cases of carbimazole induced neutropenia are well known in literature. Likely mechanism involves bone marrow suppression along with the effect on GCSF. There is a limited data available regarding use of carbimazole in a thyrotoxic patient who has a past medical history of treated Aplastic anaemia.

Conclusion

Although the option of admitting patient and to use Lugol's iodine before surgery could be used but there was a high risk of thyroid storm. Therefore, treated with low dose carbimazole with bloods monitoring twice per week for any signs of Aplastic anaemia relapse. This case shows that carbomazole in low dose can be used with caution and for a limited time in thyrotoxic patient with history of Aplastic anaemia as a bridge to definitive treatment in the form of surgery.

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EP111

Protean Presentations of Severe Hypothyroidism: Decompensated Liver Disease as an Unusual Co-presentation

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We report a 51-year old lady presenting to hospital with a 3 week history of abdominal and peripheral swelling. Mentation was slow and noted to be pale on admission. She also reported feeling cold, lethargic, reduced exercise tolerance and constipation. She had no prior medical problems, no regular medications and working till the day prior to admission in a garden centre. She was an ex-smoker,

teetotal and there was a family history of hypothyroidism. Physical assessment revealed pallor, ascites, generalised oedema, hypothyroid facies, mild jaundice, slow mentation and delayed reflex relaxation. TSH was >100 mU/L and fT4 <3 pmols/L. Started on Levothyroxine with improvement in overall clinical status and mentation with titration of dose. Random Cortisol 405 mmols/L. Liver function tests were significantly deranged with a cholestatic picture, and she had a small pericardial effusion on echocardiogram. CT done for ongoing abdominal discomfort showed a cirrhotic liver and large volume of ascites. Ultrasound showed gross ascites, chronic liver disease features, patent portal vein and normal flow with splenic varices. Gastroscopy showed grade 1 varices. Antinuclear and anti-mitochondrial (AMA) antibody tests were positive, with AMA titre >1/640; highly suggestive of Primary Biliary Cirrhosis. Abdominal paracentesis was undertaken and she received a blood transfusion, was started on Spironolactone. Her condition gradually improved and she was discharged, with referral to the Regional Liver Unit for consideration of transplantation.

Discussion

The co-existence of hypothyroidism with other autoimmune conditions is well known. What is unique here is the co-presentation of severe hypothyroidism with established cirrhosis and decompensated liver failure related to Primary Biliary Cirrhosis. While ascites is known to occur in patients with severe hypothyroidism it is important to consider an alternative explanation, particularly if there is no improvement in ascites and liver function with normalisation of thyroid function.

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EP112

Antibody interference in thyroid assay in a patient with abnormal Thyroid function test

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An 88 year-old male was referred to Endocrine Clinic with abnormal thyroid function test (TFT); free T4:fT4: 36.9pmol/L (NR:11-23) and a normal TSH:2.51mU/L (NR:0.35-5). Atrial Fibrilation was diagnosed recently and was on Apixiban and Bisoprolol. He had history of prostate cancer, hypertension, oesophagitis, cervical spondylosis, splenectomy and CKD3. He felt well apart from slight heartburn. He was a retired motor engineer. He had no family history of thyroid disease and never had TFT checked in the past. Examination was normal. he was followed up in clinic regularly and free T4 was found to be persistently raised (fT4 from 55 to 59pmol/L with normal TSH from December 2017 till March 2018) on 4 occasions. He remained clinically euthyroid and was not commenced on treatment. Thyroid antibodies were negative. Other blood tests, and pituitary/brain MRI were normal. Thyroid hormone assay interference was suspected; His TFTs were repeated at a different laboratory, Wythenshawe Hospital in Manchester which revealed normal TFT (f T4 12.0, f T3 3.1, TSH 1.90). Family was screened for the possibility of thyroid hormone resistance; two daughters were found to have normal TFT. Raised fT4 from blood tests carried out at Royal Preston Hospital was a result of assay interference and the patient was discharged from the clinic. This case report highlights that Thyroid hormone assay interference should be considered where TFTs do not fit the clinical picture or are incongruent to each other. Occasionally, TFTs can be difficult to interpret; careful reassessment of thyroid status is required. Failure to reach the correct diagnosis may result in inappropriate management. Following reassessment of possible confounding factors, if TFTs remain discordant, consider assay interference as a possible cause. After this, consider screening for genetic disorders of the hypothalamic-pituitary-thyroid axis – rare causes of anomalous TFTs.

