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CONTENTS

Society for Endocrinology BES 2022

Plenary Lectures

Clinical Endocrinology Trust Visiting Professor Lecture

PL1

Novel approaches for cushing's medical management: Guidelines to clinical practice

Maria Fleseriu
Professor of Medicine and Neurological Surgery, Director of Pituitary Center, Oregon Health and Science University, Oregon, USA

A personalized patient treatment regimen for endogenous Cushing's syndrome (CS) should be developed by a specialized multidisciplinary team, taking patient values and preferences into consideration. Comorbidities, which may compromise patient health and QoL need to be addressed, in many cases concomitant with or even before CS-specific treatments to restore eucortisolemia. Treatment of endogenous CS is initially primarily surgical and aims at complete resection of the underlying tumor source. Medical therapy for CS is mostly used as second-line treatment after failed surgery or recurrence and comprises several pituitary-directed drugs (for Cushing's disease), adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers for CS. Medical therapy should be individualized for all patients, based on the clinical scenario, including severity of hypercortisolism. Adrenal steroidogenesis inhibitors are usually used first, given their reliable effectiveness. Long-term data from new prospective (osilodrostat, levoketoconazole) and retrospective studies with ketoconazole and metyrapone has been recently added. In patients with severe disease, the primary goal is to treat aggressively to normalize cortisol levels (or cortisol action if using mifepristone). There are few rigorous data supporting specific regimens for combination therapy, but several have been described. For all patients, regular monitoring for treatment efficacy is required, including cortisol measurements, symptoms and comorbidities, especially weight, glycemia, and blood pressure. In addition, QoL is important to take into account, preferably through patient-reported outcomes. Multiple serial tests of both UFC and LNSC are used to monitor biochemical treatment outcomes. There are no rigorous data supporting use of primary or preoperative medical therapy, though is frequently done if surgery is delayed. Patients who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular/thromboembolic complications also may benefit from preoperative medical therapy in select cases. Guidelines recommendations for use in clinical practice should be considered alongside patient- and disease-specific factors for individualized care and improved patients' outcome.

DOI: 10.1530/endoabs.86.PL1

Society for Endocrinology Starling Medal Lecture

PL2

Abstract Unavailable

DOI: 10.1530/endoabs.86.PL2

Society for Endocrinology Dale Medal Lecture

PL3

Mining the genome for translational gold

Mark McCarthy[1,2]
[1]Genentech, South San Francisco, USA. [2]University of Oxford, Oxford, United Kingdom

Advances in human genetics over the last two decades have discovered genes causal for thousands of monogenic conditions, characterized the mutational landscape of most forms of cancer, and identified tens of thousands of genetic variants influencing common complex traits such as diabetes and Alzheimer's. Sequence-based diagnostics are now routinely deployed in early-onset genetic disease and in cancers, and the genetic analysis of complex traits has provided many novel and profound mechanistic insights about disease biology. Despite this, the translational impact of human genetics on late-onset disease remains limited, in part because individual variant effects are typically small. Using examples drawn from my research into the genetic basis of metabolic and endocrine disease gathered in both academia and industry, I will describe complementary approaches that are now making it possible to address this translational deficit. One involves the aggregation of genetic effects into polygenic scores that summarize individual genetic predisposition, the other the partitioning of genetic risk across diverse processes that contribute to disease pathology. These provide powerful tools for delivering increasing personalization of therapeutic care, especially when combined with non-genetic factors that also impinge on disease risk and phenotypic heterogeneity.

DOI: 10.1530/endoabs.86.PL3

Society for Endocrinology Jubilee Medal Lecture

PL4

The MRAP files: Supporting the blob

Adrian Clark
Queen Mary University of London, London, United Kingdom

An intact pituitary-adrenal axis is essential for life, yet is entirely dependent on a system with no inbuilt redundancy. Central to its activity a single peptide hormone, ACTH, acts on a single G protein-coupled receptor (GPCR) at the adrenal cortex. This ACTH receptor, otherwise known as the Melanocortin 2 receptor (MC2R) is the smallest of all GPCRs, consequently being highly hydrophobic and lacking a signal sequence – hence its resemblance to a "blob". Multiple and varied attempts to demonstrate functional expression of this receptor were unsuccessful, and it became apparent that an adrenal-specific co-factor was required. Genetic exploration of the basis of Familial Glucocorticoid Deficiency type 2 revealed the existence of a small protein that we called the Melanocortin Receptor Accessory Protein (MRAP). MRAP exists in a unique antiparallel homodimer structure interacting with the MC2R at the endoplasmic reticulum, and trafficking with it to the plasma membrane where it is required for ACTH-dependent signal generation. In contrast to MC2R, MRAP protein turns over quite rapidly and it seems likely that this results in significant amounts of uncombined (MRAP-free) MC2R at the cell surface – spare receptor. In evolution, MRAP arose through duplication of an older MRAP-like gene, MRAP2, and has developed a highly specialized role in conjunction with the MC2R. MRAP2 appears to have a far more diverse role, interacting with multiple GPCRs in the hypothalamus and elsewhere and exhibiting a complex role in the regulation of feeding and metabolism. Further understanding of the biology of these proteins should provide potential new targets for therapeutic manipulation.

DOI: 10.1530/endoabs.86.PL4

Society for Endocrinology International Medal Lecture

PL5

Insights into the Cell and Molecular Control Pathways that Regulate Cancers in the Skeleton

Peter Croucher
Garvan Institute of Medical Research, Sydney, Australia. UNSW Australia, Sydney, Australia

Early detection, surgery and targeted treatments have seen remarkable improvements in cancer survival. Yet for many patients, cancers still relapse in distant organs after seemingly successful treatment of primary disease. The skeleton is one of the most common sites. Multiple myeloma develops directly in bone, whereas solid tumours, including breast and prostate cancers, spread to bone, often early in the clinical course, giving rise to incurable disease. It remains unclear how cancer cells survive in a dormant state in bone before causing disease. Unfortunately, understanding of dormant cells is limited, as they are rare, hard to isolate and difficult to study. To address this we developed intravital imaging to identify and track individual cancer cells as they disseminate to the skeleton. Cancer cells colonised the skeleton, engaged in specialised niches in the endosteal bone compartment and were retained in a dormant state. These cells were reactivated by osteoclastic remodeling of the dormant cell niche. Single-cell RNAseq analysis showed dormant cells differ from reactivated cells and are re-programmed to express a unique set of genes enriched for immune-related genes in a niche-dependent manner. Dormant cells from myeloma, breast and prostate cancer adopt a common 'myeloid' gene signature, taking on the persona of resident cells to avoid immune detection. A single-cell map of the endosteal bone compartment and ligand-receptor dormant cell-niche mapping identified $Lepr^{High}$/$Cxcl12^{High}$ mesenchymal stromal cells as key regulators of dormancy and common molecular control pathways for all three cancers. Analysis of cells from patients identified a population of

myeloma cells with a similar myeloid signature and the same $Lepr^{High}$/$Cxcl12^{High}$ mesenchymal cells and molecular control pathways. Together this approach is identifying pan cancer, cell and molecular mechanisms controlling dormant cancer cells in the skeleton and providing the prospect of dormancy-targeted therapies to prevent cancer development in the skeleton.

DOI: 10.1530/endoabs.86.PL5

Society for Endocrinology Transatlantic Medal Lecture
PL6

The impact of adipocytes and adipose tissue on systemic metabolism

Philipp E Scherer
University of Texas Southwestern Medical Center, Dallas, USA

A number of different cell types contribute to the cellular architecture of fat tissue. While the fat cell is making important functional contributions to the systemic metabolic well-being, several additional cell types contribute a supportive role to bestow maximal flexibility on the tissue with respect to many biosynthetic and catabolic processes. The adipocyte has morphed into a cell type whose complexity we only start to appreciate. We now understand that: 1) the contributions of the adipocytes depend on their location, e.g. visceral vs. subcutaneous location. In fact, there are many more distinct fat pads in the body that act as "miniorgans" that play major roles in their local microenvironment; 2) we have different types of fat cells, some of them geared for energy storage (white adipocytes), some of them geared towards energy and heat generation (beige or brown adipocytes); under some physiological conditions, adipocytes can de-differentiate into (myo)fibroblasts and adipocyte precursor cells; 3) the ability to store excess calories and thereby acting as an anti-lipotoxic tissue is a key role for adipose tissue; 4) adipocytes produce hormones and other signaling molecules that integrate the systemic energy reserves and convey that to the brain and other organs; these adipokines should not be judged in isolation but rather be looked upon as a carefully orchestrated group of multiple different components that act in concert; Understanding the mutual influence of adipokines on each other is an essential part of understanding the endocrinology of the fat cell, but also helps us better understand their impact on the cardiometabolic syndrome.

DOI: 10.1530/endoabs.86.PL6

British Thyroid Association Pitt-Rivers Lecture
PL7

TED/GO from bench to bedside

Anja Eckstein
AFFILIATIONS

Graves orbitopathy (GO) or thyroid eye disease (TED) is an inflammatory orbitopathy most commonly associated with hyperthyroid autoimmune thyroid disease (Graves' disease). Most patients have TSHR autoantibodies (TRAb) in their blood. They usually have a stimulating effect and cause hyperthyroidism. About half of the patients also show more or less pronounced eye symptoms. Factors, which are significantly associated with the occurrence of clinically overt orbitopathy include smoking, high TRAb, a long period of hyperthyroidism, and the presence of already mild ocular symptoms. Risk groups can be assessed with TRAb measurement with the new assay technologies (using a monoclonal antibody for binding competition, or with a bioassay) by certain cut off levels at different time points during the course of GO. In vitro experiments showed that stimulation of the TSHR triggers a cross talk to the growth factor receptor IGF1R, which mediate essential pathomechanisms of GO. Targeted therapies for both the TSHR (small molecules, inhibiting antibodies) and the IGF1R (inhibiting antibodies) are in development. However, preventive measures relate to the regulation of the immune system. Results of several trials in the animal model support this. Influencing the gut microbiome or T-cell migration can prevent GO. In addition, local factors such as tissue hypoxia due to the configuration of the bony orbit do also play a decisive role for the extent of inflammation in the orbit. Optimal future treatment address the action of TSHR but also the regulation of the immune system.

DOI: 10.1530/endoabs.86.PL7

Society for Endocrinology European Medal Lecture
PL8

Skeletal cell metabolism: more than bioenergetics and bystander effect

Geert Carmeliet
KU Leuven, Belgium, Belgium

Bone development, remodeling and repair are metabolically very demanding processes. Chondrogenic and osteogenic cells are highly anabolic as they have a high proliferation rate and produce a substantial amount of extracellular matrix. Not only hormones and growth factors control these processes, but recent evidence shows that cell metabolism might also regulate skeletal cell properties. Adequate nutrient supply and metabolic pathways are certainly essential to prevent an energy deficit. However, skeletal cell metabolism supports also other cellular functions beyond bioenergetics as it is also required for biosynthesis, redox homeostasis and epigenetic regulation of gene expression. We could show that a low lipid supply because of poor vascularization induces skeletal stem and progenitor cells (SSPCs) to differentiate into chondrocytes. The chondrogenic transcription factor SOX9 on its turn promotes glutamine metabolism in chondrocytes. Glutamine metabolism is necessary for optimal expression of genes characterizing chondrocyte identity and it supports biosynthesis and redox homeostasis. On the other hand, SSPCs are highly metabolic flexible as they can proliferate when oxidative phosphorylation is blocked, a characteristic tumor cells do not have. SSPCs can maintain their NAD+ levels by increasing glycolysis side pathways, rewiring the TCA cycle and by using fumarate as electron acceptor in the oxidative phosphorylation instead of oxygen. This normal proliferation rate did not exhaust their SSPC properties and even resulted in more bone being formed when these SSPCs were implanted ectopically in mice. Thus, SSPCs have a high plasticity to metabolically adapt to metabolic stressors and they can change cell fate when the supply of certain nutrients is limited.

DOI: 10.1530/endoabs.86.PL8

Society for Endocrinology Medal Lecture
PL9

Abstract unavailable

DOI: 10.1530/endoabs.86.PL9

Clinical Endocrinology Trust Lecture
PL10

Why don't we cure all patients with Graves' disease?

Simon Pearce
Newcastle University, Newcastle upon Tyne, United Kingdom

Graves' disease is characterised by an autoimmune response to the TSH receptor leading to circulating stimulatory TSH receptor antibodies (TRAbs) which directly cause hyperthyroidism and goitre. Patients with thyroid eye disease, children and teenagers, and those with large goitre, severe hyperthyroidism or high TRAb titres have unmet clinical needs and frequently have unsatisfactory outcomes with current therapies. In common with all other antibodies, TRAbs are secreted from terminally differentiated B lymphocytes, plasma cells, which may reside in the thyroid, lymphoid tissues and bone marrow, and from circulating plasmablasts. Once long-lived TRAb-secreting plasma cells become established in a bone marrow niche, it is likely that Graves' disease becomes intractable and definitive therapy is necessary. B lymphocyte and plasma cell immunotherapies, with different cell depleting and cytokine modulating activities appear to have additional efficacy on top of antithyroid drugs, and recent trials of these agents will be reviewed. In addition, other novel approaches including antigen-specific immunotherapies will be discussed. A better understanding of the immunopathogenesis of Graves' disease will allow stratification of particular patient groups to more aggressive therapies in the future.

DOI: 10.1530/endoabs.86.PL10

Presidential Lecture

PR1

Antibodies and antibody mimics as pharmaceutical drugs

Gregory Winter
Trinity College, Cambridge, United Kingdom

During the last century the conjunction of chemistry, structural biology and a molecular understanding of disease processes, was responsible for driving the widespread development of chemicals as pharmaceutical drugs. The development of biologicals (manufactured by cell fermentation) was much slower, and had to await the advent of recombinant DNA technology, and in the case of antibodies, of hybridoma technology. Antibodies have since become established as the paramount biological drug, particularly for the treatment of cancer and autoimmune disease, and are now making inroads into other areas poorly served by chemical drugs. Even as the application of antibodies expands, Darwinian selection technologies are leading to new drug platforms capable of creating tiny antibody mimics based on peptides. Will such developments spark another wave of innovative medicines based on chemicals?

DOI: 10.1530/endoabs.86.PR1

Debate

D1.1

This house believes that Vitamin D supplementation should be a high public health priority. For the motion

Martin Hewison
University of Birmingham, Birmingham, United Kingdom

This year marks the 100th anniversary of vitamin D. Since its discovery in 1922 - as a factor that protects against the bone disease rickets - our understanding of vitamin D has evolved dramatically. Vitamin D has morphed from environmental/nutritional factor to steroid hormone endocrine regulator to intracrine modulator of transcription. Despite this, vitamin D-deficiency continues to be prevalent in the UK and nutritional rickets remains a significant clinical problem, notably in ethnic minority groups. For this reason alone, vitamin D supplementation should be a high public health priority. Added to this are the many pre-clinical and observational studies highlighting health benefits of vitamin D beyond rickets. These extraskeletal effects have been less consistent in randomized control trials (RCTs) and Mendelian Randomization (MR) analyses, but both RCTs and MR have limitations that hamper interpretation of the health impact of vitamin D. In particular RCTs are very expensive, frequently involve vitamin D-sufficient cohorts and never target an optimal vitamin D level (we still do not know the level of vitamin D required for key extraskeletal actions). So why not take a pragmatical approach? Assume that a proactive national strategy of vitamin D supplementation will finally eradicate rickets (100 years later than expected) but may also have some broader health benefits across the nation. In a time of increased pressure on our health services this could be a simple and cost-effective strategy. Current UK public health measures have largely failed to tackle vitamin D-deficiency not only because they aim for a low threshold, but also because of inconsistent policies and lack of implementation strategies, leading to confusion for both the general public and healthcare professionals. As we move into the second century of vitamin D, a pro-active programme of vitamin D supplementation, along with food fortification, should be a high public health priority.

DOI: 10.1530/endoabs.86.D1.1

D1.2

Abstract Unavailable

DOI: 10.1530/endoabs.86.D1.2

Society for Endocrinology Journal Awards

Society for Endocrinology Journal Award – *Journal of Endocrinology*

JA1

Early or delayed time restricted feeding prevents metabolic impact of obesity in mice

Prashant Regmi, Rajesh Chaudhary, Amanda J Page, Amy T Hutchison, Andrew D Vincent, Bo Liu & Leonie Heilbronn

Journal of Endocrinology, 2021, **248**(1): 75-86 (DOI: https://doi.org/doi.org/10.1530/JOE-20-0404)

DOI: 10.1530/endoabs.86.JA1

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

JA2

Diversification of mineralocorticoid receptor genes in a subterranean rodent, the naked mole-rat

Kaori Oka, Hidemasa Bono, Asato Kuroiwa, Shusuke Fujioka, Atsushi Shimizu, Yoshinao Katsu & Kyoko Miura

Journal of Molecular Endocrinology, 2021, **66**(4): 299-311 (DOI: https://doi.org/10.1530/JME-20-0325)

DOI: 10.1530/endoabs.86.JA2

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

JA3

Developmental role of PHD2 in the pathogenesis of pseudohypoxic pheochromocytoma

Luise Eckardt, Maria Prange-Barczynska, Emma J Hodson, James W Fielding, Xiaotong Cheng, Joanna D C C Lima, Samvid Kurlekar, Gillian Douglas, Peter J Ratcliffe & Tammie Bishop

Endocrine-Related Cancer, 2021, **28**(12): 757-772 (DOI: https://doi.org/10.1530/ERC-21-0211)

DOI: 10.1530/endoabs.86.JA3

Society for Endocrinology Journal Award – *Endocrine Connections*

JA4

Phaeochromocytomas overexpress insulin transcript and produce insulin

Ivar Følling, Anna B Wennerstrøm, Tor J Eide & Hilde Loge Nilsen

Endocrine Connections, 2021, **10**(8): 815-824 (DOI: https://doi.org/10.1530/EC-21-0269)

DOI: 10.1530/endoabs.86.JA4

Society for Endocrinology Journal Award – *Clinical Endocrinology*

JA5

Cardiac phenotype in familial partial lipodystrophy

Abdelwahab Jalal Eldin, Baris Akinci, Andre Monteiro da Rocha, Rasimcan Meral, Ilgin Yildirim Simsir, Suleyman Cem Adiyaman, Ebru Ozpelit, Nicole Bhave, Ramazan Gen, Banu Yurekli, Nilufer Ozdemir Kutbay, Zeynep Siklar, Adam H. Neidert, Rita Hench, Marwan K. Tayeh, Jeffrey W. Innis, Jose Jalife, Hakan Oral & Elif A. Oral

Clinical Endocrinology, 2021, **94**(6): 1043-1053 (DOI: https://doi.org/10.1111/cen.14426)

DOI: 10.1530/endoabs.86.JA5

Awards and Prizes

Teaching Achievement Award

TAA1

SIMBA and CoMICs – developing evidence-based, minimal cost, and sustainable medical education programmes

Punith Kempegowda[1,2] & SIMBA and CoMICs Team[1]
[1]University of Birmingham, Birmingham, United Kingdom. [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

SIMBA (Simulation via Instant Messaging- Birmingham Advance) is a novel pedagogical simulation-based learning model which improves clinicians' confidence in managing conditions in endocrinology and diabetes. More than 25 SIMBA sessions have been conducted between May 2020 and August 2022. Each session included 4 to 6 real-life anonymised case scenarios followed by an interactive discussion. SIMBA effectively adopts Kolb's theory to provide the best possible experience to learners, highlighting the advantages of utilising social media platforms for SBL in medical education. Participants' self-reported confidence improved significantly post-SIMBA in their approach to simulated cases. SIMBA has also proved to be effective at cultivating leadership and teamwork skills among medical students and junior doctors when they participate in delivering the session. The ability to conduct SIMBA sessions at a low cost with high fidelity has levelled the learning ground for healthcare professionals from across the globe, irrespective of their country of origin. CoMICs, a medical education initiative conceptualised by medical students and junior doctors, produces bite-sized videos with illustrations and infographics. Each video depicts a specific disease or medical condition, from presentation and investigations to stepwise management and follow-up options. Creating CoMICs provides medical students and junior doctors with invaluable experience in medical education, revision of key concepts and the opportunity to work closely with the leaders in the field. CoMICs reviewers also get the chance to contribute to an exciting initiative which is growing in popularity each week. Building on the success of CoMICs, the team has recently collaborated with the European Journal of Endocrinology (EJE) to produce short videos presenting selected articles published in the EJE. A new video is shared weekly as part of our #CoMICWednesday initiative. So far, over 120 episodes have been released, covering various complex topics in endocrinology and diabetes.