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EP113

Non-thyroidal illness syndrome in the setting of amiodarone use, a diagnostic challenge

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Non-thyroidal illness syndrome is the alteration in thyroid function tests (TFTs) that occurs in critically ill patients, including those using thyrotoxic medications. Therefore, it is a challenge to interpret thyroid function tests in a critically ill patient on amiodarone. Case of 66-year-old male with history of heart failure with reduced ejection fraction, atrial fibrillation, and hypertension who presented to the emergency room due to progressive shortness of breath. Physical examination with tachycardia, positive jugular venous distention, crackles on pulmonary auscultation and tachypnea requiring eventual endotracheal intubation. Electrocardiogram showed atrial fibrillation with fast ventricular response. Afterwards, he was transferred to the coronary intensive care unit (CCU) where Amiodarone was started due to lack of response to other rate control medications. TFTs were requested prior initiation of amiodarone which showed thyroid stimulating hormone at 0.01 uIU/ml. During admission, patient developed ventilator associated pneumonia with subsequent septic shock. Thyroid function tests were repeated in 1 week and revealed thyroid stimulating hormone (TSH) at 0.008 uIU/ml, free T4 at 3.2 ng/dl and total T3 at 124 ng/dl. Amiodarone was discontinued and methimazole therapy was started. In the following days, clinical deterioration progressed resulting in the patient's death. Hyperthyroidism can be significantly detrimental, particularly in critically ill patients with cardiac disease. In contrast, Non-thyroidal illness syndrome needs to be considered in patients with low/normal T3 levels which are expected to be elevated in hyperthyroidism. The most common hormone pattern of Non-thyroidal illness syndrome is low total T3 and free T3 levels, with normal T4 and TSH levels. However, patients on amiodarone therapy might present with increased free T4 levels due to decreased conversion of T4 to T3. This case illustrates the challenges of interpretation of TFTs in a critically ill patient on amiodarone.

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EP114

Marine Lenhart syndrome: A case report

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A 19-year-old male referred from the Ophthalmology clinic on account of staring gaze of 1 year, and an anterior neck swelling which was noticed 3 months before presentation. Anterior neck progressively increased in size. It was not painful. No history of dysphagia, voice changes or yellowness of the eyes. There was positive history of heat intolerance, weight loss despite increased appetite, irritability, restlessness, palpitations and hyperdefeacation. No history of exposure to goitrogens or chronic drug use. Patient consumes iodized salt. No skin discolouration. No known family history of anterior neck swelling or similar swelling in the neighborhood. On examination, patient was restless, palms were warm and moist, with fine tremors of outstretched hands. He had bilateral lid retraction, lid lag and exophthalmos. There was anterior neck swelling which moved with swallowing but not with tongue protrusion. Swelling was firm, non-tender, nodular, not attached to underlying structures or overlying skin. No retrosternal extension or scalp swelling. No cervical lymph node enlargement. Pulse rate was 104bpm and regular. Results of investigations revealed, free T3-30.3 (3.1–6.8) pmol/L, free T4 – 88.2 (12.0–22.0) pmol/L, sTSH – 0.01 (0.27–4.2) uIU/ml. An assessment of toxic multinodular goiter was made, to rule out Graves' disease. He was subsequently placed on tab carbimazole and propranolol and to review with results of investigations. On follow up, results of investigations revealed PCV 36%, total white cell count of 4300/cmm3, neutrophils 42%, lymphocytes 58% and ESR of >150 mm/hr. Thyroid ultrasound scan showed diffusely enlarged thyroid gland with multiple nodules. Thyroid antibodies were markedly elevated; anti TPO Ab- 855.20 (0-35) IU/ml, anti Tg Ab- 420.0 (up to 40) IU/ml, TSHR Ab- 27.13 (< 1.75) IU/L. A final assessment of Marine-Lenhart syndrome was made. Patient is being planned for surgical intervention once thyroid function normalizes.

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EP115

Case Series of unusual presentations of Thyrotoxicosis

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Thyrotoxicosis is a relatively common condition affecting 1–2% of women and 0.1–0.2% of men. Common symptoms are usually straightforward and easily identified. Rarer presenting features such as confusion and headache have been published in the literature as case reports. We hereby report two cases of Graves Thyrotoxicosis presenting unusually and therefore misleading the initial diagnostic pathway. The first case is a 45-year-old female with a 4-day history of headache which started acutely. She described a daily morning headache which

improved through the day. Other symptoms were dizziness, weakness, nausea, palpitations and intermittent dyspnoea. She was noted to be in sinus tachycardia. Other examination findings were unremarkable. Thyroid Function Tests requested in view of the tachycardia showed TSH < 0.01 mu/L, FT4 > 155 pmol/L and FT3 30.8 pmol/L. TPO antibodies were negative, but TSH Receptor antibodies were positive. The patient was safely discharged on Carbimazole 40mg OD. At 6 weeks clinic review, she complained of no headache and had TSH < 0.01 mu/L and FT4 16.4 pmol/L. The second case is a 48-year-old male who presented acutely confused. He was found naked and doubly incontinent by family. He was noted to have intermittent word-finding difficulties and therefore referred to the Stroke Consultant who requested routine TFTs. A sinus tachycardia was noted. The working diagnosis was Encephalitis and the patient had CT brain and Lumbar Puncture which revealed CSF with 41 white cells (mainly Lymphocytes) and 32 red cells, with negative culture and PCR. After 2 days, the TFTs results showed undetectable TSH and FT4 48 pmol/L. TSH Receptor antibody was strongly positive. The patient was started on carbimazole 20mg OD and at 3-month review, he improved clinically and had TSH 2.09 and FT4 8.6.