DOI: 10.1530/endoabs.86.TAA1

Outstanding Clinical Practitioner Award

OCP1

What Endocrinology has taught and given me

William Drake
St Bartholomew's Hospital, London, United Kingdom

What does a clinical endocrinologist actually do? There are no angiogram, pacemaker, bronchoscopy, ERCP, kidney biopsy or joint injection lists to be done. Our only practical procedure is venepuncture, albeit multiple times and occasionally at odd times of day. Within a single clinic an endocrine physician will have to 'key in' very quickly to a variety of symptomatic issues that often go to the core of human identity. There may be two successive patients with secondary amenorrhoea, with final diagnoses of anorexia nervosa and Cushing's syndrome; both of which are associated with deep-seated sensitivities about body image. The next two patients may complain, respectively, of hirsutism and failure of development of secondary sexual hair, with final diagnoses of an ovarian tumour or Kallman syndrome. In each case the endocrinologist must, within a few minutes, strike up a professional but simultaneously intimate relationship with a stranger and use a solid knowledge of physiology and biochemistry, together with sensitive phraseology to extract the relevant history, perform a honed physical examination and plan appropriate informative investigations. Separate to this there is a responsibility to train the next generation of doctors and to contribute towards the improvement of clinical standards and outcomes by a range of activities from local audit through recruitment into clinical trials to paradigm-changing translational research. In my talk I will present some clinical material that 'goes somewhere' - into a piece of clinical research; into a collective departmental effort to provide high quality clinical care for a group of patients previously under-provided for; or simply to illustrate a point of clinical and/or professional philosophy. In doing so I hope to be true to the spirit of this award which I am thrilled and honoured to receive.

DOI: 10.1530/endoabs.86.OCP1

Nikki Kieffer Medal

NKM1

Abstract Unavailable

DOI: 10.1530/endoabs.86.NKM1

Early Career and Plenary Orals

Early Career Prize Lecture Basic Science

EC1.1

The diverse and distinct roles of adipose tissue on metabolic heath

Karla Suchacki
The University of Edinburgh, Edinburgh, United Kingdom

Obesity and its associated cardiometabolic complications place a huge burden on global health. The key feature of obesity is increased white adipose tissue (WAT) mass, however the role of 'lesser known' depots such as bone marrow adipose tissue (BMAT) and brown adipose tissue (BAT) is not clear in adult humans. Over the last decade I have undertaken a variety of metabolic studies in both mice and humans to determine the metabolic role and regulation of BMAT, BAT and the wider skeleton. I have developed entirely novel imaging techniques (primarily using positron emission tomography) to quantify BMAT and identify metabolic networks between organs. Using these approaches I have: **(1)** determined that BMAT plays a key role in glucose clearance and is functionally distinct from WAT and BAT; **(2)** identified a novel pathway regulating human BAT thermogenesis, revealing how antidepressants may cause metabolic dysfunction; **(3)** used novel PET tracers to quantify BAT mass in humans; **(4)** identified complex metabolic networks in the skeleton and a bone-derived therapeutic target for the treatment of obesity and diabetes. This lecture will explore these topics and highlight how this knowledge can be used to develop new strategies to diagnose and treat obesity and associated metabolic disease.

DOI: 10.1530/endoabs.86.EC1.1

Early Career Prize Lecture Clinical

EC1.2

Central adiposity raises serum calcium concentrations and increases risk of kidney stone disease

Catherine Lovegrove[1,2], Jelena Besevic[3], Akira Wiberg[4,2], Ben Lacey[3], Thomas Littlejohns[3], Naomi Allen[3], Michelle Goldsworthy[5], Jihye Kim[6], Fadil Hannan[7], Gary Curhan[8], Ben Turney[1,2], Mark McCarthy[9], Anubja Mahajan[9], Rajesh Thakker[5], Michael Holmes[10], Dominic Furniss[4,2] & Sarah Howles[1,2,5]
[1]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom. [2]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom. [3]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [4]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, United Kingdom. [5]Academic Endocrine Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom. [6]Chan School of Public Health, Boston, USA. [7]Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom. [8]Channing Division of Network Medicine and Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, USA. [9]Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom. [10]Medical Research Council, Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom

Background
Kidney stone disease (KSD) has been linked to obesity, metabolic syndrome and higher serum calcium concentration (SCa). The mechanisms underlying these associations are uncertain. Using conventional and genetic epidemiological techniques, we aimed to investigate the effects of adiposity on KSD.
Methods
Observational associations between adiposity and incident KSD in 479, 405 people from the UK Biobank were assessed. Genome-wide association studies (GWAS) of KSD in combined and sex-specific subsets of the UK Biobank were undertaken to facilitate Mendelian randomisation (MR). Univariable, multivariable and mediation MR analyses were undertaken to calculate odds ratios (OR) and beta coefficients (β) per genetically instrumented higher marker of adiposity, metabolic syndrome, biochemical phenotype, and inflammation.
Results
Central adiposity (waist-to-hip ratio (WHR) and waist circumference (WC)) were more strongly associated with KSD than general adiposity (body mass index (BMI)) on observational analyses. The association of BMI with KSD was almost completely attenuated adjusting for WC (HR = 1.03, 95% CI = 0.97-1.10 per 5kg/m2), whereas WC and WHR remained positively associated following adjustment for BMI (HR = 1.26 95% CI = 1.19-1.33 per 10cm higher WC, and HR = 1.22, 95% CI = 1.18-1.27 per 0.05 higher WHR). Three novel KSD-GWAS loci were identified (SLC2A12, TRPV5, and SLC28A1); no sex-specific loci were detected. Higher central adiposity was causally linked to KSD and higher adjusted SCa independent of BMI (1-standard deviation higher WHR: OR KSD = 1.43, $p = 4.1 \times 10\text{-}6$; β SCa = 0.11mmol/L, $p = 2.7 \times 10\text{-}7$) on MR analyses. Mediation analyses indicate that 12% of the effect of WHR on KSD is due its role in elevating SCa. Other components of metabolic syndrome, serum urate, and biomarkers of inflammation were unlikely to cause KSD.
Conclusions
We demonstrate that SCa is elevated by higher visceral adipose depots and this increases risk of KSD. There may be utility in using therapies that target central adipose deposition to modulate calcium homeostasis to prevent KSD.

DOI: 10.1530/endoabs.86.EC1.2

Clinical Endocrinology Trust Best Abstract Clinical

EC1.3

Individuals on levothyroxine have higher HADS anxiety and depression scores than the general population and this is exacerbated by the Thr92Ala substitution in DIO2

Peter Taylor[1], Eirin Haug[2], Adrian Heald[3], Lakdasa Premawardhana[1], Onyebuchi Okosieme[1], Michael Stedman[4], Bjørn Asvold[2] & Colin Dayan[1]
[1]Cardiff University, Cardiff, United Kingdom. [2]NTNU, Trondheim, Norway. [3]University of Manchester, Manchester, United Kingdom. [4]Res Consortium, Andover, United Kingdom

Introduction
Around 15% of people diagnosed with primary hypothyroidism remain significantly symptomatic despite TSH normalisation with levothyroxine (LT4). The Thr92Ala substitution (rs225014) in a key deiodinase that activates T4 to T3, DIO2 may influence tissue levels of T3 but previous studies have been inconsistent regarding symptoms on LT4 and the presence of this polymorphism.
Methods
We assessed HADS anxiety and depression scores in the HUNT2 study in 52, 609 individuals (6, 906 with the Thr92Ala substitution) of whom 1, 569 had a history of LT4 use (194 with the Thr92Ala substitution). Anxiety and depression scores were assessed by comparing patients on LT4 to the general population, initially overall and then by Thr92Ala status, with adjustment for age, sex and educational attainment.
Results
The Thr92Ala substitution was present in 13% of the population and was not associated with increased HADS scores in individuals not on LT4. Compared to individuals not on LT4, after adjustment HADS total score was 0.71 points higher (0.39, 1.02, $p < 0.001$) in subjects on LT4 overall, 0.56 points higher (0.22, 0.89, $p < 0.001$) in individuals on LT4 but not homozygous for Thr92Ala, and 1.83 points higher (0.93, 2.73 $p < 0.001$) in individuals on LT4 who were homozygous for Thr92Ala. Thr92Ala non-homozygous individuals on LT4 were 22% more likely than those not on LT4 to reach the threshold for HADS anxiety caseness, while homozygous individuals were 208% more likely.
Conclusion
Individuals homozygous for DIO2 Thr92Ala on LT4 have significantly reduced quality of life compared to those non-homozygous, but there is no effect in the absence of LT4. Since individuals are not aware of their genotype, this provides strong objective evidence for a biological basis to persistence of symptoms in some individuals on LT4. Previous inconsistent results on the effect of Thr92Ala are likely to have been due to low statistical power.

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Clinical Endocrinology Trust Best Abstract Basic

EC1.4

Characterising the G-protein signalling mechanisms activated by short chain fatty acids in human enteroendocrine cells which mediate production and release of the anorectic gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1)

Aanya Hirdaramani, Gary Frost & Aylin Hanyaloglu
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The anorectic gut hormones glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY) are secreted by enteroendocrine L cells in response to short chain fatty acids (SCFAs) produced by gut microbiota following dietary fibre consumption. SCFAs, acetate, propionate and butyrate, activate the G protein-coupled receptors Free Fatty Acid Receptor 2 and 3 (FFAR2, FFAR3). Increasing intestinal levels of propionate can prevent weight gain in overweight adults. In rodents, FFAR2-mediated gut hormone release occurs via both classical calcium signalling and non-canonical Gαi/p38 signalling from intracellular endosomal compartments.

However, the underlying mechanisms mediating human FFAR2-dependent gut hormone production and release, is poorly understood. Here, we characterise the effects of SCFAs on FFAR2-G protein signalling mechanisms in a human L cell model and investigate the role of these pathways on gut hormone production. In human colonic NCI-H716 cells, Homogeneous Time-Resolved Fluorescence (HTRF) assays were employed to measure secondary messengers downstream of G protein activation, and quantitative Reverse Transcription PCR (qPCR) for PYY and glucagon mRNA levels. All SCFAs activated Gαi and Gαq responses in a dose-dependent manner, with similar potencies but distinct efficacies. Both Gαi and Gαq signalling was abolished by pre-treatment with an FFAR2-specific antagonist GLPG0974, confirming that FFAR2 is the primary SCFA receptor in this cell type. Interestingly, all SCFA-induced signalling was inhibited by Dyngo-4a, an inhibitor of dynamin-dependent receptor internalisation. Butyrate induced a large upregulation in expression of PYY, but not glucagon, which was reduced by GLPG0974 and the Gαq-inhibitor YM-254890. Overall, the SCFAs activate pharmacologically distinct FFAR2 responses in human colonic cells, which are sensitive to spatial regulation. An FFAR2-Gαq response might underlie the upregulation of PYY expression by butyrate that may suggest each SCFA has distinct roles in regulating gut hormone production and release and could be exploited to promote long-term health properties of SCFA actions in humans.

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Symposia

Bone cross-talk with other organs

S1.1

Abstract Unavailable

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S1.2

Bone cross talk with other organs

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Over the last 15 years there has been a revolution in our understanding of how bone and the marrow communicate with other tissues and organs. It is now clear that adipose tissue, brain, the adrenal, the pancreas, and the marrow itself are targets of skeletal mediators. The means of communication are now starting to be delineated. Neural pathways including the sympathetic system and sensory nerves have been delineated. Hormonal function of skeletal peptides has also been delineated. The three mediators so far identified are osteocalcin, lipocalin-2, and FGF-23. Each of these molecules can have a profound effect on non-skeletal tissue. In addition, stromal cells release peptide factors that can influence neighboring adipocytes, and bone marrow fat cells can target peripheral fat and the pancreas. These mediators will be discussed in detail during the presentation.

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S1.3

Skeletal fragility and diabetes

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The incidence of diabetes, a disease characterized by high blood glucose levels, is increasing worldwide. Besides the well-known complications of diabetes including cardiovascular disease, retinopathy, nephropathy, and neuropathy, also bone fragility has recently been recognized as a complication of diabetes. In fact, type 1 diabetes is associated with a 6-fold increase in hip fractures with a marked loss of bone mineral density, while type 2 diabetes is associated with a 1.5-fold increase of hip fractures even in the presence of a higher bone mineral density. In both cases, diabetic bone disease is characterized by a low bone turnover and an increased incorporation of advanced glycation end-products into the collagenous matrix, rendering it stiff and inflexible. Moreover, bone vascularization is reduced in diabetic animals; in particular the number of pro-osteogenic H-type vessels is diminished. Experimental evidence shows that elevated ROS production, senescence, and suppressed Wnt signaling contribute to diabetic bone disease. Suppressed Wnt signaling also stimulates the differentiation of adipocytes in the bone marrow, which contribute to an inflammatory, pro-osteoclastogenic milieu. Finally, several miRNAs are differentially expressed any may contribute to diabetic bone disease.

DOI: 10.1530/endoabs.86.S1.3

Drugable hormones and their receptors: past, present and future. Are we running out of targets? Are there more hormones to find?

S2.1

Therapeutic potential of an old friend – the dichotomy of amylin in physiology and pathophysiology

Thomas Lutz
University of Zurich, Zurich, Switzerland

The mature 37 amino acid peptide amylin is derived from the IAPP (islet amyloid polypeptide) gene and is produced in pancreatic beta-cells and – in much lower amounts – in other tissues, like the stomach, spinal ganglia and in the brain. Amylin is characterized by an interesting dichotomy because amylin has to propensity to aggregate into fibrils in some species, but on the other hand also to the physiological control of metabolism (probably in all species). These dichotomous roles seem to be "functionally independent" in that some amylin forms (e.g., human, feline) aggregate into oligomers and eventually mature amyloid fibrils; this process is probably independent of the cell membrane bound amylin receptor (AMY) because aggregation is initiated intracellularly. On the other hand, the soluble monomeric form of mature amylin activates the AMY in the brain to produce hormonal effects on glucose metabolism (inhibition of glucagon secretion, control of gastric emptying) and nutrient intake (induction of satiation), hence beneficial weight-lowering and anti-diabetic effects. The AMY is a specific heterodimer receptor that consists of the calcitonin receptor core protein (CTR) and one of several receptor activity modifying proteins (RAMP). The mechanisms underlying amylin's metabolic effects and the responsible AMY subtypes have been amply investigated in recent years and are the basis for the development of amylin agonists that are already in clinical use for the treatment of diabetes mellitus or that are in clinical development as weight lowering drugs, respectively. Similarities and differences between amylin and its receptor agonists will be discussed.2

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S2.2

Abstract Unavailable

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S2.3

Can we drug receptors for microbially-produced metabolic hormones?

Graeme Milligan
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Can we drug receptors for microbially-produced metabolic hormones and for what indications? G protein-coupled receptors (GPCRs) have been a major group of druggable cell surface receptors and therapeutics targeting many hormone-activated GPCRs have been developed. A number of products of the processing and metabolism of foodstuffs act in a hormone-like manner and these include both short and medium chain length free fatty acids. Short chain fatty acids produced in large amounts by the intestinal microbiota act on the receptors FFA2 and FFA3, whilst medium chain fatty acids activate the receptor GPR84. Various studies have suggested that activation or blockade of these receptors may be therapeutically attractive ways to treat various inflammatory conditions, as well as diseases ranging from diabetes to cancers. One challenge in assessing such questions in rodent models is that many identified ligands that target these receptors, although with high affinity at the human receptor have little or no effect at the rodent orthologues. I will discuss ways in which we have defined the molecular basis for such differences and then developed transgenic mouse models expressing modified forms of FFA2 and GPR84 to explore if these are worthy targets for therapeutic development.

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Therapy extension and repurposing in endocrine cancer

S3.1

Abstract Unavailable

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S3.2

Abstract Unavailable

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S3.3

Abstract Unavailable

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Old hormones, new tricks: new approaches for treating reproductive diseases

S4.1

Size matters. Small molecule targeting of gonadotrophin hormone receptors

Sharika Hanyroup[1], Ross Anderson[1], Selvaraj Nataraja[2], Henry Yu[3], Annika Kreuchwig[4], Gerd Krause[4], Arieh Katz[5], Robert Millar[1] & Claire Newton[1]
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G protein-coupled receptors (GPCRs) are critical for signal transduction within neuroendocrine signalling pathways, and genetic mutations in G protein-coupled GPCRs underlie numerous diseases. Inactivating GPCR mutations can impede ligand interactions or signal transduction, or can result in misfolding of nascent receptor proteins and subsequent retention in the endoplasmic reticulum (ER) and thus failure to traffic to the cell surface. Examination of the functionality and cell surface expression of a number of mutations of the gonadotrophin hormone receptors (luteinising hormone receptor and follicle-stimulating hormone receptor) have revealed that the majority of mutations in these receptors result in severely reduced cell surface expression. Pharmacological chaperones (PCs) are cell-permeant small-molecules that engage misfolded proteins in the ER, stabilising their folding and 'rescuing' cell surface expression. The ability of existing small-molecule ligands to act as PCs for gonadotrophin receptor mutants with poor cell surface expression revealed that they can exhibit PC activity. Importantly, following treatment with the PC compounds, in addition to an increase in cell surface expression of the mutant receptors, a corresponding increase in hormone-induced signalling was observed for many of the 'rescued' receptors, indicating restored functionality. Furthermore, some of the test ligands that interact with their target receptors at allosteric sites distinct from the natural ligand (allo-agonists), were able to elicit a robust response from mutant receptors with normal cell surface expression, but impaired hormone/binding/signalling. These findings aid in advancing understanding of the effects of genetic mutations on GPCR function, and the actions of small molecule ligands on such, and provide a proof of therapeutic principle for neuroendocrine PCs/allosteric agonists.

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S4.2

Abstract Unavailable

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S4.3

Abstract Unavailable

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New approaches to diagnosing and treating thyroid cancer

S5.1

Abstract Unavailable

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S5.2

Are we overtreating low-risk thyroid cancer?

Megan Haymart
University of Michigan, Ann Arbor, USA

Patients with low-risk thyroid cancer are at risk for overtreatment. Autopsy studies and survival statistics suggest that many patients with thyroid cancer have indolent disease that is unlikely to lead to death. Prior studies have found similar long-term outcomes with less intensive management. Yet, there remains marked variation in care, with some patients at risk for overtreatment. Data from large cancer registries, as well as patient report, provide evidence that overtreatment of low-risk thyroid cancer leads to harmful side effects from therapies that may not have been needed. Overdiagnosis of low-risk thyroid cancer fuels overtreatment. In addition, over-treatment continues as there are barriers to implementing less intensive management options. Ultimately, reducing overtreatment will require a multipronged approach and involve patient education as well as physician directed interventions.

DOI: 10.1530/endoabs.86.S5.2

S5.3

Novel target therapies for advanced thyroid cancers

Jonathan Wadsley
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An increased understanding of the genetic changes leading to thyroid cancers in recent years has led to a rapid increase in the number of effective targeted systemic therapies available for patients with advanced thyroid cancer. The multi-kinase inhibitors were the first drugs to show significant benefit but more recently more specific inhibitors of RET, BRAF, MEK and NTRK have been developed and are showing great promise. In this session I will discuss this paradigm shift in the management of advanced thyroid cancer, including iodine refractory differentiated thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer. I will discuss issues around patient selection for treatment, the data supporting these novel therapies, and the importance of molecular genetics testing of advanced thyroid cancers to ensure that the most appropriate treatment is chosen for each patient.

DOI: 10.1530/endoabs.86.S5.3

Novel therapeutics and diagnostics in adrenal disease

S6.1

Stem cell therapy in adrenal insufficiency

Charlotte Steenblock, Ioannis Oikonomakos, Maria Malyukov & Stefan Bornstein
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Primary adrenal insufficiency is due to impairment of the adrenal gland with ~80% of the cases being due to autoimmune adrenalitis (Addison's disease). Other cases of primary adrenal insufficiency might be idiopathic, caused by adrenal metastases, or due to congenital adrenal hyperplasia. Adrenal insufficiency might also be induced by infectious diseases e.g. COVID-19 and, as seen lately in an increasing number of patients, by novel medications targeting hypertension and cancer. Lastly, surgical bilateral adrenalectomy as required in certain adrenal tumors cause complete adrenal insufficiency. Currently, hormone replacement therapies are the main treatment option

for adrenal insufficiencies, but are often coupled with significant side effects. Therefore, therapeutic alternatives are desirable for these patients. We have shown that transplantation of bovine adrenocortical cells is successful in animal models of adrenal insufficiency, and that the expression of progenitor markers is associated with the functionality. Thus, stem cell replacement therapy is an attractive alternative to current treatments. Stem cell-based therapies could involve either adult adrenal stem cells or stem cells derived through in vitro differentiation of pluripotent cells. Until now, limited in vivo studies have been performed using reprogrammed mouse or human cells in the adrenal field. Differentiation into steroidogenic cells has only been achieved by forced expression of NR5A1 (SF-1), the master regulator of steroidogenesis and differentiation of pituitary gonadotrophs, adrenal glands, and gonads. Although cells are viable after implantation into mice, full functionality and responsiveness to adrenal stimuli have not been reported. These observations might be due to incomplete differentiation and limited steroidogenic potential of the cells before transplantation. Thus, optimization is required. Looking forward, generation of bona-fide steroidogenic cells from humans combined with novel biomaterials and encapsulation in immune-isolating devices might offer alternative therapies for patients with adrenal insufficiency.

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S6.2

Abstract Unavailable

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S6.3

New applications of steroid metabolomics to adrenal tumours

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Steroid biosynthesis and metabolism are reflected by the serum steroid metabolome and, in even more detail, by the 24-hour urine steroid metabolome, which can provide unique insights into alterations of steroid flow and output indicative of underlying conditions. Mass spectrometry-based steroid metabolome profiling has allowed for the identification of unique steroid signatures associated with disorders of steroid biosynthesis and metabolism that can be used for personalised approaches to diagnosis, differential diagnosis, and prognostic prediction. Machine learning is uniquely suited to analyse high-complexity datasets and its application to the wealth of information generated through steroid metabolome profiling has facilitated the development of powerful customised diagnostic approaches. This talk will provide an overview of the utility of steroid metabolome analysis for the diagnosis and management of autonomous adrenal steroid excess in the context of adrenal tumours. Topics covered will include early diagnosis of adrenal cancer and its recurrence, the diagnosis and risk stratification of cortisol excess, and the diagnosis and subtype classification of aldosterone excess.

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What is New?

WIN1

Abstract Unavailable

DOI: 10.1530/endoabs.86.WIN1

WIN2

What is new (Clinical)

Aled Rees
Cardiff University, Cardiff, United Kingdom

This presentation will review clinical advances in Endocrinology over the last year, highlighting studies selected on the basis of their impact on clinical care.

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Clinical Management Workshops

Endocrine disease in pregnancy: pitfalls in testing and challenges in management; before, during and after

CMW1.1

Diagnosis and management of adrenal insufficiency in pregnancy

Mark Sherlock
Royal College of Surgeons in Ireland, Dublin, Ireland. Beaumont Hospital, Dublin, Ireland

During pregnancy there are a number of physiological changes in the regulation of the hypothalamo-pituitary-adrenal (HPA axis). These changes make the diagnosis of adrenal insufficiency and management of patients with known adrenal insufficiency challenging in pregnancy. The management of patients with known adrenal insufficiency needs to be altered during pregnancy and the management of labour and delivery needs MDT input. This session will review the physiological changes that occur in pregnancy, the pitfalls in relation to diagnosis of adrenal insufficiency in pregnancy and the management of labour.

DOI: 10.1530/endoabs.86.CMW1.1

CMW1.2

Abstract Unavailable

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CMW1.3

Hyperthyroidism

Tim Korevaar
Department of Endocrinology and Academic Center for Thyroid Disease, Erasmus University Medical Center, Rotterdam, Netherlands

In this presentation I will discuss various aspects of hyperthyroidism during pregnancy. First of all, I will discuss that the epidemiology points towards a physiological underlying cause but I will also exhibit the differential diagnoses that should be addressed. Second, I will discuss preconception and gestational management of Graves' disease, specifically focusing on new concepts regarding antithyroid drug choice, cessation and options in case of antithyroid drug failure. Third, I will focus on the risks related to the pregnancy and the development of the fetus. Finally, I will also discuss fetal assessment during pregnancy using ultrasound, maternal thyroid function and fetal heart rate.

DOI: 10.1530/endoabs.86.CMW1.3

State of the art in identifying and managing aggressive pituitary disease

CMW2.1

Abstract Unavailable

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CMW2.2

Technological advances in surgical therapy for pituitary adenoma

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Pituitary adenomas are among the most common brain tumours and can result in significant morbidity (e.g. blindness), reduced quality of life, and death if left untreated. Transsphenoidal surgery is the mainstay of treatment for the majority of symptomatic pituitary adenomas and has the potential to offer a cure. However, many series describe high rates of treatment failure and recurrence - in functioning adenomas (e.g. up to 20% in Cushing's Disease) and non-functioning adenomas (e.g. up to 50% on long term follow-up).This is influenced by significant challenges in finding, seeing, and treating pituitary disease during surgery. To meet these clinical challenges, there have been numerous advances in the surgical treatment of pituitary adenomas, with the field benefiting from the recent enormous expansion of novel medical technologies (e.g. augmented reality, robotics, and artificial intelligence). These innovations have the potential to benefit each step of pituitary surgery, and ultimately, drive improved outcomes. Thus, we aim to explore the scope of existing challenges and potential technological advances in pituitary adenoma surgery – distilling the surgery of the future.

DOI: 10.1530/endoabs.86.CMW2.2

CMW2.3

Non-surgical therapies for aggressive pituitary tumours

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Aggressive pituitary tumours (APT) are not controlled by standard therapies. Pituitary carcinomas (PC) share many properties with APT and are defined by the presence of metastases. Temozolomide (TMZ), an oral alkylating with good penetrance into the brain, is the recommended first line chemotherapy. The survival has markedly been improved in patients with APT/PC during the last two decades. Prior to the TMZ-era, 66% of patients with PC were dead within a year after detection of metastases, today the median survival is about 5 years. TMZ results in tumour regression in 40% of patients. The TMZ effect can be counteracted by the DNA repair enzyme MGMT; complete tumour regression has only been observed in tumours with low MGMT content. TMZ is considered to be a radiosensitizer and is given concurrently with radiotherapy in malignant glioblastomas. In APT /PC this combination may be superior to TMZ monotherapy, but the experience is limited. Management remains challenging in TMZ failures and relapsing tumours. A second radiotherapy had transient effects in about 40% of 55 re-irradiated patients. Peptide Receptor Radionuclide Therapy has resulted in partial tumour regression in 4 of 19 evaluable patients. Targeted therapies interfering with growth factor receptors on tumour cells (tyrosine kinase inhibitors) or intracellular signaling pathways (mTor inhibitors), reported in 11 cases, have mostly been unsuccessful. Bevacizumab is a monoclonal which blocks binding of VEGF to its cell surface receptor. Of 12 patients treated with bevacizumab monotherapy, 2 achieved a partial response and 6 tumor stabilization. Treatment with immune checkpoint inhibitors seems promising with complete response in 1 and partial regression in 7 (9) of 29 treated patients. There is no clear difference between the effects of PD-1 blockers and dual inhibitors (anti-CTLA-4 + anti-PD-1). Biomarkers for selecting patients who will benefit from ICI remain to be identified.

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Basic Physiology Workshop

New techniques and approaches

BPW1.1

Abstract Unavailable

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BPW1.2

Modelling exercise in cells, mice and man - the importance of timing

Brendan Gabriel
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Regular exercise training has widespread health benefits by positively affecting nearly all organ systems of the body. Human physiology and the adaptive response to acute and chronic exercise training have largely been elucidated in the field of exercise science. This field has used model systems, organisms and has a strong history of human studies. Recently, the effect of exercising at different times of day and the interaction of exercise with circadian rhythm has been of growing interest in the field. Environmental cues, such as the Earth's day-night rhythm, partly regulate diurnal endocrine signalling molecules and metabolites. Circadian physiology consists of highly conserved biological processes over ~24-h cycles, which are influenced by external cues (Zeitgebers – 'time-keepers'). Skeletal muscle has diurnal variations of a large magnitude, owing in part to the strong nature of physical activity throughout the day and other external Zeitgebers. Exercise also interacts with circadian rhythm in a bi-directional manner. Skeletal muscle contractions can alter the rhythmic cycling of the molecular clock, and exercise capacity is altered at different times of the day. Modelling this in cell and mouse models has many challenges, although these models are essential to uncovering the chronobiology connected to exercise. From integrating these models, and human data, our evidence suggests these diurnal variations are disrupted in the skeletal muscle of people with Type 2 Diabetes and this disruption is linked to aberrant cross-talk between the molecular clock and mitochondria. Additionally, exercise is a potent therapeutic intervention in many metabolic diseases. However, exercise at different times of the day in people with Type 2 Diabetes may have opposing outcomes on glycaemia during the day of exercise. Optimising exercise timing, therefore, might be a valuable contributor to improving treatment regimens of people with metabolic and endocrine disorders.

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BPW1.3

Female endocrine adaptation to arduous training

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Our understanding of endocrine adaptation to exercise is underpinned by studies which demonstrated a causative link between low energy availability, hypothalamic-pituitary-adrenal (HPA) axis activation and hypothalamic-pituitary-gonadal (HPG) axis suppression. These and myriad other effects have been observed in elite athletes, termed Relative Energy Deficiency in Sport (RED-S), whereby negative hormonal and metabolic ramifications of exercise can be mitigated by increasing the nutrition: exercise ratio. However, many individuals experience non-exercise stressors concurrent to exercise (e.g., dealing with conflict, insufficient sleep, or time pressures) and there is uncertainty around hormonal adaptation to exercise in this 'arduous' training context. This talk will explore some contentious issues surrounding exercise endocrinology, presenting data from longitudinal studies of military women and men who exercised during multi-stressor training. The findings are not solely explained by the RED-S paradigm and are pertinent to the current debate between RED-S and overtraining syndrome. The need for future studies will be discussed, including how we might attempt to delineate the impact of non-exercise stressors from low energy availability.

DOI: 10.1530/endoabs.86.BPW1.3

New advances in neuroendocrinology

BPW2.1

How does the brain know what you've eaten?

Cristina Garcìa-Cáceres
Helmholtz Munich, Munich, Germany

The underlying basis for understanding of how brain control energy homeostasis, resides in a functional and coordinate communicating pathways between peripheral endocrine organs and the brain, in which the hypothalamus plays a pivotal role in the integration and processing of peripheral metabolic cues into satiety and feeding signals. Glial cells in particular astrocytes, as being an integral cell type of the neurovascular unit forming direct physical contacts with cerebral blood vessels, occupy a privileged position within the brain parenchyma to survey the metabolic status of the organism and to, in turn, modulate the activity of local neurocircuitries to match with whole-body energy demands. Via both physical contact and by releasing an array of soluble factors, astrocytes crucially contribute to control the selective access of circulating factors into the brain. Consistent with this, our previous studies have demonstrated that insulin signaling in astrocytes regulate the glucose entry into the brain and in turn cooperate with neurons in the regulation of feeding and systemic glucose metabolism. We have recently reported that astrocytes also respond to other peripheral hormones like leptin to promote hypothalamic angiogenesis and hypertension in diet-induced obesity. Interestingly, we observed that silencing specific metabolic receptors in hypothalamic astrocytes prevent microvascular dysfunction and the rise of systemic blood pressure in response to high-calorie diets. Therefore, our findings and ongoing studies are focused on unraveling the cellular and molecular basis in the communication between astrocytes and neurovascular beds for the brain control of metabolism, as representing potential cellular targets to fight obesity and its comorbidities such as hypertension.

DOI: 10.1530/endoabs.86.BPW2.1

BPW2.2

New methods to investigate the GnRH pulse generator

Kevin O'Byrne
King's College London, London, United Kingdom

The neural construct underlying the hypothalamic GnRH pulse generator has only recently been identified despite its elegant electrophysiological manifestation (abrupt increases in multiunit electrical activity volleys invariably associated with LH pulses) described over 40 years ago by Ernst Knobil. Following the identification of the arcuate KNDy (Kisspeptin/Neurokinin-B/Dynorphin) neurones as the critical component of the GnRH pulse generator, direct in-vivo calcium imaging of their activity at a population (fibre photometry) and single-cell (gradient-index [GRIN] lens microendoscopy) level has revealed a pattern of episodic synchronisation invariably associated with LH pulses. Although these cutting-edge techniques have greatly advanced our understanding of the GnRH pulse generator, our mathematical modelling highlights that the KNDy neuronal population undergoes sudden qualitative changes in its dynamic behaviour as the basal activity of the population is modulated. In particular, as the basal activity level is increased the system transitions from a silent into a pulsatile mode, while higher levels of basal activity inhibit pulses and reinstate the quiescent state. Crucially, these sudden transitions are a rudimentary characteristic of the mechanisms underlying pulse generation per se. These experimental and modelling techniques will be explored in this presentation.

DOI: 10.1530/endoabs.86.BPW2.2

BPW2.3

How does the pituitary decode GnRH signals?

Daniel Bernard
McGill University, Montreal, Canada

Gonadotropin-releasing hormone (GnRH) plays fundamental roles in the control of reproductive physiology. Perturbations in GnRH production or secretion cause infertility or subfertility. GnRH analogs are used clinically to both promote and inhibit the reproductive axis. GnRH is produced in neurons in the hypothalamus and is released in pulses into the pituitary portal system. The hormone binds to its cell surface receptor, GnRHR, on pituitary gonadotrope cells, where it stimulates the synthesis and secretion of the gonadotropins, luteinizing hormone (LH) and

follicle-stimulating hormone (FSH). LH and FSH regulate key processes in the gonads, including steroidogenesis and gametogenesis. Gonadal steroids feedback to the brain and pituitary to regulate their own synthesis through both negative and positive (in females) feedback. Steroid negative feedback inhibits GnRH secretion, slowing pulsatile GnRH release. Estrogen positive feedback may promote a surge of GnRH release (at least in some species) and amplifies the pituitary response to GnRH, leading to a surge of LH, which triggers ovulation. More than four decades ago, it was discovered that the frequency of GnRH pulses differentially impacts LH and FSH secretion. High and low GnRH pulse frequencies favor LH and FSH release, respectively. However, the mechanisms through which gonadotropes 'decode' pulse frequency have remained elusive. In this lecture, I will discuss our recent efforts, using genetically modified mice, to understand how GnRH differentially regulates LH and FSH synthesis and secretion. Our data may challenge the concept of the gonadotrope as a GnRH pulse frequency decoder or at least may require a change in thinking about the nature of GnRH signaling in gonadotropes.

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How Do I...? Sessions

How Do I…? 1

HDI1.1

Abstract Unavailable

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HDI1.2

How do I diagnose and manage post-bariatric hypoglycaemia?

Tricia Tan
Imperial College London, London, United Kingdom

Bariatric or metabolic surgery, such as Roux-en-Y gastric bypass and sleeve gastrectomy are becoming increasingly prevalent as these treatments are now recommended as treatment choices for obesity and type 2 diabetes. Post-bariatric hypoglycaemia (PBH), typically a post-prandial hyperinsulinaemic hypoglycaemia occurring 1-3 hr after ingestion of food, is now more commonly encountered in practice, presenting either to endocrine/metabolic outpatient clinics or during medical on-calls. In this talk I will review the presentation and aetiology of this condition, with remarks on the diagnostic tests. I will also speak about the management of this condition.

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HDI1.3

How do answer the common difficult questions from patients with hypothyroidism?

Annice Mukherjee
Spire Manchester Hospital, Manchester, United Kingdom

Many people are now obtaining health information from social media. Misinformation and conflicts of interest are rife on these platforms and can filter into the clinical setting, where patients increasingly attend with unrealistic expectations. The thyroid clinic is a prime example. Misconceptions can sometimes set the agenda and make consultations challenging. Here I will share my clinical experience about how to answer common difficult questions in the thyroid clinic and respectfully challenge and debunk patient misconceptions.

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HDI1.4

How do I use TRAb measurements to guide management in my patient with Graves' disease (GD)

Prakash Abraham
Aberdeen Royal Infirmary, Aberdeen, United Kingdom

TSH receptor antibody (TRAb) assays are highly sensitive and specific for the diagnosis of Graves' disease. TRAb can minimise need for additional radiological modalities such as ultrasound and isotope scan in excluding other causes of hyperthyroidism. The relapse rates of hyperthyroidism following a course of anti-thyroid drugs (ATDs) remains disappointingly high at between 50-70%. TRAb levels at diagnosis and at the completion of a course of ATDs can be useful in predicting potential relapse rates of over 80% where perhaps the patient is better served by choosing a definitive treatment option such as radioiodine (RAI) or surgery at an earlier stage. For patients who choose RAI as the definitive treatment options a high TRAb level is a predictor of potential Graves' opthalmopathy and can influence the choice of using steroid prophylaxis. TRAb measurement is useful in pregnancy planning in suitable patients, for consideration of definitive options to minimise the use of ATD (and risk of congenital defects). High TRAb concentrations (>3 times cut off) during pregnancy can prompt additional monitoring of the fetus for thyroid dysfunction. TRAb levels are useful in determining duration of therapy in Paediatric Graves' disease with the recommendation to stop ATD therapy only when TRAb levels have been low for several months. TRAb levels can help guide duration of ATD therapy in patients with immune reconstitution Graves' disease.

Key References:

Kahaly G, J, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce S, H: 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J 2018;7:167-186. doi: 10.1159/000490384 Hesarghatta Shyamasunder, A. and Abraham, P. (2017), Measuring TSH receptor antibody to influence treatment choices in Graves' disease. Clin Endocrinol, 86: 652-657. https://doi.org/10.1111/cen.13327

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HDI1.5

How do I monitor a patient on mitotane?

Cristina Ronchi
University of Birmingham, Birmingham, United Kingdom

Adrenocortical carcinoma (ACC) is a rare endocrine tumour with a generally poor prognosis. Mitotane is the only approved drug for treatment of advanced ACC ("palliative" setting). However, response is relatively poor with up to 20% of patients experiencing objective response (Megerle 2018). Moreover, adjuvant treatment with mitotane is frequently recommended for patients at high risk of disease recurrence after surgery (Terzolo 2007, Fassnacht 2018). Of note, mitotane is a difficult drug to manage, with a long half-life, a narrow therapeutic window and a high degree of dose-limiting toxicity. In fact, mitotane is associated with several adverse events, including adrenal insufficiency, gastrointestinal-, central nervous system-, liver- and other endocrine-related. Also, mitotane interferes with the metabolism of several medications due to the activation of the liver enzyme CYP3A4. Currently, there are no reliable biomarkers predictive of response to treatment, mitotane plasma levels greater than 14 mg/L have been associated with longer survival (Hermsen 2011, Puglisi 2019, Puglisi 2020). Therefore, the management of patients under treatment with mitotane requires careful evaluation and frequent monitoring, which should be carried out in an expert centre. During the session, I will summarise the recommendation for the management of patients treated with mitotane, according to the current European Guidelines (Fassnacht 2018 and 2020). This will include the following points:

1. Choice of initial mitotane dose regimen
2. Hydrocortisone replacement treatment
3. Regular monitoring by clinical assessment and surveillance blood tests
   - U&E, liver function, blood count and plasma mitotane concentrations (initially every 3–4 weeks, then every 2–3 months).
   - Plasma renin, thyroid function, testosterone (in males), lipid profile should be monitored every 3-4 months.
     1. Mitotane dose titration
     2. Mitotane treatment duration

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HDI1.6

How to manage normocalcaemic hyperparathyroidism

Marian Schini
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Normocalcaemic hyperparathyroidism (NPHPT) is characterised by persistently normal calcium levels and elevated PTH values on at least two consecutive measurements, after excluding other causes of secondary hyperparathyroidism. This group of patients is challenging to identify and characterise. The prevalence of the disease in the literature varies significantly due to the various definitions used and the fact that not all causes of secondary hyperparathyroidism have been excluded. Its natural history is also quite unclear, with studies showing persistent normocalcaemia, progression to hypercalcaemia, or even intermittent hypercalcaemia. Clinical features of NPHPT can be similar to those in primary hyperparathyroidism (PHPT). Some, but not all studies from referral centres have shown that the frequency of skeletal complications, is similar to PHPT. The data on kidney stones and nephrolithiasis is also inconclusive. There have been some studies which showed potential benefit from surgical intervention, but the definitions in these studies vary, so, until more studies are available, the recommendation is to observe and follow up these patients with blood tests and BMD measurements

DOI: 10.1530/endoabs.86.HDI1.6

How Do I….? 2

HDI2.1

Outstanding clinical practioner award: how do i wean patients who have had pituitary or adrenal cushings syndrome off glucocorticoids once they are in remission?