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EP116

Unusual thyroid dysfunction in a patient treated with Alemtuzumab for Relapsing-remitting Multiple sclerosis

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Introduction

Alemtuzumab is humanized monoclonal antibody used in the treatment of relapsing–remitting multiple sclerosis (MS). The 5year incidence of thyroid adverse events in phase-3 clinical trials is up-to 40.7%. In most cases, the thyroid dysfunction is mild and easily manageable. Hyperthyroidism, particularly Graves' disease (GD) is more common. We describe a case of unusual thyroid dysfunction in a patient treated with Alemtuzumab.

Case

A 30years old female diagnosed with relapsing-remitting MS at the age of 15yr was initially treated with Natalizumab. She conceived and was off treatment between November 2014 and April 2016. She was commenced on Alemtuzumab in April 2016. In October 2017 she had routine follow-up Thyroid function tests (TFT) which showed supressed TSH < 0.02 mIU/L, normal free T4 (fT4) and free T3 (fT3) at 19.1pmol/L and 6.6 pmol/L respectively suggesting subclinical hyperthyroidism. As she was asymptomatic, monitoring was continued. Repeat TFT's in a months' time showed TSH = 11.32 mIU/L and fT4 = 5.8 pmol/L suggesting overt hypothyroidism. Thyroid peroxidase antibodies = 61.7 (0–34) and TSH receptor antibodies > 40. She was subsequently commenced on Levothyroxine 75 mcg OD. Repeat TFT's after 3weeks revealed TSH = 0.09 mIU/L and fT4 = 37.5 pmol/L. Levothyroxine dose was reduced to 25 mcg OD. Further interval testing showed TSH < 0.02 mIU/L and fT4 = 39.4 pmol/L; hence Levothyroxine was stopped. Isotope uptake scan showed increased (6.5%) uniform uptake suggesting GD. Subsequent TFT's 2weeks later showed overt thyrotoxicosis with TSH < 0.02 mIU/L, fT4 = 56.8 pmol/L and fT3 = 29.3 pmol/L. At this stage, she was symptomatic and so commenced on Propylthiouracil 150 mg BD and Propranolol 10 mg TDS. Clinically she improved and recent TFTs showed TSH = 0.11 mIU/L, fT4 = 13.5 pmol/L and fT3 = 7 pmol/L.

Conclusion

Thyroid dysfunction is the commonest autoimmune disease in patients treated with Alemtuzumab for relapsing-remitting MS. GD being the most common subtype. Our patient initially had a hypothyroid phase subsequently converting into hyperthyroidism, which is uncommon.

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EP117

The extreme of graves' disease

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Graves disease is an autoimmune disorder of the thyroid gland. It is a very rare condition that a Graves patient presents with spontaneous hypothyroidism. Hypothyroidism during the course of Graves' disease occurs commonly due to radio-iodine (RAI) therapy or thyroidectomy. It may also develop after anti-thyroid drug (ATD) treatment. We present a case of 44 years old Emarati male heavy smoker diagnosed with graves' disease after thyrotoxic manifestations, associated with graves opthalmopathy. He received a course of ATD for one year then reverted to euthyroid state. Patient was off treatment for 18months when he started to have thyrotoxic manifestations again with high TPO and thyroglobulin antibodies. Patient was restarted on carbimazole (required high dose). RAI uptake scan showed diffuse uptake. Two years later while he was still on carbimazole he developed graves dermopathy and improved on topical steroid. Later steroid pulse therapy was started for the worsening Graves opthalmopathy. Planned for surgery after opthalmopathy improvement, but patient refused surgery and opted to stay on ATD. Carbimazole tapered according to thyroid function test (TFT) until he was off ATD for 2 months. Then he had developed hypothyroid manifestation. TFT revealed hypothyrodism, started on thyroxine adjusted according to TFT reaching 200mcg currently. This case highlights the importance of spontaneous development of hypothyroidism in hyperthyroid graves. Hyper- and hypothyroidism occur depending on the predominant antibody during that period. Switching between stimulating and blocking antibodies. Thioamides have been associated with decreased levels of stimulating-TRAb, allowing blocking-TRAb to dominate. Nonetheless, the switch from one end of the spectrum to the other remains difficult to predict. Also its worth to mention that, our patient had the extreme of hyperthyroidism to hypothyroidism with out sever symptoms of both.

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EP118

Goitre with Unusual Thyroid Function Test and Congenital Hypothyroidism Due to DUOX2 Gene Mutation And Iodine Deficiency

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Introduction

Dual oxidase 2(DUOX2) is NADPH oxidase complex at the apical membrane of the thyroid follicular cells which produce H2O2 required for thyroid hormone synthesis. DUOX2 gene mutation is a well known cause of congenital hypothyroidism (CH), the phenotype depends on the type of mutation and environmental factors.