Karim Meeran
Imperial College, London, United Kingdom

Following pituitary or adrenal surgery, an undetectable morning cortisol suggests remission, and the patient needs to be discharged on replacement glucocorticoid, either thrice-daily hydrocortisone (commonly 10mg in the morning, 5 mg at noon and 2.5mg at 4pm) or once-daily prednisolone (commonly 3mg to 4mg)[1]. Low-dose once-daily prednisolone is seven times more potent than hydrocortisone[2]. Weaning prednisolone is easier than weaning hydrocortisone[3]. Corticosteroid replacement will be required until the axis recovers. Previous prolonged exposure to cortisol will have suppressed pituitary corticotrophs and in the case of a unilateral adrenal adenoma secreting cortisol, the contralateral adrenal may also have atrophied, further prolonging recovery of the HPA axis. Recovery can take over a year. Because the patient is acclimatised to high levels of glucocorticoids, they start of with generous replacement. Prednisolone 6mg once daily for the first week reducing to 5mg daily after a week, and then they are continued on 4mg daily. We run a uPLC-LCMS/MS assay[4] and a single 6h (30-44mcg/l) or 8h (15-25mcg/l) level will suffice to confirm of refute excessive replacement. A hydrocortisone day curve is used on some units. Where levels are high, the dose can be reduced to 3mg daily. They usually stay on 3mg or 4mg for several months. An early morning cortisol is checked every 8 weeks. An early morning cortisol measured before a morning dose of prednisolone serves as a guide to HPA axis recovery. Once the morning cortisol is over 200nM, the prednisolone can be weaned further[5]. We are recruiting further NIHR centres to the HYPER-aid study to compare prednisolone with hydrocortisone replacement and generate evidence in favour of one of these agents. Please let me know if your centre is interested in joining this study.

DOI: 10.1530/endoabs.86.HDI2.1

HDI2.2

Outstanding clinical practioner award: how do i rationalise withdrawal of liothyronine (T3) in a symptomatic tired, depressed and vulnerable patient with chronic fatigue syndrome or long COVID who may or may not have hypothyroidism?

Karim Meeran
Imperial College, London, United Kingdom

Patients on thyroxine have lower psychological well-being than controls using the GHQ12 questionnaire, which gives patients a score between 0 (very happy and well) and 36 (profoundly exhausted and feeling worthless). Average GHQ was 11.39 in controls and 12.09 in patients optimised on thyroxine($P=0.028$)[1]. Liothyronine has a large and sustained placebo effect with the GHQ improving from 13.5 to 11.0 in the WATTS study[2]. This placebo effect needs careful explaining to patients. A genetic reanalysis of the WATTS study suggested an association between one point mutation and response to liothyronine in the subset of patients with one particular allele[3]. Various websites wrongly interpret this and suggest that those patients with "the gene" (allele CC in the SNP rs225014 which was associated with a Thr92Ala mutation) would be tired unless they were given liothyronine, despite having normal plasma T3 levels. A trial of liothyronine for patients who are tired despite adequate thyroxine replacement is fraught with the placebo effect, and benefit is also seen with placebo when patients are blinded but not in open label studies. Further studies have found no linkage of this gene with tiredness, even in those who are particularly tired on levothyroxine and apparently responded to liothyronine[4]. Resolution of life events that may have occurred after patients started liothyronine makes patients associate liothyronine with improvement in quality of life. They are often taking other placebos such as Ashwaganda, Turmeric and Co-enzyme Q. Listening to their story, reassuring such patients, and monitoring thyroid function while slowly weaning liothyronine has been the most successful method. It is essential that any future studies of liothyronine are carefully planned and properly randomised and blinded to avoid all the biases of previous studies. Open label studies of liothyronine are misleading and should not be carried out.

DOI: 10.1530/endoabs.86.HDI2.2

HDI2.3

How do I choose an oral contraceptive for my patient with PCOS?

Michael O'Reilly
Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland

This talk will focus on contraceptive options for patients with polycystic ovary syndrome (PCOS). Key considerations for clinicians will be explored, including the choice of appropriate formulations for cycle regulation, control of symptoms of androgen excess and suppression of dysfunctional menstrual bleeding. Other issues covered during this session will include contraceptive options in patients with obesity or at high risk of complications such as venous thromboembolism, as well as the potential metabolic effects of distinct systemic preparations.

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HDI2.4

How do I manage a patent with menopausal symptoms in whom HRT is contra-indicated?

Julia Prague[1,2]
[1]Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom; [2]University of Exeter, Exeter, United Kingdom

Seventy percent of menopausal women experience vasomotor symptoms (hot flushes and/or night sweats), and 10% will describe them as intolerable, but many will have a contraindication and/or aversion to hormone replacement therapy which is the most effective treatment. Therefore, for those women current treatment options are limited and include herbal remedies, centrally acting modulators of neurotransmitter concentrations (eg SSRIs/SNRIs), clonidine, and cognitive behavioural therapy. However, oral neurokinin 3 receptor antagonists should be available in the near future and could revolutionise management by offering an effective therapeutic for menopausal vasomotor symptoms that does not require oestrogen exposure. In view of the recent media coverage regarding testosterone for menopausal symptoms, this will also be discussed as will the use of vaginal oestrogen for local vaginal symptoms.

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HDI2.5

How do I investigate hypophosphataemia?

Jeremy Turner
Department of Endocrinology, Norfolk and Norwich University Hospital, Norwich, United Kingdom

Hypophosphataemia is a common mineral metabolic abnormality affecting 2-3% of all hospital in patients and up to 34% of ICU patients. The causes are numerous. Over the last two decades following the identification of Fibroblast growth factor-23 (FGF-23) as the phosphaturic hormone responsible for Autosomal Dominant Hypophosphataemic Rickets (ADHR) in 2000 there has been an explosion in the understanding of phosphate homeostatic physiology and disorders of phosphate homeostasis. In this brief presentation I will provide an overview of hypophosphataemia, a structured approach to considering the causes of hypophosphataemia, review the physiology of phosphate homeostasis and go through a suggested approach to the investigation of this problem. I also aim to demystify the tubular maximum reabsorption of phosphate (TmP) / GFR test including a, hopefully fairly simple, description of the TmP/GFR test, when and how to perform it and how to interpret it. Finally, I will cover specific situations such as measuring FGF-23 in renal failure and the merits of using the C terminal vs the intact FGF-23 assays.

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HDI2.6

Abstract Unavailable

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Meet the Expert Sessions

Nurse

MTE1

Interventions for preventing adrenal crisis - behavioural insights

Lisa Shepherd[1, 2], Kelly Ann Schmidtke[3], Jonathan Hazlehurst[1,2], Eka Melson[1,2], Janine Dretzke[2], Noel Hawks[4], Wiebke Arlt[1,2], Abd Tahrani[1,2], Amelia Swift[2] & Debbie Carrick-Sen[2]
[1]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [2]University of Birmingham, Birmingham, United Kingdom; [3]University of Warwick, Warwick, United Kingdom; [4]Addisons Disease Self Help Group, Bristol, United Kingdom

Adrenal crisis and death still occur frequently in people with adrenal insufficiency, despite interventions being developed to prevent this. Interventions focus on increasing patients' knowledge of their medication, their condition, and the action to take during acute stress. It is not known why the application of this knowledge does not happen during times of need. Behaviour change models/frameworks can aid the understanding of this knowledge gap. We performed a systematic review that aimed to identify and evaluate interventions developed to prevent adrenal crisis in people with primary adrenal insufficiency. Interventions were described using the TiDIER checklist, along with the identification of behaviour change techniques applied. Then, techniques were mapped onto the Behaviour Change Wheel components to identify barriers and facilitators targeted by the interventions and gaps which could be filled by future interventions.

DOI: 10.1530/endoabs.86.MTE1

MTE2

Endocrine complications after childhood cancer

Cecilia Follin
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Due to remarkable improvements in treatment and supportive care over the past several decades, survival rates for childhood cancer currently exceed 85%. Nevertheless, survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications and cardiovascular morbidity. Research report that 40-50% of survivors will develop an endocrine disorder over their lifetime. Deficiencies of one or more anterior pituitary hormones have been described following therapeutic CRT for primary brain tumours, nasopharyngeal tumours, and following prophylactic CRT for childhood acute lymphoblastic leukemia (ALL). For at risk-survivors, new endocrinopathies can develop decades following cancer treatment, and life-long surveillance is mandatory. Studies have consistently shown a strong correlation between the total radiation dose and the development of pituitary deficits. Further, age at treatment and also time since treatment has strong implications on pituitary hormone deficiencies. Risk factors for low BMD include high dose methotrexate, cumulative doses of glucocorticoids, male gender and low physical activity. Any combination of these factors may result in osteopenia, not reaching optimal peak bone mass and osteoporosis later in life. Detailed information about the past cancer treatment including surgery, the type and cumulative doses of chemotherapy, and radiotherapy volumes and doses are needed to estimate health risks associated with childhood cancer. A risk-based care approach, for all childhood cancer survivors, should include a systematic plan for lifelong screening, surveillance, and prevention that incorporates risk estimates.

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Adrenal and Cardiovascular

MTE3

Abstract Unavailable

DOI: 10.1530/endoabs.86.MTE3

Thyroid

MTE4

Abstract Unavailable

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Endocrine Cancer and Late Effects

MTE5.1

Abstract Unavailable

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MTE5.2

How to identify brittle bones after childhood cancer therapy

Jenneke van Atteveld[1] & Sebastian Neggers[2]
[1]Princess MÁxima Center for Pediatric Oncology, Utrecht, Netherlands; [2]Erasmus University Medical Center, Rotterdam, Netherlands

In this workshop, we would like to discuss several clinical cases in the context of our recently published/collected data on bone health after childhood cancer therapy (below). Although risk factors for reduced BMD in childhood cancer survivors (CCS) had been identified, it remained unknown which survivors were at highest absolute risk of reduced BMD and might benefit from BMD assessment by DXA. In collaboration with the American SJLIFE cohort (n = 2, 032), we developed prediction models for low and very low BMD in adult CCS, and externally validated these models on a single-center Dutch cohort ($n = 403$). The models included male sex, lower weight, shorter height, younger attained age, smoking, and cranial and abdominal irradiation and correctly identified BMD status in most white adult survivors. In addition, we and others developed an evidence-based international guideline for BMD surveillance in CCS. In short, BMD surveillance is now recommended for survivors treated with cranial/craniospinal or total body irradiation using DXA at entry into long-term follow-up (2-5 years after completion of therapy), and if normal (Z-score >-1), again at 25 years of age. Several of the gaps in knowledge that had been identified in the guideline could be addressed in our subsequent study in a national cohort of adult Dutch CCS ($n = 2, 003$). We observed that CCS have a 3.5 times (males) or 5.4 times (females) increased risk of any fracture, and also the frequency of vertebral fractures seems to be increased in this group (13.3%). For the first time, it was shown in a multivariable model that reduced BMD (especially very low lumbar spine BMD) is indeed significantly associated with a history of fractures in CCS, which highlights the importance of BMD surveillance. Several novel associations between previous cancer treatment, endocrine disorders, and vitamin deficiencies and reduced BMD and fractures were observed.

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Bone and Calcium

MTE6

Imaging of bone for endocrinologists; from DXA onwards

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Osteoporosis causes bones to become weak, porous and fracture more easily. While a vertebral fracture is the archetypal fracture of osteoporosis, it is also the most difficult to diagnose clinically. Patients often suffer further spine or other fractures, deformity, height loss and pain before diagnosis. There were an

estimated 520, 000 fragility fractures in the UK in 2017 (costing È4.5 billion), a figure set to increase 30% by 2030. One way to improve both vertebral fracture identification and the diagnosis of osteoporosis is to assess a patient's bones during routine Computed Tomography (CT) scans, often done for monitoring of endocrine conditions. Patients attend routine CT for diagnosis and monitoring of various endocrine conditions, but the skeleton can be overlooked as radiologists concentrate on the primary reason for scanning. More than half a million CT scans done each year in the NHS could potentially be screened for osteoporosis (increasing 5% annually). Several companies have developed software methods to diagnose osteoporosis/ fragile bone strength and/or identify vertebral fractures in CT datasets, using various methods that include image processing, computational modelling, artificial intelligence and biomechanical engineering concepts. These and other methodologies of interest to the endocrinologist will be evaluated in the session.

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Reproductive and Neuroendocrinology

MTE7

How to study sex: new approaches for investigating sex determination pathways

Roberta Migale
The Francis Crick Institute, London, United Kingdom

Unlike most organs whose fate is pre-determined, mammalian gonads are unique as they originate from a pair of bipotential genital ridges that can develop as either ovaries or testes depending on which genetic program is activated during embryonic life. The discovery of genes important for sex determination, notably SRY/SOX9 in the testis and FOXL2/WNT4 in the ovary, has benefited from the study of human disorders of sex development (DSD) and animal models, such as the mouse. However, half of DSD cases typically remains undiagnosed. Advances in next-generation sequencing technologies have enables the genome-wide profiling of ovaries and testes during the window of sex determination, down to single cell level, thus providing a comprehensive overview of which genes are expressed and what is the chromatin epigenetic status at critical developmental stages. Together with the advent of CRISPR-Cas9 technology, a powerful genome editing tool, these technologies have allowed to uncover the role of the noncoding genome, which represents 98% of the human genome, in controlling conserved sex determination pathways. Recent data have also demonstrated that female sex determination is not a default pathway but an active, gene-directed process which must be maintained active throughout life. Interaction proteomics approaches have been used to dissect the molecular mechanism of sex maintenance in the ovary thus allowing the identification of the critical players that safeguard the ovary from ovary-to-testis transdifferentiation in adulthood. The latest developments in the application of omics technologies to the investigation of sex determination and gonadal development pathways will be discussed in this session.

DOI: 10.1530/endoabs.86.MTE7

Metabolism, Obesity and Diabetes

MTE8

Metabolic lessons from patients undergoing sex reassignment

Martin den Heijer
Amsterdam UMC, Amsterdam, Netherlands

It is well known that cardiovascular risk differs between men and women and that this difference also changes over life. Sex hormones are thought to play a critical role in these differences, although it is difficult to distinguish between hormonal, chromosomal and environmental factors. Part of the effect of sex hormones can be explained by the effects of sex hormones on body composition, blood pressure, and lipid and glucose metabolism. Transgenders feel incongruence between their experienced gender and their sex characteristics. Today, many of them want to start hormonal treatment to get the sex characteristics that match their gender identity. In the past, doctors were concerned about the effects of this treatment on cardiovascular disease, cancer and osteoporosis. This led to short and long follow-up studies on the safety of this new treatment. In my talk, I will present the results of these studies and show how they inform physicians involved in transgender care. Furthermore, I would like to present how these studies also provide mechanistic insights into the effect of sex hormones, which are not easy to obtain outside the transgender population.

DOI: 10.1530/endoabs.86.MTE8

Clinical Skills

Radiology for the endocrinologist

SK1.1

Trials and tribulations of targeting 11β-HSD1

Jeremy Tomlinson
University of Oxford, Oxford, United Kingdom

Within tissues, glucocorticoids (both endogenous and exogenous) are metabolised by a series of enzymes that have the ability to tightly control local hormone availability and thus regulate binding to, and activation of, the glucocorticoid receptor. The 11β-hydroxysteroid dehydrogenases (type 1 [11β-HSD1] and type 2 11β-HSD2]) interconvert active (cortisol, prednisolone and corticosterone) and inactive glucocorticoids (cortisone, prednisone and 11-dehydrocorticosterone). 11β-HSD1 is highly expressed in metabolically active tissues (including liver, adipose and muscle) where it regenerates active glucocorticoids, amplifying their action. Increased 11β-HSD1 activity and expression have been postulated to drive adverse metabolic features in rodents and humans. As a result, selective 11β-HSD1 inhibitors have been developed as a treatment for the metabolic syndrome acting to limit tissue-specific glucocorticoid regeneration and action. Whilst cellular and preclinical data showed marked promise, data from clinical studies were less impressive and as a result, interest in their use as metabolic modifying drugs has waned. However, more recently data are emerging to suggest that these drugs may have a re-purposed role to limit the adverse effects of prescribed glucocorticoids. However, rodent studies have added a note of caution suggesting that in addition to limiting adverse effects, there may be some amelioration of the desirable, anti-inflammatory actions.

DOI: 10.1530/endoabs.86.SK1.1

SK1.2

Abstract Unavailable

DOI: 10.1530/endoabs.86.SK1.2

Basic Skills

How to go from bench to bedside

SK2.1

Abstract Unavailable

DOI: 10.1530/endoabs.86.SK2.1

SK2.2

Abstract Unavailable

DOI: 10.1530/endoabs.86.SK2.2

Early Careers Session

Research Pathways Outside of Academia

ECS1.1

Abstract Unavailable

DOI: 10.1530/endoabs.86.ECS1.1

ECS1.2

Abstract Unavailable

DOI: 10.1530/endoabs.86.ECS1.2

ECS1.3

Abstract Unavailable

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ECS1.4

An introduction to working in the world of scientific storytelling for the pharmaceutical, biotechnology, medical device and consumer health industries

Elly Spreckley
Random42, London, United Kingdom

‘MedComms’ involves the creation of content based on medical and scientific data to educate a wide-ranging audience on mechanisms of disease and mechanisms of action. Medical animation is a tool used in MedComms that intertwines the worlds of science, art and technology, to produce impactful scientific imagery, stories and interactive experiences. Scientists work closely with artists, animators and programmers, who collaborate to bring to life the complex workings of the body at the molecular level, which can be used to form the foundations of pharmaceutical marketing campaigns, educational pieces, or even produced for documentaries on the big screen.

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ECS1.5

Abstract Unavailable

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Career Perspectives Session

CPS1.1

Biological clocks and the endocrine system

Andrew Loudon
University of Manchester, Manchester, United Kingdom

Two major timing systems control all living organisms. The first is the "circadian" clock, which drives a vast array of internal physiological systems. This includes timing of hormone secretion, and interaction with intra-cellular signalling pathways. The second system is the less understood photoperiodic clock, in which virtually all life forms adapt to the passage of the seasons. Here, processes as diverse as reproduction, sexual behaviour, parental care, metabolism and fattening, hibernation, and seasonal migration are all driven by internal timers, entrained to daylength changes. The two systems (circadian and seasonal) are actually driven by common genetic mechanisms, such that some hormones (ie melatonin) are sculpted by the light dark cycle but interpreted by the clock. A major step forwards here has been the rapid increase in knowledge of the core genetic mechanisms driving the circadian clockwork in cells. With this, we have been able to explore how specific elements couple to and engage with key output circuits driving rhythmic physiology. I will illustrate this by offering two examples as a perspective. First, how the circadian clockwork is used to drive responses to the hormone melatonin, and links from this to how thyroid hormone signalling is employed to drive annual cycles. Secondly, we will touch on how the clock-work is used to tune inflammatory responses, and the cross-talk with anti-inflammatory glucocorticoids. In this session, my goal is to emphasise how little we yet still know, and offer options for interested young researchers to join this fast-growing field, with its untapped potential for application in medicine and beyond.

DOI: 10.1530/endoabs.86.CPS1.1

CPS1.2

Another insulin! what's not to like?

Jeff Holly
University of Bristol, Bristol, United Kingdom

Humans have 10 insulin-like genes, the most closely related being insulin and the adjacent gene, insulin-like growth factor II (IGF-II). Despite insulin being at the vanguard of endocrinology, the role of IGF-II has remained an enigma. IGF-II was first discovered with the observation that after all detectable insulin was depleted from serum with very specific antibodies, the vast majority of insulin activity remained. While insulin is a very simple gene, the IGF-II gene is far more complex. The activation of target cells by insulin is also relatively simple, enabled via the insulin receptor (IR) which has two alternatively spliced forms, IR-A and IR-B. In contrast, IGF-II activates both the IGF-I receptor and the IR-A with comparable affinities but is also tightly regulated by a very high affinity decoy-receptor and by 6 specific binding proteins. As IGF-II is vastly more abundant than insulin within the body it will be the primary activator of IR-A, other than during the immediate post-prandial phase. While genetic variants and defects of the IGF-I gene are associated with alterations in body growth; those of IGF-II are associated with metabolic defects. Lower mammals maintain their activity via grazing-eating providing continuous metabolic fuels. Higher mammals have evolved to stay active for long periods between meals and developed specialised visceral adipose stores to maintain energy supplies throughout the prolonged periods of fasting. This evolutionary transition was accompanied by a dramatic change in the pattern of IGF-II expression. I suggest that this has important consequences for humans who now revert to grazing-eating patterns. The more stringent regulation of IGF-II than the other insulin-like genes implies an important role, but the research community has devoted the least interest in it. I will give a perspective of a career attempting to address this question and the problems of challenging dogmas.

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CPS1.3

What talks to brown fat?

Barbara Cannon
Stockholm University, Stockholm, Sweden

The thermogenic activity of brown adipose tissue (BAT) may be a major determinant of energy balance and thus of obesity versus slimness. The acute and chronic regulation of BAT may therefore be a significant issue in body weight control. From a classical aspect where BAT is only controlled by nervous input, we see today a growing array of factors that have been forwarded as being physiologically important regulators. These factors include both classical hormones such as thyroid hormone and glucocorticoids but also a series of agents released from organs that are not classically considered endocrine (adipose tissue, the gut, muscles, etc.). Here I will discuss some of what is known today regarding the question "what talks to brown fat?"

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Nurse Sessions

Neuroendocrine tumours

NS1.1

The management of neuroendocrine tumours

Ashley Grossman[1,2]
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Neuroendocrine tumours, or NETs, are a heterogeneous group of tumours which may arise from many sites, but primarily from the gastro-entero-pancreatic (GEP) system, and the respiratory system as bronchial and occasionally thymic NETs. Many small NETs are diagnosed incidentally as appendiceal or gastric NETs, and generally act in a totally benign manner. Diagnosis is contingent on positive histopathology (positive chromogranin immunostaining, grading 1-3 based on the Ki-67 index), CT and MRI scanning, and especially functional imaging with ^{68}Ga-dotatate PET scanning for somatostatin receptors and ^{18}FDG-PET scanning for proliferative activity. However, there is no clear distinction between benign NETs and those which become metastatic, and all should be assessed in specialist centre with a multidisciplinary team. In many cases, such as most gastric NETs on a background of atrophic gastritis, or small pancreatic NETs, these may simply be observed with periodic surveillance. For more advanced NETs, the only curative option is surgery; however, this may be also offered even when the tumour is metastatic, with residual disease treated with a somatostatin analogue such as monthly octreotide LAR or lanreotide autogel, both of which have been shown to retard tumour progression. For more extensive or progressive disease, peptide receptor radionuclide therapy (PRRT) is a well-tolerated and highly effective treatment. In the face of more aggressive disease, various chemotherapy regimes are available, especially capecitabine/temozolomide for well-differentiated tumours and etoposide-platinum for poorly differentiated tumours. Molecular targeted therapy can also be used, such as sunitinib for pancreatic NETs, or everolimus for GEP/bronchial NETs. Currently, the outlook for patients treated at major centres is relatively good, with prolonged survival and a good quality of life even even metastatic. Increasing studies into new targeted therapies should further improve these outcomes in the near future.

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NS1.2

Abstract Unavailable

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NS1.3

Patient perspective of multiple endocrine neoplasia syndromes

Jo Grey
AMEND, Tonbridge, United Kingdom

AMEND provides information resources and support services to families with MEN syndromes, offering free membership, educational and peer support events, and a free Counselling Service provided by rare disease specialist psychotherapy organisation, Rareminds. Our 2021 Counselling Service feedback data ($n=24$) showed that the biggest issue by far for patients is dealing with their diagnosis (39% of respondents). Managing symptoms and treatment are also significant issues. The service showed that 78% of counselling service users presented to the service with moderate to severe distress, however, on completion of their sessions, 78.5% were scoring in the low-distress or healthy range. The preliminary results from our 2022 Member Survey ($n=38$) show that while around 90% of members feel confident discussing their condition with their specialist doctor, almost 60% felt that their GP did not understand their condition. Almost 45% of respondents felt that their biggest challenge related to their condition had been getting diagnosed, and 40% felt that their condition had a negative impact on their emotional health. Regarding helpful AMEND resources, around 90% of survey respondents rate our website and free membership pack as good/excellent. AMEND uses a variety of ways to provide information and support to MEN patients, including videos, books, comics, cartoons, virtual peer support meetings, an annual patient information day, and much more.

DOI: 10.1530/endoabs.86.NS1.3

Hot topics in endocrinology

NS2.1

Endocrine effects of checkpoint inhibitor immunotherapy

Helen Turner
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Immune checkpoint inhibitors are a new group of monoclonal antibodies against checkpoints in normal T Lymphocyte activation enabling immune system activation in order to target cancer cells. First used for treatment of melanoma in 2011, they are currently indicated for management of an increasing spectrum of malignancy. Endocrinopathy secondary to checkpoint inhibitors is commonly observed. This has led to a new group of patients requiring specialist investigation, management, follow-up and advice/support. In addition, these patients may have pre-existing endocrine problems, receive glucocorticoid treatment for other immune related inflammatory adverse effects and need steroid safety advice, or may have an incidentally detected abnormality detected in an endocrine organ during their extensive long-term follow-up. The endocrine specialist nurse is integral to all these aspects and collaboration with oncology is essential for optimal patient outcomes.

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NS2.2

Abstract Unavailable

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NS2.3

Menopause; it's not just a hot flush

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Over the last two decades, the menopause management pendulum has swung wildly from very few women wanting HRT to so many women wanting it, with the recent increased awareness in the media, that shortages have occurred. Some narratives have resulted in greater fear about menopause and unrealistic expectations about HRT. Conflicting reports have led to much confusion among women. In this talk, I will discuss the implications of menopause today for women in context, including relevance in the workplace, implications for long-term health, risks and benefits of HRT and how to help empower women realistically and holistically.

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NS2.4

Abstract Unavailable

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Craniopharyngiomas and new investigations

NS3.1

Abstract Unavailable

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NS3.2

Abstract Unavailable
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NS3.3

Abstract Unavailable
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Defining the Future of Endocrinology

FOE1.1

Abstract Unavailable
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FOE1.2

Abstract Unavailable
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FOE1.3

Abstract Unavailable
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FOE1.4

Abstract Unavailable
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FOE1.5

Abstract Unavailable
DOI: 10.1530/endoabs.86.FOE1.5

Cutting Edge Session

Endocrinology in a Warming Dirty World

CE1.1

Endocrine disrupting chemicals: new knowledge of health effects and policy implications

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Since reports published in 2015 and 2016 identified 15 probable exposure-outcome associations due to endocrine-disrupting chemicals (EDCs), new studies in humans has now deepened understanding of their effects on human health. Particularly stronghas emerged for relations between perfluoroalkyl substances and child and adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, reduced semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer. Evidence also exists for relations between bisphenols and adult diabetes, reduced semen quality, and polycystic ovarian syndrome; phthalates and prematurity, reduced anogenital distance in boys, childhood obesity, and impaired glucose tolerance; organophosphate pesticides and reduced semen quality; and occupational exposure to pesticides and prostate cancer. EDCs substantially cost society as a result of increases in disease and disability but-unlike other toxicant classes such as carcinogens-have yet to be codified into regulations as a hazard category. This presentation examines economic, regulatory, and policy approaches to limit human EDC exposures and describes potential improvements. In the EU, general principles for EDCs call for minimisation of human exposure, identification as substances of very high concern, and ban on use in pesticides. In the USA, screening and testing programmes are focused on estrogenic EDCs exclusively, and regulation is strictly risk-based. Minimisation of human exposure is unlikely without a clear overarching definition for EDCs and relevant pre-marketing test requirements. We call for a multifaceted international programme (eg, modelled on the International Agency for Research in Cancer) to address the effects of EDCs on human health-an approach that would proactively identify hazards for subsequent regulation.

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CE1.2

Abstract Unavailable

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CE1.3

Environmental endocrine disruption of brain and behavior across generations

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Environmental endocrine-disrupting chemicals (EDCs) are exogenous chemicals that perturb hormones and their actions. In our laboratory, we are studying how early life exposures to EDCs affect the developing brain and lead to behavioral dysfunctions in exposed individuals and their descendants across generations. To do this, pregnant rats are fed one of three treatments: the weakly estrogenic commercial polychlorinated biphenyl (PCB) mixture, Aroclor 1221 (A1221, 1 mg/kg); vinclozolin (VIN, 1 mg/kg), a fungicide with anti-androgenic properties; or the vehicle (3% DMSO in sesame oil). We monitor birth outcomes and postnatal development in female and male offspring. In adulthood, animals are run through a battery of behavioral tests to assess functional neurobiological changes. The brains of these rats are subsequently used to identify molecular and cellular changes underlying the behavioral phenotype. For multigenerational work, rats are bred to the F3 generation, which have no direct exposure to EDCs, in order to assess transgenerational epigenetic inheritance. Results show that directly exposed (F1 generation) rats exhibit sex-specific alterations in social, sociosexual, and anxiety-like behaviors. Gene-expression profiling of brains from these animals has identified suites of genes differentially affected by the EDCs compared to vehicle rats. From the transgenerational studies we find that social and anxiety-like behaviors are altered in a sex-specific manner, and that the lineage from which the F3 rats descend (paternal or maternal) plays a key role in outcomes, potentially due to differences in epigenetic programming of the germline between males and females. Current research seeks to determine how epigenetic marks may be retained across generations and lead to a behavioral phenotype. As a whole, this body of work indicates that gestational exposure to EDCs has life-long effects on the developing brain, neuroendocrine systems, and reproductive and social behaviors of exposed individuals, and their descendants. (Supported by NIH ES029464).

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Endocrine Network Sessions

Metabolism, Obesity and Diabetes

EN1

Abstract Unavailable
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Endocrine Cancer

EN2

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN2

Neuroendocrinology

EN3.1

Abstract Unavailable
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EN3.2

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN3.2

EN3.3

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN3.3

EN3.4

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN3.4

EN3.5

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN3.5

EN3.6

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN3.6

Thyroid

EN4

Abstract Unavailable
DOI: 10.1530/endoabs.86.EN4

Adrenal and Cardiovascular

EN5.1

"Management of iatrogenic adrenal insufficiency – tip of the iceberg"

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Approximately 1% of the population are on some form of long-term glucocorticoid therapy, either as an immunosuppressant or as replacement therapy for adrenal suppression. In recent years, it has become increasingly evident that many of these patients (even those on inhaled steroids) develop adverse consequences of this therapy with the development of iatrogenic Cushing's syndrome (and its adverse metabolic profile) and associated tertiary adrenal insufficiency due to hypothalamic pituitary adrenal axis suppression.
This session will discuss several challenges in relation to how best to manage these patients including:

- Who and how to screen for adrenal insufficiency?
- Balancing the need for steroids due to underlying conditions and management of adrenal insufficiency
- Strategies to aid recovery of adrenal function
- Reducing long term morbidity associated with adrenal insufficiency/ iatrogenic Cushing's syndrome in these patients

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EN5.2

Abstract Unavailable
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Bone and Calcium

EN6

Abstract Unavailable

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Endocrine Consequences of Living With and Beyond Cancer

EN7.1

Abstract Unavailable

DOI: 10.1530/endoabs.86.EN7.1

EN7.2

Incidence of endocrine deficits after management of brain tumours

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The adverse effect of childhood cancer and treatment thereof on growth was firmly established in the mid-1970's.The impact on growth is multifactorial, however, cranial irradiation was quickly established as one of the most important contributors. Exposure of the hypothalamo-pituitary (HP) region to radiation in childhood cancer survivors is now a well-established risk factor for the development of anterior hypopituitarism. The degree of hypopituitarism can vary between isolated deficiency of one axis to deficiency of all the anterior pituitary hormones. Irradiation of brain tumours accounts for the majority of childhood cancer survivors who receive HP axis exposure, however the HP region can also be exposed in treatment of other childhood cancers including nasopharyngeal carcinomas, acute leukaemias with central involvement and total body irradiation. The degree of hypopituitarism is dependent on a number of factors including radiation dose delivered to the HP region; dose fractionation; time since radiation; and degree of compromise of the axes from the tumour and prior surgery. Development of hypopituitarism most frequently follows a pattern, with GH almost exclusively the first axis affected. Thereafter the evolution of deficiencies is gonadotropin, ACTH and TSH deficiency, however TSH deficiency is now recognised to occur earlier than previously thought when based on a fall in free T4 values within the normative range. Diabetes insipidus is not a direct consequence of irradiation and when present other causes should be considered. Under-recognised and less frequently investigated has been the development of hypopituitarism in adult brain tumour survivors, who appear to have a similar incidence of hypopituitarism to childhood brain tumour survivors. Outwith of hypopituitarism, a number of childhood brain tumours receive craniospinal radiation placing these individuals at additional risk of primary hypothyroidism, benign and malignant thyroid nodules, hyperparathyroidism, low bone mass and possibly diabetes mellitus.

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EN7.4

Abstract Unavailable

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Reproductive Endocrinology and Biology

EN8.1

Clinical Management of Menopause

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Over the last two decades, the menopause management pendulum has swung wildly. After the publication of the Women's health initiative study in 2002, few women were prescribed HRT. With the recent increased awareness in the U.K. media, many women are requesting HRT, to the point that medication shortages have occurred. This overview will summarise the current national recommendations and how we arrived here. The talk will cover the implications of the increased menopause awareness among women, where we are now concerning the implications of menopause on long-term health, workplace concerns, risks and benefits of HRT and other relevant approaches to improve the menopause transition and postmenopausal health safely.

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EN8.2

Abstract Unavailable

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Endocrine Teaching Network

ETN1.1

The biomedical kitchen: Demystifying the laboratory for students

Niamh Martin
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I am a Consultant Endocrinologist and Reader in Endocrinology. I have a strong interest in undergraduate education and hold various educational roles at Imperial College London, including Head of Year 1, BSc in Biomedical Sciences. This is a new degree course aimed at students who want careers as biomedical researchers, tackling important human diseases. Hence, early development of laboratory skills is the backbone of this course and we have worked hard to develop new approaches to instil these skills in our students. To increase confidence in the laboratory, particularly in team working and practical skills, colleagues and I have worked together to develop 'The Biomedical Kitchen'. This is a new inter-departmental collaboration with Chemistry, drawing on parallels between cookery and science to support student confidence in starting in the molecular laboratory. My talk will describe how we developed and implemented 'The Biomedical Kitchen' and subsequently refined its delivery in response to student feedback, demonstrating how to foster learning of new, key laboratory skills in an enjoyable and novel way.

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Oral Communications

Bone and Calcium

OC1.1

Evaluation of efficacy and safety of a novel gene therapy drug (ARU-2801) for hypophosphatasia in non-human primates

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Objectives
Hypophosphatasia (HPP) is an inborn error of metabolism resulting from loss of function mutations in the tissue-nonspecific alkaline phosphatase (TNAP) gene. Asfotase alfa is an approved enzyme replacement therapy for HPP, while effective, it requires chronic multiple injections up to 6 times per week. We have developed a one-time gene therapy drug (ARU-2801: an adeno-associated viral vector expressing TNAP-D_{10}) for HPP and examined the safety and efficacy of ARU-2801 in *Alpl*$^{-/-}$ HPP mice. To develop the ARU-2801 for clinical use, we evaluate the efficacy and safety of ARU-2801 in non-Human primates.
Methods
Juvenile WT macaques were injected intramuscularly with either saline or 5.0E12, 1.0E13, 2.0E13, and 4.0E13 vector genome/kg dose levels of ARU-2801. Blood samples were collected from anesthetized animals and assessed for plasma ALP enzymatic activity and clinical chemistry evaluation. Deeply anesthetized primates were sacrificed and tissues were collected for histopathology and examination of the biodistribution of ARU-2801. Toxicities of chronic exposure to TNAP-D_{10} were evaluated using Von Kossa staining and CT scan.
Results
Following treatment with a single dose of ARU-2801, durable high plasma ALP levels (100-10,000 U/l) were achievable with normal physical activity and a healthy appearance. The clinical chemistry parameters of these animals did not show signs of liver toxicity, which is consistent with histopathology examination. ARU-2801 DNA was detected in only injected side muscle but not other organs by quantitative PCR analysis. Von Kossa staining and CT scan of the animal sacrificed at 9 months did not show any ectopic calcification.
Conclusion
Durable transgenic plasma ALP levels without any toxicities are achievable with ARU-2801 in NHPs, at levels that potentially could be efficacious in the clinic. ARU-2801, which can be administered as a single dose, has the potential to improve the quality of life for HPP patients by eliminating chronic administration.

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OC1.2

Hypercalcaemic mice harbouring a germline ablation of G-protein subunit alpha-11 have anaemia that is corrected by treatment with erythropoietin

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G-protein subunit α-11 ($G\alpha_{11}$), which is encoded by *GNA11*, plays a major role in calcium homeostasis by regulating parathyroid hormone (PTH) secretion, and germline loss-of-function mutations cause familial hypocalciuric hypercalcaemia type 2 (FHH2). Since $G\alpha_{11}$ is ubiquitously expressed, we investigated whether FHH2 is associated with additional non-calcitropic phenotypes by analysing mice harbouring a homozygous germline deletion of *Gna11 (Gna11*$^{-/-}$*)*. Studies were conducted in male and female mice aged 16-28 weeks in accordance with institutional welfare guidelines. *Gna11*$^{-/-}$ mice had significantly reduced body weight and viability. The proportion of viable *Gna11*$^{-/-}$ mice was ~25% less than expected from a Mendelian pattern of inheritance ($P=0.01$). Biochemical analysis showed that *Gna11*$^{-/-}$ mice were hypercalcaemic compared to wild-type (WT) mice (plasma adjusted-calcium $= 2.70 \pm 0.02$ mM vs. 2.33 ± 0.01 mM, $P<0.0001$), and hypercalcaemia was associated with significant increases in plasma PTH and 24-hour urine calcium excretion. Further detailed phenotyping demonstrated that *Gna11*$^{-/-}$ mice had reduced haemoglobin (13.3 ± 0.1 g/dL vs. 14.5 ± 0.1 g/dL, $P<0.0001$) and haematocrit compared to WT animals. The anaemia was not associated with altered serum iron or ferritin. Moreover, bone marrow histology did not detect fibrosis or reduced cellularity. Importantly, the haemoglobin values were negatively correlated with plasma adjusted-calcium ($r=-0.73$, $P<0.0001$), indicating that the hypercalcaemia may have an underlying role in the cause of the anaemia. As extracellular calcium has previously been reported to affect renal erythropoietin secretion, we assessed whether the anaemia was due to alterations in erythropoietin. Reverse transcription-quantitative PCR and protein blotting did not reveal any alterations in erythropoietin mRNA or protein expression in *Gna1*$^{-/-}$ mouse kidneys. However, subcutaneous administration of recombinant erythropoietin (1200U/kg bolus) normalised haemoglobin and haematocrit values in *Gna11*$^{-/-}$ mice at 4-days post-treatment. In summary, these studies highlight potential roles for $G\alpha_{11}$ and/or plasma calcium in erythropoiesis.

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OC1.3

X-linked osteoporosis caused by a novel c.892-2A>G plastin 3 (*PLS3*) splice variant

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A 24-year-old male was referred to endocrinology with multiple severe atraumatic vertebral fractures. In the preceding 10 years the patient had experienced a bimalleolar ankle fracture and numerous metacarpal and metatarsal breakages unrelated to trauma. There was no family history of osteoporosis and examination did not reveal any abnormalities in scleral colour, stature, dentition or facial/thoracic morphology. Dual-energy x-ray absorptiometry demonstrated severe densitometric spinal osteoporosis with a Z score of -4.5 (T score: -4.2). Bone mineralisation density (BMD) was estimated to be 44% below average for age. Femoral neck and total hip Z scores were -1.8 and -3.1, respectively. No disorders of calcium or phosphate homeostasis, thyroid disease, hypogonadism, malabsorption, or myeloma were identified, although 25-hydroxy vitamin D was deficient (22 nmol/l). C-terminal telopeptide (CTX) was elevated (0.95 mg/l) signifying increased bone turnover. DNA was extracted and demonstrated a novel hemizygous X-chromosome plastin 3 (*PLS3*) sequence variant (c.892-2A>G), which is predicted to abolish the acceptor splice site. *PLS3* mutations are associated with X-linked male osteoporosis, however, the mechanism responsible is unclear. PLS3 is integral to cytoskeletal actin bundle formation and these variants may facilitate dysregulated osteocyte mechanosensing signalling pathways responsible for bone homeostasis. We report a previously unrecognised *PLS3* splice variant (c.892-2A>G) responsible for the development of X-linked male osteoporosis. Subsequent cascade genetic testing confirmed the patient's mother, who has normal BMD, to be a homozygous carrier, while the patient's brother, who has significant history of fragility fractures, is heterozygous for this variant and awaiting densitometric assessment. Therefore, genetic analysis of *PLS3* should be considered in all young men with evidence of bone fragility to facilitate the timely identification of osteoporosis aetiology and management of patients and affected family members. Moreover, further research is required to understand the role of PLS3 in bone health and disease.