Case

We present a case of 29 years old female delivered a male baby with large neonatal goitre and severe CH who was started immediately on levothyroxine.Maternal thyroid function test (TFTs) showed an unusual pattern of TSH being marginally elevated at 6.4 miu/L (0.35–4.5 miu/L), Free T3 in upper normal range at 6.8 pmol/L (range 3.9–6.8 pmol/L) and Low Free T44.8 pmol/L(10.5–26 pmol/L). Similar pattern was seen when confirmed with another laboratory excluding assay interference. Random Cortisol was 579 nmol/L and serum Prolactin was appropriately raised at 1268 mIU/L being post-partum. She had benign goitre for more than 7 years. She was vegetarian and was vegan for 13 years. Subsequent TFTs in both mother and baby showed an elevated free T3/T4 ratio suggesting inadequate iodination either due to lack iodine or dyshormonogenesis. Spot urine Iodine and 24 hours urinary iodine measurement in mother showed profoundly low iodine level (0.05 micromol) suggesting severe iodine deficiency. Gene sequencing showed rare, novel heterozygous DUOX2 missense mutation (c.3956C > G, p.T1319R) in both baby and mother. Three half-brothers of the child had Wild type Variants. She was commenced on oral iodine supplement with dose titration according to urine Iodine excretion.

Discussion

DUOX2 mutation being heterozygous is less likely to cause CH however combined with environmental factor like maternal dietary Iodine deficiency could explain overt dyshormogenesis in the baby and unusual thyroid function tests with longstanding goitre in the mother. Other siblings not carrying the mutation didn't develop neonatal goitre although they were exposed to similar maternal iodine deficiency.

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EP119

Pembrolizumab Induced Thyroiditis in patient with Graves' Disease Kamal AbouglilaDiabetes centre, University Hospital of North Durham

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New immune-modulatory therapies for malignancies have transformed their management with significantly enhanced survival outcomes. Pembrolizumab is an antibody against the programmed-death-1 molecule that increases the

cytotoxic function of T-cells with excellent tumor response rates. Endocrinopathies including thyroiditis are an increasingly recognized side effect of this medication. We describe a unique a case where Thyroiditis occurred as a result of treatment with Pembrolizumab. A 55-yr-old male a known case of eu-thyroid Graves' disease (TSH 1.11 mU/l (NR 0.35–5.5), FT4 11 nmol/L (NR 9–23) on maintained dose of 5 mg of carbimazole for the last 6 months, who was receiving treatment with pembrolizumab for malignant squamous lung cancer develop painless Thyroiditis after 8 weeks of a taking this treatment. He developed symptoms of thyroiditis, which it confirmed in his repeat TFT (TSH 53.2 mU/l, FT4 4 nmol/L and FT3 3 nmmol/L). Thyroid peroxidase Antibodies were positive $>$1300 ku/L and TSH Binding site inhibition antibodies is 22.5 U/L. He was treated with Levothyroxine treatment to control his symptoms and normalised his thyroid function test. He did require a higher dose of thyroxine treatment (250 mcg daily) compared to standard dose replacement of thyroxine which was 1.6 mcg/kg. His thyroid function remains stable on current treatment and Pembrolizumab treatment had been withdrawn following deterioration of lung cancer.

Conclusions

Thyroid dysfunction is common in cancer patients treated with pembrolizumab. Reversible destructive thyroiditis and overt hypothyroidism are the most common clinical presentations. The mechanism of thyroid destruction appears independent of thyroid autoantibodies and may include T cell or monocyte-mediated pathways. To our knowledge this is the first case report of pembrolizumab induced thyroiditis in GD. Given the short duration onset and rate of development of thyroid dysfunction, regular frequent testing of TFTs should be performed.

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Featured Clinical Cases

CC1

Pitfalls in the diagnosis of an infant with 46,XX DSD with Congenital Adrenal Hyperplasia due to Cytochrome P450 Oxidoreductase deficiency - the value of simultaneous genetic analysis to the diagnosis in DSD

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Background
Congenital adrenal hyperplasia (CAH) is the underlying diagnosis in most newborns presenting with 46,XX disorders of sex development (DSD). Cytochrome P450 oxidoreductase deficiency (PORD) is a rare form of CAH caused by inactivating mutations in the POR gene. The hallmark feature of PORD is combined sex-steroid and glucocorticoid deficiency due to impairment of CYP17A1 and CYP21A2. Skeletal malformations resembling the Antley-Bixler Syndrome phenotype are common in PORD.
Case report
Clitoromegaly, fused labia majora and a single opening was noted after term birth of the infant (46,XX). No overt skeletal malformations were evident. Her 17OHP was normal (3.6 nmol/l) with insufficient cortisol increase after synacthen (baseline: 210 nmol/l; peak: 239 nmol/l). Under the clinical assumption of CAH due to CYP21A2 deficiency, hydrocortisone and fludrocortisone replacement was initated. Urinary steroid profiling performed by an external service lab at 7 days of age showed high amounts of 16-alpha hydroxypregnenolone, but steroid metabolites typically raised in common forms of CAH were not elevated. Next generation sequencing employing a multi-gene DSD panel revealed a homozygous mutation (p.Gly539Arg) of the *POR*gene previously reported in four 46,XY DSD patients.
Summary and conclusions
This is the first 46,XX patient carrying the p.Gly539Arg *POR*mutation, which was shown to have a mild effect on CYP17A1 17-alpha hydroxylase catalytic activity *in vitro*. The diagnosis of PORD via urinary steroid profiling in a clinical service lab was not achieved, although impaired 17,20 lyase activity was suggested by accumulation of pregnenolone metabolites in an early neonatal sample. This case highlights the benefits for the management of DSD patients when employing a simultaneous approach of clinical, biochemical and genetic testing. Secondly, it emphasizes the challenges in establishing the correct diagnosis of rare steroidogenic disorders via urinary steroid profiling, in particular in neonatal samples.

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CC2

Missplicing due to a silent exonic substitution in the T-box transcription factor TBX19 resulting in Isolated ACTH deficiency

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Background
Congenital isolated ACTH deficiency (IAD) is a rare condition characterised by low plasma ACTH and serum cortisol with normal production of other pituitary hormones. TBX19 is a T-box pituitary restricted transcription factor important for POMC gene transcription and terminal differentiation of POMC-expressing cells. *TBX19* gene mutations have been shown to cause neonatal-onset congenital IAD. To date 25 mutations in *TBX19* have been described, five of which are splicing mutations. The previously described splice mutations are all within canonical splice site motifs.
Patient and methods
We report a neonate of Romanian origin, who presented at 15 hours of life with respiratory arrest and hypoglycaemia. Over the following 2 weeks, recurrent hypoglycaemia was documented. On examination, he had normal male genitalia and no hyperpigmentation. Biochemical investigations revealed IAD, with undetectable serum cortisol (cortisol <1 µg/dl; NR 7.8–26.2) and inappropriate plasma ACTH levels (22.1 pg/ml; NR 4.7–48.8). He responded to hydrocortisone treatment and continues on replacement. Patient DNA was analysed by a HaloPlex next-generation sequencing array targeting genes for adrenal insufficiency. The effect of the novel mutation was assessed by an *in vitro* splicing assay, pET01 ExonTrap cloning vector (MobiTec), comparing wild type and mutant heterologous minigenes.
Results
A novel homozygous synonymous mutation p.Thr96= (g.1:168260482; c.288G>A; rs376493164; allele frequency $1x10^{-5}$, no homozygous) was found in exon 2 of the *TBX19* gene. In an *in vitro* splicing assay, the mutation resulted in aberrant splicing of exon 2 giving rise to a mutant mRNA transcript whereas the wild-type vector spliced exon 2 normally.
Conclusion
We have identified a silent *TBX19* mutation causing aberrant splicing as the likely cause of isolated ACTH deficiency in the patient. The predicted protein product would be non-functional in keeping with the complete loss of cortisol production and early presentation in the patient.

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CC3

A Rare Genetic Variant of Type 1 Familial Hypocalciuric Hypercalcaemia (FHH)

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A 60 year old Caucasian woman was referred to endocrine clinic with persistent hypercalcaemia between 2.8 and 2.9 mmol/l (2.2–2.6), with inappropriately normal PTH at 7 pmol/l (1.48–7.63). Her hypercalcaemia was noted first in 2008. She had no signs or symptoms associated with hypercalcemia. However, she has a strong family history of hypercalcaemia, where her mother required Cinacalcet to control her hypercalcaemia despite two previous parathyroid resections. She has 3 children in their 30's who had not had calcium screening before. However, the son had a renal stone. There was no history of pancreatitis. Her creatinine was 105 mmol/l (eGFR 47). She received replacement for her 25OH vitamin D deficiency at 20.8 nmol/l. Under the context of strong family history of hypercalcaemia with normohormonal hyperparathyroidism, further tests were done to explore the possibility of FHH, or syndromic presentation such as Multiple Endocrine Neoplasia. Her anterior pituitary axes and plasma normetanephrine/metanephrine were normal. However, her urine calcium:creatinine clearance ratio was <0.01 with urine volume of 965ml/day leading to suspicion for FHH. A genetic screening revealed a heterogenous pathogenic variant in CASR: c.488C>G, p.(Pro163Arg), which is an extremely rare variant not listed in population frequency databases. This has previously been reported in patient with Tropical Chronic Pancreatitis (Murugaian, et al., 2008). Segregation studies in three families performed by the Oxford Genetics laboratory has shown the variant to segregate with hypercalcaemia in two affected first-degree relatives in each family. This is consistent with the clinical presentation in this patient. Therefore, we seek to offer her first-degree relatives genetic counselling and screening. This further emphasise the importance of investigating the calcium:creatinine clearance ratio and genetic testing for CASR mutations, (Familial hypocalciuric hypercalcaemia panel and isolated familial hyperparathyroidism panel) in the context of strong family history to avoid unwarranted parathyroid surgery.