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OC1.4

Measurements of circulating conjugated and unconjugated vitamin D metabolites by enzyme hydrolysis combined with liquid chromatography mass spectrometry

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Recent in-vitro studies have shown that vitamin D metabolites undergo conjugation reactions by sulfation and glucuronidation and may be important mechanisms for the inactivation, storage and excretion of analytes. However the circulating concentrations and clinical significance of phase II vitamin D conjugation is unclear as current analysis has almost exclusively been restricted to measuring their unconjugated metabolite forms. In this study we aimed to develop an analytical method comprising enzymatic hydrolysis and liquid chromatography mass spectrometry (LC-MS/MS) to quantify circulating phase II conjugated vitamin D metabolites relative to unconjugated levels across

population groups. An optimized enzyme hydrolysis method by recombinant arylsulfatase and beta-glucuronidase was achieved for the deconjugation of four vitamin D sulfate and glucuronide conjugates respectively; 25-hydroxyvitamin D3 (25OHD3), 25OHD2, 3-epi-25OHD3 and 24,25-dihydroxyvitamin D3 (24,25(OH)2D3). The method conditions were validated according to industry guidelines and was applied to the analysis of conjugated and unconjugated metabolites in 170 human serum samples categorised by vitamin D supplementation status. As a proportion of the total vitamin D metabolite concentrations in circulation, sulfate conjugates ranged between 18-53%, whereas the proportion of glucuronide conjugate metabolites was lower, ranging between 2.7-11%. The abundance of conjugated metabolites varied between the four vitamin D forms: 25OHD3 48 ± 9%, 25OHD2 29 ± 10%, 3-epi-25OHD3 30 ± 8%, and 24,25(OH)2D3 62 ± 10%. This study has demonstrated for the first time that conjugated metabolites of vitamin D circulate in high abundance, often matching or exceeding levels of their unconjugated forms. The optimised analytical methods and findings from this study could have significant implications for interpreting vitamin D status in health. Our findings suggest combined measurements of both conjugated and unconjugated measurements may provide a more accurate interpretation of vitamin D status, particularly in light of the differences in conjugation activity observed across metabolites and in individual samples.

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OC1.5

Can pre-operative treatment with intravenous bisphosphonates or cinacalcet have an effect on intra-operative parathyroid hormone measurements?

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Introduction
Primary hyperparathyroidism is a common endocrine disorder, surgery is curative. Patients with severe hypercalcemia receive cinacalcet or intravenous bisphosphonates as bridging. Intra-operative-parathyroid-hormone (IOPTH) measurement improves surgical accuracy. Bisphosphonates may increase PTH, while cinacalcet reduces it. The main aim was to assess the effect of zoledronate and cinacalcet on IOPTH.
Method
Patients over 15-yo who underwent surgery between 2018-2022 for non-cancerous-single-gland enlargement were retrospectively selected through a prospectively maintained data-base at University-College Hospital, London. The magnitude of IOPTH drop was defined as a percentage at post-excision 5,10,15 minutes, relative to the highest pre-excision value.
Results
Total of 153 were included, 16 were excluded due to missing IOPTH values. Fifteen received zoledronate pre-operatively. 11 had cinacalcet in which four were also given zoledronate. Comparisons were made between the zoledronate only ($n=15$) vs non-treatment group ($n=111$) and cinacalcet ($n=11$) vs non-treatment-group. There was no significant difference between the IOPTH-percentage-drop in the zoledronate and non-treatment groups (Table). The number of patients who achieved at least 50% drop at 5 minutes was not significantly different. The IOPTH-percentage-drop at all time points was significantly higher in the cinacalcet group compared to the non-treatment group (Table), but no significant difference in the number of patients who achieved at least a 50% drop at 5 minutes. 133 of 137 were proven cured at three months while four had no three-month data.
Conclusion
Pre-operative treatment with cinacalcet, but not zoledronate gave rise to significantly higher IOPTH-percentage-drops but had no effect on the surgical outcomes. The small numbers, and overlapping treatments are limitations. This important finding warrants further evaluation through larger studies to assess implications of pre-operative cinacalcet on IOPTH measurements.

IOPTH-percentage-drop	5min		10min		15min	
	Median	p	Median	p	Median	p
Zoledronate	69.9%	0.743	75.3%	0.958	84.5%	0.86
Cinacalcet	79.5%		82.5%		88.4%	
No-treatment	66.5%	0.045	76.5%	0.018	83.6%	0.081

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OC1.6

The AXT914 calcilytic compound increases plasma calcium and PTH in a mouse model for autosomal dominant hypocalcaemia type 1 (ADH1)

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Heterozygous germline gain-of-function mutations of the extracellular calcium-sensing receptor (CaSR), a G-protein coupled receptor (GPCR), result in autosomal dominant hypocalcaemia type 1 (ADH1), which may cause symptomatic hypocalcaemia with low circulating parathyroid hormone (PTH) concentrations and hypercalciuria. Negative allosteric CaSR modulators, known as calcilytics, rectify the gain-of-function caused by CaSR mutations and are a potential targeted therapy for ADH1. However, calcilytic drugs are unavailable for clinical use and their effectiveness for the treatment of ADH1-associated hypocalcaemia is unclear. We investigated the orally active calcilytic AXT914, a quinazolinone derivative, for the treatment of ADH1 by *in vitro* and *in vivo* mouse studies of a heterozygous gain-of-function CaSR mutation, Leu723Gln, known as *Nuf*. Treatment of HEK293 cells stably expressing *Nuf* mutant (Gln723) CaSR with AXT914 concentrations ranging from 1-20nM decreased extracellular calcium-mediated intracellular calcium responses of the *Nuf* mutant CaSR in a concentration-dependent manner. Moreover, at 10nM, AXT914 successfully normalised the gain-of-function caused by the *Nuf* mutant CaSR. *In vivo* studies involving adult *Nuf* mice were performed in accordance with institutional welfare guidelines. A single 10 mg/kg dose of AXT914 or vehicle was administered by oral gavage to adult male and female *Nuf* mice. *Nuf* mice treated with AXT914 ($n=7$) had significant increases in plasma PTH concentrations at 30min post-dose (104 ± 29 pmol/l vs. 23 ± 4 pmol/l for vehicle-treated mice ($n=6$), $P<0.05$) and significant increases in plasma albumin-adjusted calcium at 120min post-dose (2.03 ± 0.02 mmol/l vs. 1.84 ± 0.02 mmol/l for vehicle-treated mice, $P<0.001$). AXT914 treatment did not alter plasma phosphate, magnesium, or creatinine concentrations. In summary, these studies demonstrate that AXT914 rectifies the gain-of-function caused by the *Nuf* mutant (Gln723) CaSR *in vitro*, and increases plasma calcium and PTH in *Nuf* mice *in vivo*. Thus, AXT914 represents a targeted therapy for clinical use in hypocalcaemia caused by ADH1.

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Endocrine Cancer and Late Effects

OC2.1

Generation of conditional *MEN1* knockout human induced pluripotent stem cells (iPSCs) provide a genetically-tractable disease model to investigate cell-type specific gene function

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Introduction
Germline and somatic inactivating *MEN1* variants are associated with a wide range of inherited and sporadic endocrine tumours. *MEN1* encodes the tumour suppressor Menin, a ubiquitously expressed scaffold protein, implicated in multiple cellular processes including transcription, epigenetic regulation, and modulation of key signaling pathways. Despite intensive study, the mechanisms leading to endocrine tumorigenesis remain ill-defined, in part reflecting a lack of physiologically relevant model systems. Here, applying a methodology known as CRISPR-FLIP, we report a conditional *MEN1* knockout human iPSC line, offering a novel platform to investigate cell-type specific gene function.
Methods
A targeting strategy was designed to introduce an invertible 'FLIP' cassette into exon 2 of the *MEN1* gene. Appropriate gRNA/Cas9 and custom-designed donor repair template (containing the FLIP cassette) vectors were generated and electroporated into the ChiPS4 cell line. Successfully targeted cells were then transfected with a piggyBac-GFP ERT2-Cre-ERT2 vector. GFP-expressing cells (indicating stable incorporation of ERT2-Cre-recombinase) were isolated, expanded and assessed for maintained pluripotency.

Results
Clonal cell populations with bi-allelic integration of the FLIP cassette within the *MEN1* gene and stable integration of ERT2-Cre recombinase were successfully generated. Maintained pluripotency was confirmed by retained expression of pluripotency markers and embryoid body formation. Confirming the utility of the cell model, treatment of undifferentiated cells with tamoxifen resulted in undetectable Menin expression after 5-days as assessed by Western blot and immunocytochemistry. Subsequently, the consequence of Menin depletion during differentiation was evaluated using RNA sequencing of tamoxifen-treated pancreatic endoderm cells (PDX1/SOX9 positive) undergoing differentiation to pancreatic progenitors (PDX1/NKX6.1 positive), identifying alterations in multiple genes and pathways relevant to endocrine development and tumorigenesis.
Discussion
Conditional *MEN1* knockout human iPSCs provide a powerful model to investigate gene function in physiologically-relevant cellular environments, thereby providing a tool that can offer novel insights into tumour biology and may be exploited for drug discovery.

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OC2.2

Promotion of thyroid cancer cell migration and invasion by the proto-oncogene PBF is mediated by FGD1 and N-WASP

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Thyroid tumor progression is dependent on cell motility, a highly complex process that involves the co-ordination of cell adhesion, actin dynamics and signal transduction. The proto-oncogene pituitary tumor-transforming gene (PTTG)-binding factor (PBF/PTTG1IP) is a transmembrane glycoprotein that is overexpressed in thyroid cancer and associated with a poorer prognosis. PBF significantly promotes thyroid cancer cell migration and invasion through phosphorylation at PBF-Y174 by Src kinase. The aim of this study was to identify downstream mediators of PBF-induced thyroid cancer cell motility. A phosphoproteomic screen was performed in normal thyroid epithelial cells (Nthy-ori 3-1) with and without stable PBF overexpression. Alterations in the phosphoproteome following PBF overexpression in Nthy-ori 3-1 cells revealed an enrichment of proteins involved in cytoskeletal arrangement, cell adhesion and small GTPase activity. The phosphorylation of FGD1 (FYVE, RhoGEF and PH domain-containing protein 1) and N-WASP (Neural Wiskott-Aldrich syndrome protein) was significantly altered with PBF upregulation. Given their involvement in small GTPase signaling and cell motility we investigated a role for FGD1 and N-WASP in PBF-induced motility of TPC-1 thyroid cancer cells by scratch wound migration and Transwell invasion assays. Notably, siRNA-mediated knockdown of either FGD1 or N-WASP significantly abrogated both PBF-induced cell migration and invasion. Co-expression of either FGD1 or N-WASP with PBF did not further stimulate cell invasion. However, PBF and N-WASP acted additively to induce cell migration. Taken together, our data suggest that both FGD1 and N-WASP mediate the induction of cell motility by PBF in thyroid cancer cells, revealing novel signaling events in thyroid tumor progression.

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OC2.3

Identification of five prolactin receptor variants with diverse effects on receptor signalling

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The prolactin receptor (PRLR) signals predominantly through the JAK2-STAT5 pathway regulating multiple physiological functions relating to fertility, lactation, and metabolism. Understanding of PRLR signalling is incompletely defined, with progress hampered by a lack of reported disease-associated variants in the genes for the prolactin hormone (PRL) and/or PRLR. To date, two common germline PRLR variants are reported to demonstrate constitutive activity, with one, Ile146Leu, overrepresented in benign breast disease, whilst a rare activating variant, Asn492Ile, is reported to be associated with an increased incidence of prolactinoma. In contrast, an inactivating germline heterozygous PRLR variant (His188Arg) was reported in a kindred with hyperprolactinaemia whilst an inactivating compound heterozygous PRLR variant (Pro269Leu/Arg171Stop) was reported in an individual with hyperprolactinaemia and agalactia. We hypothesised that additional rare germline PRLR variants, identified from large-scale sequencing projects (ExAC and GnomAD) may be associated with altered *in vitro* PRLR signaling activity. We therefore evaluated >300 previously uncharacterised non-synonymous, germline PRLR variants and selected ten variants for *in vitro* analysis based on protein prediction algorithms, proximity to known functional domains and structural modelling. Five variants, including extracellular, transmembrane and intracellular domain variants were associated with altered responses when compared to the wild-type receptor. These altered responses included both loss- and gain-of-function activities related to STAT5 signalling, Akt and FOXO1 activity as well as proliferation and apoptosis. These studies provide further insight into PRLR structure-function and indicate that rare germline PRLR variants may have diverse modulating effects on PRLR signalling, although the physiological relevance of such alterations remain to be defined.

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OC2.4

Delta-like non-canonical Notch ligand 1 (DLK1) – a novel biomarker in adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare malignancy with limited treatment options and a heterogenous prognosis. The histological diagnosis of ACC is complex and there is increasing interest in identifying and validating new immunohistochemical markers. Delta-like non-canonical Notch ligand 1 (DLK1) is a cleavable single-pass transmembrane protein. In humans, DLK1 is present in many tissues during foetal development, is restricted to progenitor/stem cells in a few adult tissues but is expressed in numerous malignancies. We have previously shown that DLK1 is overexpressed in ACC compared to normal adrenal gland and aldosterone producing adenomas. In a validation cohort of 196 ACC tumour samples (149 primary, 47 secondary), we have found that DLK1 is expressed in 96% of samples. Level of expression is independent of ENSAT stage, Ki67 index or hormonal activity of the tumour and consistent in primary and secondary disease in the same patients ($P=0.034$). Additionally, higher levels of DLK1 expression (above vs below median) are associated with a two-fold increased risk of disease recurrence after surgery (HR 1.93, $P=0.042$). Furthermore, we have found that serum DLK1 levels are detectable in patients with ACC and in an initial cohort are significantly higher in patients with ACC (mean = 20.41ng/ml, $n=8$) than patients undergoing adrenalectomy for other suspected adrenocortical pathologies (mean = 13.14ng/ml, $n=27$; $P=0.0003$). Pre-operative DLK1 serum levels can predict the diagnosis of ACC with a high level of specificity and sensitivity (ROC AUC = 0.8796; CI 0.7590 – 1.000, $P=0.0013$). Finally, raised serum DLK1 levels in ACC patients are significantly reduced post-operatively (17.55 to 10.77ng/ml, $n=4$; $P=0.0123$). Our data suggest that DLK1 expression is a disease defining event in ACC that may have a pathological role. In addition, DLK1 serum levels, in combination with immunohistochemical expression in tumours, may provide a clinically useful novel biomarker for the diagnosis and monitoring of ACC.

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OC2.5

Plasma metabolites correlate with disease in sdhx deficient cancer syndromes

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Approximately 40% of phaeochromocytomas and paragangliomas (PPGL) are associated with a germline mutation. These individuals have a lifetime tumour risk and in the case of SDHx germline mutations, there is a risk of multiple tumours and malignancy. We sought to discover plasma metabolites associated with succinate dehydrogenase (SDH) deficiency and tumorigenesis for potential use as predictive and/or prognostic biomarkers. Plasma samples were collected prospectively from a clinically well-characterized patient cohort (Cambridge, UK) with SDHx and non-SDHx variants. We performed liquid chromatography/mass spectroscopy (LC/MS) analysis of polar compounds profiling 124 enrolled patients. Concurrently, we collected clinical data including; plasma metanephrine and 3-methoxytyramine measurements and imaging characteristics. Of the 124 patients (age range 17 – 81, mean 45), 45.9% had an SDHx germline predisposition, of which 47.4% (27/57) had a current benign/metastatic tumour and 21.1% (12/57) had a previous tumour. We found that the levels of the proposed metabolic biomarker, succinate, were not significantly altered in SDHx carriers and patients with SDH deficient tumours. The untargeted analysis of the plasma ($n=72$) detected 2300 chromatographic features and we ranked them based on their discriminatory ability. We discovered one with mass-to-charge (m/z) = 328.24 was significantly elevated in SDHx carriers compared to non-SDHx carriers with AUROC = 0.765, Mann-Whitney U test P-value = 0.0074, and Hedge's g = -1.01. Furthermore, compared to SDHx carriers with no current tumour or past tumour, we found significantly altered chromatographic signals (m/z = 304.29, AUROC = 0.75, P-value = 0.011, Hedge's g = -0.228; m/z = 512.33, AUROC = 0.726, P-value = 0.022, Hedge's g = 0.929; m/z = 585.27, AUROC = 0.75, P-value = 0.011, Hedge's g = -0.8) in SDHx patients with benign and metastatic tumours. Identification of these features is in progress. These preliminary findings are being extended in further patients/samples and SDHx knockout mouse models but suggest several LC/MS signals may be pursued as candidate diagnostic biomarkers to track tumour development, progression and recurrence.

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OC2.6

Repurposing disulfiram as a therapeutic agent to enhance sodium iodide symporter activity in radioiodide therapy

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Background
New drug approaches are urgently needed that enhance radioiodide (RAI) uptake leading to efficient ablation of thyroid cancer, especially in RAI-refractory disease. We recently utilised high-throughput screening and identified FDA-approved compounds that induce sodium iodide symporter (NIS) function to enhance iodide uptake, including the proteasomal/ VCP inhibitor disulfiram. *In vivo*, disulfiram is rapidly metabolized to diethyldithiocarbamate (DDC), which binds metal ions, and is being investigated for use in wide-ranging therapeutic applications including cancer. Here, we aimed to gain a mechanistic understanding of how disulfiram and its related DDC-metal complexes impact NIS function *in vitro* and *in vivo*.
Methods
NIS function was monitored *in vitro* by RAI (^{125}I) uptake assays, and NIS expression via TaqMan-RTPCR and Western blotting. Technetium-99m pertechnetate (^{99m}Tc) uptake was used to evaluate NIS function in BALB/c mice.
Results
Disulfiram, as well as DDC-metal complexes $Cu(DDC)_2$ and $Zn(DDC)_2$, induced significant NIS protein expression (36.2-fold;250nM;$P<0.001$) and ^{125}I uptake (5.7-fold;250nM;$P<0.001$) in multiple thyroid cell types, including human primary thyrocytes. Disulfiram and $Cu(DDC)_2$ retained the ability to enhance NIS function in VCP-ablated cells, indicating their effect on NIS was via VCP-independent pathways. Importantly, $Cu(DDC)_2$ revealed potent transcriptional activity, inducing NIS mRNA expression in TPC-1 (13.9-fold;$P<0.001$) and 8505C (104.8-fold;$P<0.001$) cells. Similarly, $Cu(DDC)_2$ induced expression of other thyroid-specific genes, including thyroid peroxidase (28.3-fold;$P<0.001$). MTS assay IC_{50} values of $Cu(DDC)_2$- and $Zn(DDC)_2$-treated TPC-1 cells (0.39μM and 26.32μM respectively) demonstrated greater sensitivity to $Cu(DDC)_2$. In BALB/c mice, disulfiram failed to enhance thyroidal uptake of ^{99m}Tc. However, $Cu(DDC)_2$ significantly induced ^{99m}Tc uptake at 30min post-administration (~47%;$n=5$; 3 mg/kg dose;$P=0.0095$), demonstrating *in vivo* activity.
Conclusions
Our results demonstrate that disulfiram-related DDC-metal complexes represent a promising drug strategy to modulate NIS function, with clinical potential to enhance radioiodide therapy.

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Reproductive and Neuroendocrinology

OC3.1

Depot somatostatin receptor ligand therapy reverses tissue thyrotoxicosis in thyrotropinomas and aids microadenoma localization via ^{11}C-Methionine PET

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Context
Surgery is the first-line treatment option for thyrotropinomas, but medical therapy with somatostatin receptor ligands (SRL) may be used as neoadjuvant treatment and to facilitate safe surgery.
Objectives
To determine the extent to which neoadjuvant SRL (i) corrects clinical, laboratory and tissue hyperthyroidism in thyrotropinomas, (ii) induces tumour shrinkage in macroadenomas, and (iii) aids microadenoma detection by ^{11}C-methionine PET.
Design/setting
Prospective cohort study; specialist pituitary referral center.
Patients
20 patients with previously untreated thyrotropinomas (10 microadenomas and 10 macroadenomas).
Intervention
Depot SRL therapy for minimum of three and maximum of six injections given at 28-day intervals.
Main outcome measures
Changes in hyperthyroid symptom score (HSS), thyroid function, body composition (BC), resting energy expenditure (REE), sleeping heart rate (SHR), biomarkers of thyroid hormone action, glycaemic control, and imaging (MRI, PET) parameters. Age- and sex-matched healthy volunteers served as controls for BC, REE and SHR.
Results
Following treatment, patients had a marked improvement in thyrotoxic symptoms, thyroid function tests (median ΔFT3 -4.05 pmol/l; $P=0.0001$), biomarkers of thyroid hormone action (SHBG: pre-SRL 1.22xULN vs post-SRL 0.85xULN; $P=0.004$), with normalisation of REE [pre-SRL 0.163 MJ/kg/d vs post-SRL 0.136 MJ/kg/d ($P=0.0001$) vs healthy controls REE 0.135 MJ/kg/d ($P=0.92$)] and SHR [pre-SRL 67 bpm vs post-SRL 59 bpm ($P=0.002$) vs healthy controls SHR 54 bpm ($P=0.05$)]. Macroadenomas had a modest decrease in tumour volume (median change-14% from baseline). PET tracer uptake reduced post-SRL (Mean SUVr 3.1 prior to SRL vs 2.4 post SRL; $P=0.001$). Subtraction of post- from pre-SRL PET localized all microadenomas that showed biochemical response to SRL.
Conclusions
Treatment with neoadjuvant depot SRL results in marked improvements/normalisation in clinical, laboratory and tissue markers of hyperthyroidism. Tumour shrinkage and suppression of ^{11}C-methionine tumoral uptake is observed, with the latter enhancing PET's ability to accurately localize microthyrotropinomas.