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CC4

A novel case of primary hypogonadism in female associated with Loeys-Dietz syndrome type 5

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A 31-year-old female was referred to Endocrinology clinic for review of her hypergonadotrophic-hypogonadism. She had cleft palate operation at age 3. At age 15y lack of pubertal signs prompted investigations showing XX genotype, FSH:120 IU/L, LH:32 IU/L and low E2. She was started on cyclo-progynova (elsewhere). She has tall stature, span 2.5 cm longer than height, bifid uvula, arachnodactyly with positive 'wrist sign', mild scoliosis, pectus excavatum and reduced muscle mass. There are no joint laxity, delayed wound healing, muscle hypotonia and reduced subcutaneous fat. Normal smell and hearing is reported. There is no family history of similar body habitus or fertility issues. While hypogonadotrophic-hypogonadism is well-known to be associated with cleft palate, this has not been described in hypergonadotrophic-hypogonadism. Exome sequencing identified a transforming growth factor-β3 *(TGFB3)* missense variant of a well-conserved amino-acid (NM_003239:exon7:c.C1118A:p.S373Y, not present in gnomAD) resulting in a predicted 'probably-damaging' change (PolyPhen2). Mutations in *TGFB3* cause Loeys-Dietz syndrome type-5 (LDS5, Rienhoff-syndrome) characterised by skeletal overgrowth, arterial tortuosity, aneurysms, hypertelorism, bifid uvula, cleft palate, mitral valve disease, cervical spine instability and clubfoot deformity (not all features occur in all patients). TGFB3 plays key role in development of skeletal muscle, blood vessels, bone growth, wound healing and gonadal development as demonstrated in mouse models. While several families are described with male/female transmission of the disease, more recently, variants of *TGFB3* gene have been associated with male infertility. There is no reported case associated with female hypogonadism. Gonadal failure could be an inconsistent feature of LDS5. Cardiac MRI, performed due to this new diagnosis, shows normal aorta and no significant valvular disease. Her parents are invited for genetic screening. Further studies are needed to prove the pathogenic role of this variant and establish the link, if any, to human female primary gonadal failure.

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CC5

A second GH Receptor pseudoexon mutation causing frameshift and severe postnatal growth failure

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Background
GH Insensitivity (GHI) is usually caused by mutations in the GH receptor (*GHR*). Our centre previously described the first *GHR* pseudoexon mutation (42700896A>G, c. 618+792A>G). Inclusion of this 108bp pseudoexon is predicted to lead to in-frame insertion of 36 amino acid residues in the dimerization domain of the *GHR*. This results in defective trafficking rather than impaired signalling, causing partial loss-of-function and moderate postnatal growth failure (Height SDS −3.3 to −6.0).
Objective and hypothesis
Pseudoexons outnumber exons by 10–1 and variants in them may be a major contributor to disease burden in short stature.
Methods
We designed a custom short stature gene panel that interrogates both coding and non-coding regions. In vitro splicing assays were performed using an exon trap vector (pET01, MoBiTec GmbH, Germany).
Results
We identified a homozygous GHR variant (g.5:42700940T>G, c.618+836T>G) in an Italian patient with severe postnatal growth failure (Height SDS −7.5) and classical Laron phenotype. Both unaffected, non-consanguineous parents were heterozygous for the mutation. This mutation was 44bp downstream of the previous pseudoexon mutation and predicted *in silico* to create a donor splice site. Splicing analysis confirmed inclusion of the 152bp mutant pseudoexon in all transcripts with no evidence of normal splicing in contrast to the wild-type pseudoexon which showed no such inclusion. Inclusion of the pseudoexon will lead to a frameshift and premature truncation of the mRNA.
Discussion
This novel pseudoexon inclusion event will result in a truncated message which is likely destroyed by nonsense mediated mRNA decay, in keeping with the patient's undetectable GHBP levels. This will lead to complete loss of function, consistent with the more severe growth failure observed compared to the previously described pseudoexon. Our findings highlight the potential for such splicing events to be more commonly causal for this and other rare diseases.