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OC3.2

BRF1-mediated paracrine signalling from pituitary stem cells is required for terminal differentiation of pituitary committed progenitors

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The pituitary gland is a critical endocrine organ regulating multiple essential physiological processes including growth, reproduction, metabolism and the stress response. Hormone-producing pituitary cell lineages are derived from a population of embryonic precursors expressing the transcription factor SOX2. These cells maintain multipotency into early postnatal life, acting as the resident population of pituitary stem cells (PSCs) and contributing to all the endocrine cell lineages. In addition to this direct contribution to pituitary turnover, paracrine signalling from PSCs is necessary for cell proliferation of neighbouring progenitors. It is not known if SOX2+ PSCs are involved in other aspects of neighbouring cell regulation during normal physiology. Utilising scRNA-sequencing of SOX2+ PSCs from $Sox2^{Egfp/+}$ mouse pituitaries at three postnatal stages from P3 to P56, we show that the SOX2+ PSC population consists of three subgroups (SC1, SC2 and SC3). We reveal that SC1-SC2 express abundant cytokines and secreted factors, suggesting a paracrine function. In contrast SC3, characterised by robust expression of *Lef1*, is a committing PSC cluster and its presence diminishes with age. We unearth differential and conserved markers of PSC clusters and identify RNA binding factor BRF1 as conserved in one subgroup at all ages. We show that BRF1 is highly expressed in PSCs and that its dysregulation in embryonic pituitary cells results in severe hypopituitarism due to a failure of two distinct lineage-committed progenitors to terminally differentiate into hormone-producing cells. Additionally, there is a significant reduction of the stem cell compartment. The differentiation failure can be rescued *in vivo*, in mutant pituitaries where activation of constitutively active BRF1 is restricted to few SOX2+ PSCs in a mosaic manner. Together, these data indicate the presence of functionally distinct groups of SOX2+ pituitary stem cells and reveal a critical role for PSCs in driving terminal differentiation of endocrine cells.

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OC3.3

Long-term efficacy and safety of oral, once-daily paltusotine treatment in acromegaly: Two-year interim results from the ACROBAT Advance study

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Paltusotine is an investigational oral, once-daily, non-peptide, SST2 agonist in development for the treatment of acromegaly and neuroendocrine tumors. Interim analysis results from subjects with acromegaly treated with paltusotine for up to 2 years in ACROBAT Advance (NCT04261712), an ongoing, open-label extension study are reported here. Prior to Advance, subjects previously completed one of two Phase 2 parent studies, Evolve (NCT03792555, with normal IGF-1 using injected long-acting octreotide or lanreotide monotherapy [iSRL]) or Edge (NCT0378965), which enrolled acromegaly subjects, all of whom required second line therapy beyond iSRL monotherapy in order to achieve IGF-1 normalization. Forty-three subjects enrolled in Advance. Mean (SD) age, 53 (11.61) years; 56% female; 86% had previous pituitary surgery. Median (IQR) IGF-1 was stably maintained on iSRL: baseline 1.15xULN (0.84, 1.46, $n=43$); Week 51 1.08xULN (0.87, 1.26, $n=37$); Week 77 1.00xULN (0.85, 1.27, $n=27$); Week 103 1.10xULN (0.96, 1.45, $n=10$). IGF-1 remained unchanged both in subjects with normal and elevated baseline IGF-1. Cabergoline (and pegvisomant if needed) was allowed for subjects with inadequately controlled IGF-1 at the maximum tolerated dose of paltusotine. Most (94%) of those receiving adjunctive medication in Advance were either sub-optimally controlled or required combination therapy or pasireotide in order to achieve normal IGF-1 at the parent study iSRL baseline. The most common treatment-emergent adverse events (TEAEs) reported were headache (30.2%), arthralgia (25.6%) and fatigue (18.6%). No serious drug-related TEAEs were reported. Of the 6 subjects who discontinued the study, only 1 (2.3%) was due to a TEAE (headache). With up to 2 years of follow-up, once-daily oral paltusotine is associated with stable IGF-1 control relative to that achieved by iSRLs and continues to be well tolerated.

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OC3.4

Maternally derived pancreatic extracellular vesicle miR-375 contributes to large-for-gestational-age infants in pregnancies complicated by gestational diabetes

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Pregnancies affected by GDM commonly result in large-for-gestational-age (LGA) infants, which have an increased risk of developing cardiometabolic complications. The mechanisms responsible are unclear but are associated with altered placental physiology. We have previously reported that miRNAs, including pancreatic specific miR-375, are altered in maternal serum extracellular vesicles (EVs) prior to the onset of LGA, and in term placenta. We assessed maternal pancreatic-derived EV/miRNA internalisation into human placenta and whether these could contribute to LGA by influencing placental development/function. QPCR confirmed that miR-375 was not produced in the human placenta by assessing levels of both mature miR-375 and primary transcript (pri-miR-375). Mature miR-375 was present in the placenta, but pri-miR-375 was not detected, suggesting miR-375 is likely transported to the placenta, potentially via EVs from maternal circulation. We next isolated EVs from pancreatic islets. Human pancreatic islet equivalents (20,000 IEQs/patient) were obtained through the Integrated Islet Distribution Program (IIDP) from female donors of reproductive age. Islets were cultured 3 days under normoglycaemic (5.5mM), or mild hyperglycaemic (7mM glucose) conditions. Islet purity/viability were confirmed using dithizone/trypan blue. EVs in conditioned media were isolated by size-exclusion-chromatography and characterised by nanoparticle tracking analysis (NTA; mean diameter, 83.5-163.2nm; $1.28x10^{9}$-$1.82x10^{10}$ particles/ml), Western blotting (EV-proteins) and electron microscopy (cup-shape morphology). QPCR confirmed miR-375 was present in islet-EVs and levels were altered in response to hyperglycaemia. Fluorescent microscopy confirmed placental explant uptake of maleimide-488 labelled islet-EVs. Functional impact of miR-375 on the placenta was assessed following miR-375 overexpression (30-fold, $P<0.05$; $n=6$) using specific miRNA-mimics. TMT-mass-spectrometry demonstrated that miR-375 altered the placental proteome. Functional enrichment and Ingenuity pathway analyses revealed differentially expressed proteins were significantly enriched in pathways associated with placental growth, glucose metabolism and vascularisation. Our data provides insight into the potential mechanisms contributing to LGA in GDM pregnancies.

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OC3.5

Radiomics as a tool for risk stratification of non-functioning pituitary adenomas following primary surgery

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Background
Existing biomarkers have limited ability to discriminate indolent non-functioning pituitary adenomas (NFPAs) from those with a propensity to recur following primary surgery. Radiomics, the extraction of quantitative data from medical imaging, is increasingly recognised as a tool to augment clinical decision making.
Methods
39 patients who underwent primary trans-sphenoidal surgery for an NFPA between January 2007 and April 2017, were enrolled. 19 patients required multiple therapeutic interventions (revision surgery and/or radiotherapy) or demonstrated radiological recurrence / regrowth following TSS. 20 patients demonstrated indolent behaviour, with stable post-operative appearances at a minimum of 3 years following surgery [36-111 months follow-up]. The tumour was manually segmented on pre-operative T1SE MR images using 3D Slicer. 135 radiomic features were extracted from the images using Python module pyradiomics via 3D Slicer module '*Radiomics*'.
Results
Neighbouring Gray Tone Difference Matrix (NGTDM) *Coarseness*, a measure of the spatial rate of change of pixel intensity, was the strongest predictive feature. Receiver operating characteristic curve (ROC) analysis showed an area under the curve of 0.767 [0.603 – 0.887]. Kaplan-Meier analysis, using the optimal criterion from the ROC, showed a difference in mean progression free survival of 105.7 vs 43.4 months ($P<0.0001$). Logistic regression analysis was performed to ascertain the combined predictive effect of 1) *Coarseness*, 2) *Inverse Difference Normalised* and 3) *Maximum 2D diameter*. The logistic regression model was statistically significant: $\chi 2$ 17.88, $P < 0.001$ The model correctly identified 74.4% of cases, with a positive predictive value of 80% for identifying more indolent cases.

Conclusions
In this pilot study we have shown that radiomic analyses have the potential to predict which NFPAs are likely to recur at an earlier stage, thereby potentially informing decision making in a context where biomarkers are lacking. Larger studies, with standardised image acquisition and processing are required to validate these findings.

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OC3.6

Kisspeptin enhances sexual and attraction brain processing in women with low sexual desire

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Hypoactive sexual desire disorder (HSDD) is a persistent lack of sexual desire, causing marked interpersonal distress. It is the most common global female sexual health problem, although the precise pathophysiology remains uncertain. Existing treatment options are limited by their efficacy and side effects. The neuropeptide kisspeptin offers a potential therapeutic target given its emerging role in modulating reproductive behaviour. Using a combination of psychometric, neuroimaging and hormonal analyses, the role of kisspeptin in sexual brain processing in HSDD was investigated in a randomised, double-blind, placebo-controlled crossover study. Thirty-two premenopausal women with HSDD completed the study (mean age 29.2 $\pm$ >SEM 1.2 years). Kisspeptin administration increased self-reported scores of feeling 'sexy', compared with placebo, measured using the Sexual Arousal and Desire Inventory ($t[32]=2.27$, $P=0.03$). Functional magnetic resonance imaging (fMRI) demonstrated deactivation of the left inferior frontal gyrus and activation of the postcentral and supramarginal gyrus in response to erotic videos ($Z=2.3$, $P<0.05$). This modulation of brain activity may serve to diminish negative internal monologue, lessen negative emotion and decrease response inhibition. In the facial attractiveness task, kisspeptin caused deactivation of the secondary somatosensory cortex ($Z=2.3$, $P<0.05$) in response to male faces, which may be linked to a reduction in self-consciousness and self-focus. Increased activation in the posterior cingulate cortex with kisspeptin was associated with reduced sexual aversion ($r=0.476$, $P=0.005$), which may be explained by increased feelings of romantic love. Kisspeptin administration led to a mean increase in LH of 2.75iU/l ($F(1,62)=6.084$, $P=0.02$) and FSH of 0.37iU/l ($F(1,62)=4.030$, $P=0.05$), with no effect observed on downstream circulating oestradiol, progesterone or testosterone levels. The observed changes in brain activity provide mechanistic insight for the increase in sexual desire seen with kisspeptin. This research has exciting potential therapeutic implications for kisspeptin in the treatment of psychosexual disorders.

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Adrenal and Cardiovascular

OC4.1

Introducing technology to improve patient safety in adrenal insufficiency: a proof-of-concept delivery of a new smartphone app in steroid-dependent patients

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Introduction
Although significant developments have been achieved in the management of steroid-dependent patients, little progress has been made in ensuring their safety using smartphone technology. We present the use of a novel app in steroid-dependent patients.
Methods
A group of unselected individuals currently on steroid replacement due to adrenal insufficiency (AI) were assessed regarding their access to intramuscular (IM) hydrocortisone. A smartphone app, notifying both the healthcare team and patient when IM hydrocortisone nears expiry and enabling a timely repeat prescription to be issued, was offered to all patients.
Results
$n=45$ (primary AI: $n=12$, secondary AI: $n=31$; iatrogenic AI: $n=2$). Mean age 55.8 ± 16.3 (18- 90) years, 42.2% females. Only 46.7% had an IM hydrocortisone supply in-date and 44.4% had problems renewing their prescription. 88.9% of the whole cohort were willing to be offered the app. To-date, 30 patients have started using the app with 20 renewal prescriptions already issued. The commonest feedback comment rating from patients and endocrine nurses is 'life-saving'.
Conclusions
Current methods of ensuring patient safety in steroid-dependent individuals are ineffective. The introduction of a novel smartphone app is widely endorsed by patients irrespective of their age, and can help in providing better care and ensuring their safety. Based on these preliminary results, we plan to expand the app's use to all our steroid-dependent patients locally and regionally.

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OC4.2

Generation of novel tools for the study and development of targeted therapeutic approaches for pheochromocytoma and paraganglioma

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours, which arise from neural crest (NC)-derived structures: the adrenal medulla and the paraganglia. Around one third of PPGLs are associated with inherited cancer susceptibility genes, the highest rate among all tumour types. Currently, the only diagnostic criterion for malignant disease is the presence of metastasis and no molecular or histological features have been identified that help predict risk. Additionally, understanding the pathogenesis of PPGLs and development of new therapies is hindered by the lack of validated disease models. In many tumours, cancer cells with stem-like properties are at the root of tumour initiation/maintenance due to their ability to self-renew and proliferate, but a stem cell population of the adrenal medulla has not been identified. We show that SOX2, a well-characterised marker of multiple stem cell populations, is expressed in a subset of uncommitted Schwann-cell precursors, which generate chromaffin cells and sympathetic neurons and that SOX2 expression persists postnatally in adrenomedullary sustentacular cells. Using the inducible Sox2-CreERT2 driver, *in vivo* lineage tracing demonstrates that murine neural crest-derived SOX2+ cells expand to self-renew and give rise to new chromaffin cells throughout life, supporting their function as a novel progenitor/stem cell population. This population is therefore ideal to target for expression of tumour-inducing mutations, to generate transgenic models of PPGLs. We establish a system to isolate and culture pure murine and human populations of adrenomedullary SOX2+ stem cells *in vitro* and demonstrate that these cells can be expanded and gene-edited, to express mutant forms of Succinate Dehydrogenase subunits (SDHx), responsible for most hereditary PPGL cases. Finally, normal and mutated SOX2+ adrenomedullary stem cells can be implanted *in vivo* onto the chick chorioallantoic membrane (CAM), where they can be assayed for expansion, contribution of chromaffin cells and tumourigenic properties including invasion and metastasis.

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Age group (years)	N	No access to IM hydrocortisone currently (%)	Not aware of expiry date (%)	Current supply in-date (%)	Not aware how to get prescription renewed (%)	Problems getting prescription renewed (%)	Willingness to be offered a smartphone app for automatic reminders (%)
18-40	9	22	33.3	55.6	55.6	33.3	100
41-65	21	19	19	33.3	19	52.4	85.7
66+	15	0	20	60	20	40	86.7
Whole cohort	45	17.7	22.2	46.7	26.7	44.4	88.9

OC4.3

Plasma steroid concentrations reflect disease severity during acute illness but not recovery after hospitalisation with COVID-19

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Background
Endocrine systems are known to be disrupted in acute illness, and we previously demonstrated that plasma steroid concentrations correlated with severity in patients hospitalised with COVID-19. Given their similarity to some clinical hormone deficiencies, we hypothesised that 'long-COVID' symptoms may be related to ongoing endocrine dysfunction.
Methods
Plasma steroids, precursors and metabolites were quantified by LCMS/MS in multi-centre cohorts of adults hospitalized with COVID-19 (*ISARIC/WHO CCP-UK study*), and studied post-discharge (*PHOSP-COVID study*). These were compared against disease severity (WHO ordinal scale) and validated symptom scores. Results are median (IQR)/geometric mean (geometric SD).
Results
Acute disease (*as previously presented*) Among 239 adults (67% male; age 63(52-73.5) yrs; mortality 19.7%), those with fatal disease had higher cortisol [753.3 (1.6) vs 429.2 (1.7) nmol/l, $P<0.001$] and (in males) lower testosterone concentrations (1.2 (2.2) vs 6.9 (1.9) nmol/l, $P<0.001$) than patients not requiring oxygen supplementation.
Recovery
Among 196 adults (63% male; age 58(49-65) yrs; 164(121-191) days post-discharge), cortisol concentration [275.6 (1.5) nmol/l] did not differ with in-hospital severity ($P=0.95$), or steroid therapy ($P=0.61$). There was no correlation between plasma cortisol and perception of recovery ($P=0.41$), or patient-reported symptoms of fatigue (FACIT-F score, $P=0.46$), depression (PHQ-9 score, $P=0.21$), anxiety (GAD-7 score, $P=0.21$), post-traumatic stress (PCL-5 score, $P=0.11$) or breathlessness (Dyspnoea-12 score, $P=0.12$). Similarly, male testosterone concentration of 12.8 (1.5) nmol/l was unrelated to in-hospital severity ($P=0.21$), perception of recovery ($P=0.71$) or symptom scores ($P=0.34$, $P=0.40$, $P=0.51$, $P=0.68$, $P=0.21$ respectively, ordered as above).
Conclusions
Circulating steroids in patients hospitalized with COVID-19 are representative of the acute illness response, with a marked rise in cortisol and fall in male testosterone. This relationship disappears within 6 months from discharge, and we did not identify a link between glucocorticoid or male androgen concentrations and ongoing symptoms in this cohort.

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OC4.4

Steroid and global metabolome in benign adrenal tumours with mild autonomous cortisol secretion: analysis by mass spectrometry and machine learning to understand metabolic risk

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Background
Benign adrenal tumours are found in 3-10% of adults and can be non-functioning (NFAT) or associated with adrenal hormone excess. Analysing 1305 prospectively recruited patients with benign adrenal tumours, we recently demonstrated that 45% had mild autonomous cortisol secretion (MACS), i.e. biochemical cortisol excess without signs of Cushing's syndrome (CS). MACS increases the prevalence and severity of hypertension and type 2 diabetes (Ann Int Med. 2022 Doi:10.7326/M21-1737). Here we analysed the cohort's steroid metabolome and global metabolome to reveal underlying metabolic processes.
Methods
We analysed 24-h urines from 1305 patients (649 NFAT, 591 MACS, 65 CS) using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) multi-steroid profiling assay. In addition, we performed untargeted serum metabolome analysis in a representative sub-cohort (104 NFAT, 140 MACS, 47 CS) employing two complementary LC-MS assays, HILIC and C18-lipidomics. Steroid and global metabolome data were analysed by prototype-based supervised machine learning (generalized matrix learning vector quantization and ordinal regression).
Results
Urinary glucocorticoid excretion increased from NFAT over MACS to CS, whereas androgen excretion decreased. Machine learning analysis identified increased excretion of the 11β-hydroxyandrostenedione metabolite 11β-hydroxyandrosterone as the key marker in MACS patients with hypertension and type 2 diabetes. Lipidome analysis identified glycerophospholipids, lysoglycerophospholipids, triacylglycerides, ceramides, sphingolipids, and acylcarnitines as the most relevant metabolite classes exhibiting progressive changes with increasing cortisol excess (NFAT<MACS<CS). Pathway enrichment analysis revealed distinct patterns of changes in arginine & proline metabolism and histidine metabolism with increasing cortisol excess.
Conclusions
We show a gradual change in the lipidome towards lipotoxicity with increasing cortisol excess. Increased CYP11B1-mediated 11β-hydroxyandrostenedione production in MACS patients with type 2 diabetes and hypertension points towards a causative contribution of 11-oxygenated androgens to increased cardiometabolic risk. Observed changes may hold promise for risk stratification in MACS, a highly relevant and previously largely overlooked metabolic risk condition.