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CC6

What lies beneath: cutaneous Kaposi's sarcoma as a first manifestation of ectopic ACTH-dependent Cushing's syndrome

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Introduction
Immune dysregulation is a feature of Cushing's syndrome (CS). We report a case of CS that presented with rapidly developing cutaneous Kaposi's sarcoma (KS).
Case description
A previously well 59-year-old heterosexual man presented with a two-month history of proximal muscle weakness, recurrent mouth ulcers, and purplish skin lesions. He had a background history of hypertension. Skin biopsies were compatible with KS. History of past residence in human herpesvirus 8 (HHV-8) endemic countries was confirmed. Blood tests revealed T cell lymphopenia with low CD4+ and CD8+ lymphocytes and normal natural killer and B cells. He underwent investigations in four hospital departments (neurology, dermatology, oncology and immunology) but no underlying predisposing factor was identified. Four months later, centripetal obesity, facial plethora and dorsocervical fat pad were noted, associated with hypokalaemia, which triggered a referral to the endocrine department. Work-up showed a significantly elevated serum cortisol with non-suppressibility after 1 mg overnight dexamethasone (794 nmol/l) and very high level of urinary free cortisol (>3050 nmol/24 h). ACTH dependency was confirmed by increased ACTH (100.3 pg/ml, reference range 7–63), alongside elevated androstenedione and DHEAS. A gadolinium-enhanced pituitary MRI scan showed a 5 mm focal hypointensity, possibly compatible with a pituitary microadenoma. However, there was no ACTH or cortisol response to CRH and also no central:peripheral ACTH gradient before and after CRH on inferior petrosal sinus sampling, consistent with an ectopic ACTH source. Cross-sectional imaging, FDG-PET and ^{68}Ga-DOTATE PET did not reveal any radiological evidence of a putative ACTH-producing lesion. Metyrapone treatment was commenced in advance of a scheduled bilateral adrenalectomy.
Conclusion
KS is an angioproliferative disorder related to HHV-8 infection. Severe immunodeficiency, such as with AIDS or the use of immunosuppressants, predisposes to KS. We propose that CS should be included in the differential diagnosis of immunodeficiency.

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CC7

An Atypical Presentation of Multiple Endocrine Neoplasia Type 1

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A sixty-four year old man presented for investigation of mild hypercalcaemia (2.68 mmol/L) incidentally discovered during preoperative workup for elective

removal of a testicular cyst. He had no family history of renal stones. His younger brother had undergone a parathyroidectomy at the age of 60. His father died in a road traffic accident aged 54. His mother was 84 and had no history of endocrine disease. Urine calcium:creatinine excretion ratio was 0.0207, excluding familial hypocalciuric hypercalcaemia. Bone densitometry revealed osteopaenia of the non-dominant radius. Ultrasound identified a single left superior parathyroid adenoma, concordant with an area of increased uptake and delayed washout on sestaMIBI. Gut hormone profile showed elevations of chromogranin B (233 pmol/L (0–150 pmol/L)) and pancreatic polypeptide (575 pmol/L (0–300)). Further discussion revealed that his brother's hypercalcaemia had only resolved following the resection of multiple parathyroid glands. Imaging of the pancreas with MRI, Endoscopic Ultrasound and gallium DOTATATE confirmed the presence of multiple lesions with features characteristic of neuroendocrine tumours. MRI of the pituitary was unremarkable. Genetic analysis identified a novel pathogenic *MEN1* missense variant, (p.Ile360Phe) (c.1078A>T) which lies in helix 16 of menin, a structurally important region of the protein which forms part of the wall of the JunD binding pocket. JunD, in the absence of menin, switches from a growth suppressor to a growth promoter. Almost all cases of MEN-1 present with hyperparathyroidism before the age of 50, with most cases occurring between 20 and 40 years. Sporadic hyperparathyroidism typically presents in patients over 60 years old. MEN-1 typically causes multiple gland disease, while over 80% of patients with sporadic hyperparathyroidism localise to a single gland. This case demonstrates that older age at presentation and localisation to a single gland does not exclude the diagnosis of MEN-1.

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CC8

Clinical and biochemical acromegaly associated with pituitary FSHomas

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Acromegaly is a clinical manifestation of excessive peripheral growth hormone (GH) action. Most cases result from pituitary somatotroph adenomas displaying varying degrees of GH immunoreactivity. Occasionally, GH is cosecreted with a second hormone from adenomas containing mixed cell populations (e.g. somatolactotroph tumours). Coexistence of multiple discrete adenomas, identical or distinct in hormone secretion, is infrequent. In very rare cases, acromegaly results from neuroendocrine tumours producing ectopic GHRH or even GH. We describe three male patients (P1-3) presenting with clinical acromegaly associated with elevated IGF1 (1.43×, 1.64× and 2.64× ULN), elevated basal GH (1.5, 2.4, 5.6 mcg/L) and failure to suppress GH after a 75 g glucose load (nadir GH 1.2, 2.5, 7.6 mcg/L). P1 also had elevated FSH (107 U/L [1.0–10.1]), associated clinically with macro-orchidism, whilst FSH was mildly elevated in P2, and just below ULN in P3. All three patients had pituitary macroadenomas with abundant FSH immunoreactivity, no or low LH immunoreactivity and, contrary to clinical presentation, no GH immunoreactivity (verified externally). All three expressed SF-1 ubiquitously but not Pit-1. Consistent with immunoreactivity, culture medium from a primary adenoma culture contained abundant FSH but undetectable GH. Cross sectional imaging (with functional imaging in 2/3 patients) failed to identify an ectopic source of GHRH or GH secretion. No circulating GHRH was detectable by immunoassay in any of the patients. Serial follow up of P1 and P2 revealed persistent mild biochemical acromegaly, elevated FSH and slowly enlarging pituitary remnants. A six-month trial of somatostatin analogue in P1 was unsuccessful in suppressing IGF1 or GH. Both patients underwent further tumour resection, with histology again demonstrating gonadotroph adenomas only. In summary, we describe a previously unreported phenomenon of clinical and biochemical acromegaly associated with pure gonadatroph adenomas, without evidence of somatotroph adenomas or hyperplasia, and without evidence of ectopic GH/GHRH secretion.

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CC9

A rare case of a pituitary tumour with orbital invasion and moderate propotosis

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A 61 year old female, without significant medical history, presented to her optometrist in Feb 2018 with clouding of vision and left sided proptosis. Opthalmic examination showed vision 6/7.5 right and 6/9 left eye, 3 mm proptosis on the left and diplopia on upward and right lateral gaze. Brain MRI demonstrated 6.3×5.6×5.8 cm lesion centered in the clivus and pituitary fossa, expanding in all directions; the bulk of the lesion was in the left parasellar region, encasing a patent cavernous segment of the internal carotid artery and displacing the left arm of the circle of Willis superiorly; anteriorly it was insinuating through the left superior orbital fissure and optic canal, displacing and partially encasing the left optic nerve medially, with a small component protruding into the left orbital compartment and causing moderate proptosis; posteriorly it was plastered against the surface of the midbrain and pons, partially encasing the basilar artery. Anterior pituitary profile was unremarkable. Transsphenoidal biopsy in March 2018 was consistent with a pituitary adenoma, with negative hormone staining and focally increased Ki-67 (up to 6–7%). CT neck/chest/abdo/pelvis showed 2 tiny indeterminate lung nodules, which have been discussed with respiratory and likely benign, however repeat interval imaging is advised. Transsphenoidal substantial biopsy was performed in May 2018 and pathology confirmed previous findings with Ki-67 10%. Postoperative assessment thus far reveals unchanged vision and persistent left sided proptosis. Immediate management plans include external radiotherapy and careful follow up of the lung lesions. This is a very rare case of a pituitary tumour invading the orbit causing left sided proptosis. The most common tumours with orbital invasion are meningiomas; this finding is exceptionally rare with pituitary adenomas. The prognosis of pituitary tumours with orbital invasion is considered poor, depending significantly on histology, extent of invasion and tumour burden.

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CC10

Thyroid hormone pattern in Familial Dysalbuminemic Hyperthyroxinemia (R218H mutation) on different assay platforms

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Introduction
Familial dysalbuminemic hyperthyroxinemia (FDH) is characterized by artefactual hyperthyroxinemia caused by enhanced binding affinity of thyroxine to the mutant albumin. However little is known about how FDH affects the measurement of thyroid hormones, especially FT3, across many assay platforms.
Methods
Forty-eight genetically confirmed FDH patients (R218H mutation) had FT4 and FT3 measured with 1-step (ADVIA CENTAUR®, Siemens IMMULITE® 2500, Roche ELECSYS E170) and 2-step (DELFIA®, Abbott Diagnostics

Table 1 Results of Free T4 and Free T3 in FDH expressed as % above upper limit (ULN) of reference range across different assays

ASSAYS	*n*	% FT4 Results Above ULN	*n*	% FT3 Results Above ULN
ADVIA CENTAUR®	48	87.5	44	40.9
Siemens IMMULITE®	7	0	7	14.2
Roche ELECSYS	14	92.8	13	30.7
DELFIA®	48	47.9	36	25
Abbott ARCHITECT®	8	75	8	25
VITROS	7	0	7	0
DIASORIN	7	0	7	0
BECKMAN	8	100		

(ARCHITECT®), VITROS, DIASORIN and BECKMAN) assays. Measured levels were compared to the upper limit of reference range. Patients with concomitant thyroid disease and assay interference were excluded.

Results

Both FT4 was raised in the majority of platforms (CENTAUR® 78.8–198.1% ULN, IMMULITE® 65.6–85.5% ULN, Roche 64.5–182.7% ULN, DELFIA® 62–132% ULN), as was FT3 (CENTAUR® 53.8–150.8% ULN, IMMULITE® 57.7–114.8% ULN, Roche 38.2–120.6% ULN, DELFIA 57.3–114.7% ULN). 100% denotes upper limit of reference range.

Conclusion

Thyroid hormone measurements in FDH vary depending on assay performed. Siemens IMMULITE®, DIASORIN, and perhaps DELFIA® return FT4 levels nearer the normal range, while VITROS underestimates measurements. In contrast, results from Roche Elecsys, Beckman, Abbott ARCHITECT® and ADVIA Centaur® are markedly abnormal. Notably, FT3 levels are abnormal in up to 41% of patients, raising the possibility of confusion with TSHomas or Resistance to Thyroid Hormone.

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