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OC4.5

Comparison of prednisolone and modified-release hydrocortisone capsules in the treatment of congenital adrenal hyperplasia: dose and disease control

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Introduction
First-line treatment for congenital adrenal hyperplasia (CAH) is hydrocortisone[1]. When adequate control is not achieved, prednisolone (or its prodrug prednisone) are often used. However, there has been no formal comparison of disease control in CAH comparing prednis(ol)one vs hydrocortisone and patients are often on a glucocorticoid dose that exceeds the guideline recommended dose of hydrocortisone ($\leq$25 mg/day)[1,2]. We report an interim analysis of CAH control in patients switched from prednis(ol)one to Modified-Release Hydrocortisone (MRHC) capsules, (Efmody, Diurnal Ltd, Cardiff UK), in an open label safety extension study.
Methods
Patients who completed the phase 3 MRHC study[3], were invited to join an open label extension study. We analysed results from patients with a complete dataset at Phase 3 baseline on prednis(ol)one and a minimum of 18 months follow up in the extension study ($n=30$). Control of CAH was defined as 9am 17-OHP $<$36 nmol/l and dose was reported according to whether it exceeded 25 mg/day hydrocortisone dose equivalent (prednis(ol)one dose x 5)[1,3]. Quadrant analysis was performed and Fisher's exact test applied.
Results
More patients had controlled 17-OHP on a physiological glucocorticoid dose on MRHC than prednis(ol)one, 57% vs 27% $P=0.04$.
Conclusions
Patients who are poorly controlled on prednis(ol)one and/or taking a dose above the recommended dose for adrenal replacement can benefit from a switch to MRHC capsules.
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		Dose	
Prednis(ol)one		$\leq$25 mg/day	$>$25 mg/day
Androgen control	$>$36nmol/l 17-OHP	8/30 (27%)	5/30 (16%)
	$<$36nmol/l 17-OHP	8/30 (27%)	9/30 (30%)
		Dose	
MRHC		$\leq$25 mg/day	$>$25 mg/day
Androgen control	$>$36nmol/l 17-OHP	5/30 (16%)	0/30 (0%)
	$<$36nmol/l 17-OHP	17/30 (57%)	8/30 (27%)

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OC4.6

Glucocorticoid excess elevates metabolic rate via a 11β-HSD1 dependent mechanism in C57BL/6J mice

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Introduction
Glucocorticoids are vital metabolic regulators. However, glucocorticoid excess (GE) causes severe metabolic dysfunction, ultimately leading to Cushing's Syndrome. This dysfunction is often dependent on the presence of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Whether GE also alters metabolic rate, and whether this is also dependent on 11β-HSD1, remains unclear.
Methods
Male and female wild-type (WT) C57BL/6J and 11β-HSD1KO mice were treated with corticosterone or vehicle control ad libitum via drinking water for 3 weeks. Mice were housed in a TSE Phenomaster for the final week of treatment for comprehensive metabolic assessment.
Results
Corticosterone treatment in WT mice resulted in a phenotype typical of GE, however female mice experienced greater fat accumulation. 11β-HSD1KO mice did not experience this phenotype. Corticosterone treatment elevated energy expenditure (EE) in female WT mice during the day alone (25$\pm$5.9%). Male WT mice did not experience a significant increase. Corticosterone did significantly elevate the respiratory exchange ratio (RER) towards 1 in both male (10.7$\pm$ 5.7%) and female (11.8$\pm$7.0%) WT mice during the day. RER remained elevated in female WT mice (7.6$\pm$4.8%) and moderately so in male WT mice (3.2$\pm$ 2.6%) at night. Activity, assessed in female WT mice only, was continually decreased by corticosterone treatment (-53.1$\pm$54.8%). Corticosterone treated WT mice became hyperphagic and polydipsic, continuously consuming more than controls. Male or female 11β-HSD1KO mice treated with corticosterone did not experience these effects.
Conclusion
These findings provide further insights into the metabolic consequences of GE as well as the dependency on 11β-HSD1 to facilitate them. Whilst elevations are seen in both male and female WT mice, they are greater in females. Activity is decreased meaning it is not responsible for the elevations. However, hyperphagia and the subsequent chemical energy cost of de novo lipogenesis might be responsible and merits further investigation.

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Metabolism, Obesity and Diabetes

OC5.1

Human brown adipose tissue demonstrates substantial choline uptake for incorporation into phosphatidylcholines

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Background
^{18}F-fluorodeoxyglucose (^{18}FDG) PET is commonly used to quantify brown adipose tissue (BAT) mass/activity in humans but requires cold exposure. Rodent brown (BAds) but not white adipocytes (WAds) exhibit high choline content, thus we hypothesised that human BAT would demonstrate substantial ^{18}F-fluorocholine (^{18}FCH) uptake *in vivo* during warm and cold conditions.
Methods
(1) Six male volunteers (age 21.4$\pm$1.1y, BMI 23.2$\pm$0.7kg/m^2) with detectable BAT by ^{18}FDG-PET underwent ^{18}FCH-PET/MR scanning during warm (~23°C) and cold (17°C) exposure in a randomised crossover design. **(2)** ^{18}FCH uptake by supraclavicular (SCVAT) and abdominal white adipose tissue (WAT) depots were quantified in patients with prostate cancer who had undergone ^{18}FCH-PET/CT scanning at room temperature as part of their clinical care. **(3)** Choline transporter expression levels were measured in human BAds and WAds. **(4)** Human BAds were incubated with ^{15}N-choline and incorporation into ^{15}N-metabolites was analysed by LC-MS/MS.
Results
(1) Cold exposure increased circulating noradrenaline, non-esterified fatty acids and decreased supraclavicular and sternal skin temperature without changing insulin or glucose levels. There was detectable ^{18}FCH uptake by supraclavicular BAT in all subjects during warm and cold exposure. Cold exposure increased ^{18}FCH-detected BAT volume (by ~100%) and total BAT activity (by ~50%); ^{18}FCH detected substantially lower BAT though than ^{18}FDG during both conditions. **(2)** ^{18}FCH uptake was ~2.5-fold higher in human SCVAT compared to abdominal subcutaneous WAT in patients scanned at room temperature. **(3)** In parallel with the *in vivo* data, mRNA levels of the choline transporter *SLC44A2* were higher in BAds than WAds. **(4)** ^{15}N-Choline tracing revealed that choline was incorporated into multiple phosphatidylcholine species in BAds.
Conclusion
^{18}FCH can be used to detect human BAT and acute cold exposure increases choline uptake by BAT. Human BAT utilises choline to synthesise phosphatidylcholines that may play an important role in optimal BAT function.

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OC5.2

7α-hydroxy-3-oxo-4-cholestenoic acid (7-HOCA) is a novel AKR1D1 substrate driving metabolic dysfunction and hepatocellular cancer risk in patients with non-alcoholic fatty liver disease (NAFLD)

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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease ranging from intrahepatic lipid accumulation to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Liver 5β-reductase (AKR1D1) catalyses a fundamental step in bile acid (BA) synthesis. BAs and BA intermediates are potent regulators of metabolic and proliferative phenotype. We have hypothesised that AKR1D1 plays a crucial role in NAFLD and HCC. Liver biopsies and serum samples were obtained from healthy subjects and patients with established NAFLD, cirrhosis and HCC. BA composition was determined by LC-MS. Genetic manipulation of AKR1D1 was performed in HepG2 cells. Effects on BA synthesis, lipid metabolism, cell cycle, proliferation and DNA damage were determined by LC-MS, qPCR, western blotting, flow cytometry, RNA-sequencing, biochemistry analysis, and comet assays. Serum BA and BA-intermediate levels were significantly elevated across NALFD severity, with a particular increase in the concentration of the AKR1D1 substrate 7α-hydroxy-3-oxo-4-cholestenoic acid (7-HOCA). In line with this, AKR1D1 expression was significantly decreased in liver biopsies from patients with advancing steatosis, fibrosis, and HCC. In HepG2 cells, AKR1D1 knockdown increased 7-HOCA accumulation, and RNA-sequencing analysis identified dysregulated pathways impacting lipid metabolism, cell cycle and proliferation, consistent with increased triglyceride accumulation and impaired fatty acid oxidation. In addition, AKR1D1 knockdown induced DNA damage, downstream resulting in cell cycle arrest, impaired cell proliferation and enhanced apoptosis, suggesting a role for 7-HOCA in hepatocyte health. Confirming this, RNA-sequencing in wild-type, 7-HOCA-treated HepG2 cells revealed a transcriptional profile similar to the one observed following AKR1D1 knockdown, with increased lipid and decreased proliferative gene expression, alongside enhanced DNA damage. In conclusion, AKR1D1 decreases with NAFLD severity, resulting in increased 7-HOCA accumulation and downstream adverse effects on hepatic lipid metabolism and cell proliferation. Taken together, these data demonstrate the important role of 7-HOCA in NAFLD progression and reveal the potential of AKR1D1 manipulation for hepatoprotective therapies.

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OC5.3

Normothermic machine liver perfusion as a tool to study human androgen metabolism

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Background
In women, androgen excess is associated with an increased risk of non-alcoholic fatty liver disease (NAFLD). Androgen precursors are released from the adrenal gland and converted to active androgens in peripheral tissues including adipose tissue. Although the liver plays a key role in all metabolic processes in the body, its involvement in androgen metabolism is yet to be explored. Here, we describe the investigation of androgen metabolism in human liver using normothermic machine liver perfusion.
Methods
A liver assist device was used to perfuse a human liver deemed unsuitable for transplantation. An established protocol validated for liver perfusion was used. After 2 hours, liver viability was confirmed by normalisation of the lactate concentration in perfusate and 200 nM of C13-labelled androstenedione was added. Perfusate samples were taken at regular intervals over 12 hours and steroid identification and quantification was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results
Following the addition of C13-labelled androstenedione to the perfusate, we observed the majority of downstream metabolism occurring within the two subsequent hours, with quantifiable generation of 5a-dihydrotestosterone, androstanediol, androsterone and etiocholanolone. The overwhelming majority of androstenedione served as substrate for conversion to inactive downstream metabolites via the 5b-reductive pathway, whereas the conversion of androstenedione to active androgens only occurred in negligible amounts.
Conclusion
Normothermic machine liver perfusion is a highly suitable tool for ex vivo whole organ assessment of steroid metabolism in the human liver. We provided proof-of-principle of the use of this technique to investigate androgen metabolism in the liver and will utilise it to dissect the role of androgens in the development of conditions such as NAFLD.

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OC5.4

New avenues for vertical sleeve gastrectomy-induced diabetes remission mechanisms: kidney-adipose tissue axis

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Bariatric surgery is known to improve obesity-induced systemic inflammation and glucose homeostasis, however, the exact mechanisms behind this effect are not fully understood. We have previously shown that Sodium Glucose Transporter 2 (SGLT2) is significantly inhibited in the kidney cortex following Vertical Sleeve Gastrectomy (VSG), causing a reduction in renal glucose reabsorption. In this study, we hypothesize that the observed post-operative reduction of SGLT2 is controlled by adipokines, as part of a direct kidney-adipose tissue axis. To do so, we utilised human kidney cells (HK-2) to reveal the effects of glucose, sodium, leptin, interleukin-6 (IL-6), and tumour-necrosis factor alpha (TNF-α) treatments on the expression of SGLT2, via RT-qPCR and Western Blot. Additionally, we performed VSG on high-fat diet (HFD) fed C57BL/6J mice in order to investigate changes in leptin, IL-6 and SGLT2 expression levels in kidney, liver and adipose biopsies post-operatively. Treatments of leptin (5nM) and sodium buffer, HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) were shown to directly upregulate the expression of SGLT2 in HK-2 cells. Leptin and IL-6 expression was significantly reduced in the adipose tissue and liver respectively, following VSG. This indicates that the observed renal SGLT2 inhibition is due to the reduction of post-operative leptin secretion, a result of either weight loss or regained leptin sensitivity. Decoding this novel axis can provide us with a new angle on post-bariatric surgery euglycemic effects, as well as a novel insight into inter-organ communication.

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OC5.5

Upregulation of hepatic de novo lipogenesis dissociates from changes in liver fat content and insulin sensitivity in healthy humans

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Introduction
Increased hepatic de novo lipogenesis (DNL) is often associated with greater intrahepatic triglyceride (IHTG) content and/or decreased insulin sensitivity; however, the contribution of DNL to each has not been fully elucidated. Therefore, the present work determined if increased DNL, achieved via adoption of an isocaloric high-sugar diet, resulted in concomitant increases in IHTG content and/or decreases in insulin sensitivity.
Methods
Sixteen healthy participants (6 females; (mean ± SD) aged 49 ± 4 years; BMI 27.7 ± 3.8 kg/m2; HOMA-IR 1.56 ± 1.44) adopted a high-sugar diet for up to 21 days (range 13-21 days). Fasting and postprandial metabolism were measured before and after the dietary intervention. Stable-isotope tracer methodology was utilised to assess fasting and postprandial hepatic DNL. Liver fat was measured before and after the dietary intervention by 1H-MRS using a 3 Tesla MRI scanner.
Results
Despite increasing the proportion of energy from sugar (113 ± 49 Kcal/day to 192 ± 55 Kcal/day; $P=0.002$), participants' body weight was stable during the dietary intervention. Compared to baseline, consumption of the high-sugar diet significantly increased postprandial DNL by ~54.4% ($P<0.001$). IHTG was modestly increased by ~0.6% ($P=0.006$) and insulin sensitivity (HOMA-IR) was unchanged ($P>0.05$). There was neither an association between changes in DNL and IHTG ($r=-0.2$, $P>0.05$) nor DNL and HOMA-IR ($r=0.2$, $P>0.05$). Plasma triglyceride concentration was increased by 20% post-diet ($P<0.001$), and this change tended to be positively associated with the change in DNL ($r=0.5$, $P=0.06$).

Conclusion
Hepatic DNL may be dissociated from changes in liver fat content and insulin sensitivity in healthy individuals adopting a high-sugar diet. These observations suggest that DNL may not substantially contribute to IHTG accumulation when individuals can up-regulate hepatic triglyceride export, as evidenced by the increase in plasma TG concentrations.

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OC5.6

Labelling and characterisation of somatostatin secreting D-Cells in primary human duodenal organoids culture

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Backgrounds and aims
Enteroendocrine cells (EECs) are hormone-secreting cells within the intestinal epithelium that play an important role in regulating food absorption, insulin secretion and appetite. The somatostatin (SST)-producing D-cell is an EEC of particular interest due to the profound inhibition exerted by SST over other EECs, highlighting D-cells as critical regulator of the enteroendocrine axis. The aim of this study was to profile the transcriptome of human intestinal D-cells from organoids culture and to identify the key signalling pathways involved in the regulation of SST secretion.
Materials and Methods
To label somatostatin secreting D-cells in human duodenal organoids CRISPR-Cas9 followed by homology-directed repair was used to insert Internal Ribosome Entry Site sequence, followed by the fluorescent protein tdTomato sequence and puromycin resistant cassette under control of the endogenous somatostatin promoter. Fluorescence-activated cell sorting (FACS) was used to purify organoids-derived D-cells. Bulk RNA sequencing of FACS-purified SST-tdTomato positive and negative cells was performed.
Results
The transcriptional profiles of FACS purified D-cells and control populations were analysed. The principal component analysis exhibited a wide separation between these two populations on the first component (87% of variance), and narrow separation on the second component (8 % of variance). tdTomato-positive cells were strongly enriched for SST gene, which was found at ~1000-fold-higher levels in fluorescent compared to non-fluorescent cells ($P < 0.001$). RNA sequencing identified enriched expression of several G-protein coupled receptors in D-cells including short-chain fatty acids receptor (FFAR2), bile acids receptor (GPBAR1), amino acids receptor (GPR142), trace amines receptor (TAAR1) and the vasopressin receptor (AVPR1B).
Conclusion
This study provides the first in-depth transcriptomic analysis of human intestinal D-cells which provide an important foundation to guide future studies for functional characterisation of this cell type.

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Thyroid

OC6.1

Single cell analysis for the human developing thyroid uncovers thyrocytes heterogeneity

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Normal functioning of the thyroid is of profound importance for lifetime health due to its role in hormone production. Dysfunction of the thyroid is associated with severe congenital pathologies, some of them appearing in childhood. For example, over half the babies born with congenital hypothyroidism appear completely normal and have no symptoms. However, early diagnosis of thyroid defects is lacking mainly due to a poor understanding of the development of the tissue in utero. Here we have established a comprehensive spatiotemporal atlas of the developing human thyroid during the first and second trimester of pregnancy. Our dense profiling of more than 100k cells using single-cell sequencing has revealed the main cell types, their developmental relationships and transcription factors leading to the formation of the thyroid gland. Notably, we found that thyrocytes are heterogeneous epithelial populations and split thyroid-hormones production between different subsets. We further validated the spatial heterogeneity of thyrocyte subpopulations using multiple spatial transcriptomics methods. Our results confirm the division of labour of the thyrocytes, highlighting functional specialisation amongst them. Altogether our analysis exemplifies the division of labour principle observed in other adult tissues also applies to the development of the thyroids, expanding our knowledge of thyroid-hormones synthesis and regulation. Future work includes how the function principles are altered in pathological conditions.

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OC6.2

Enhancing radioiodide uptake by addressing the mechanism of sodium/iodide symporter (NIS) endocytosis

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Background
The sodium/iodide symporter (NIS) frequently shows diminished targeting to the plasma membrane (PM) in differentiated thyroid cancer, resulting in suboptimal radioiodine treatment and poor prognosis. However, the mechanisms which govern the endocytosis of NIS away from the PM – its sole site of transport activity – are ill-defined, and may be of direct therapeutic potential. We previously showed that the proto-oncogene PBF binds NIS and enhances its internalisation, hypothesising that this was via the heterotetramer Adaptor Protein 2 (AP2). We now challenge this hypothesis experimentally.
Methods
AP2 subunits α1, μ2, and σ2 were ablated via siRNA. NanoBiT assays were used to assess the stringency of protein interactions. Technetium-99m pertechnetate (^{99m}Tc) uptake was used to evaluate NIS function *in vivo*.
Results
Acidic dipeptides are known to bind AP2σ2. We identified a putative acidic dipeptide within the NIS C-terminus; abrogation of this (E578A/E579A) significantly increased ^{125}I uptake and retention of NIS at the PM as determined by immunofluorescent microscopy. Exogenous AP2σ2 was confirmed to bind NIS in NanoBiT assays with mutation of σ2 (R15H) increasing NIS binding affinity. Importantly, ablation of AP2α1 and μ2 significantly increased radioiodide uptake and NIS protein expression. NanoBiT assays showed that AP2α1 and μ2 ablation also increased NIS:PBF binding, whereas σ2 did not. The drug chloroquine induced radioiodide uptake *in vitro* (8hr), independently of its canonical influence on autophagy, which was blocked by AP2 ablation suggesting an impact on NIS endocytosis. *In vivo*, chloroquine treatment of Balb/c mice significantly enhanced thyroidal uptake of ^{99m}Tc, in combination with the HDACi SAHA.
Conclusion
We propose that NIS internalisation is modulated by the interaction of a C-terminal diacidic motif with the AP2σ2, and that the endocytosis motif of PBF is critical to this. Given our mouse data, the internalisation of NIS may now be druggable *in vivo*.

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OC6.3

Long-Term effectiveness of ethanol ablation in controlling selected postoperative neck nodal metastases in fourteen patients presenting with ATA pediatric intermediate or high-risk papillary thyroid carcinoma

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Introduction
Childhood papillary thyroid carcinoma (CPTC), despite bilateral thyroidectomy (BT), nodal resection and radioiodine remnant ablation (RRA), recurs within neck nodal metastases (NNM) in > 30% within 20 postoperative years. However, these NNM are usually treated with re-operation or further radioiodine; US-guided ethanol ablation (EA) may be considered (j.sempedsurg.2020.150920) for patients with limited numbers of NNM

Methods
We studied long-term results of EA in 14 patients presenting with intermediate or high-risk CPTC during 1978-2013 and having EA for NNM at Mayo Clinic during 2001-18. Prior to EA, all had undergone BT and in 93% RRA. Cytologic diagnosis of 20 NNM (median diameter 9mm; median volume 203 mm^3) was confirmed by US-guided biopsy. EA was typically performed during two outpatient sessions under local anesthesia; total volume injected ranged from 0.1-2.8cc, median 0.7cc. All ablated patients were followed regularly by sonography and underwent volume re-calculation and intra-nodal Doppler flow measurements at each visit. Successful ablation required elimination of nodal vascularity and reduction in NNM volume.
Results
The ablated patients were followed for 46-209 months since EA (median 14.3 years). There were no complications, including post-procedure hoarseness. All 20 NNM shrank (mean 87%) and Doppler flow eliminated in 93%. Median NNM volume reduction in 7 identifiable foci was 72%; after EA 13 NNM (65%) disappeared on sonography; 89% disappearing in early recurrences and 45% in those diagnosed after 7-31 postoperative years (median 19). Median serum thyroglobulin post-EA was 0.6 ng/mL. 19 ablated NNM exhibited no tumor regrowth; one (of 20) was re-ablated after 15 years. Two patients with new recurrent NNM chose re-operation.
Discussion/Conclusions
EA of NNM in CPTC is effective and safe. Our results suggest that for CPTC patients, who do not wish further surgery and are uncomfortable with active surveillance of biopsy-proven NNM, EA represents a minimally invasive management option.

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OC6.4

Towards an automated app-based dose prescription of carbimazole for hyperthyroidism patients

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University Hospitals Dorset (UHD) has over 1,000 thyroid patient contacts annually. These are primarily patients with autoimmune hyperthyroidism and are treated by titration of Carbimazole. Dose adjustments are made by a healthcare professional (HCP) based on the results of thyroid function tests. Once the test results are available, the HCP decides on a prescription dose and communicates this to the patient, which is time-consuming and introduces delays. This project aims to replace some of the time-intensive manual dose-adjustment with a technological solution, in the form of a mobile app available to the patients themselves. Data of 421 hyperthyroidism patients at UHD was manually extracted and anonymised from patient records. These data were subjected to processing and cleaning stages and a total of 353 (83.85%) were included (of those 79% were female). A wide range of machine learning classification algorithms was tested under different data processing regimes in an iterative approach consisting of an initial model selection followed by a feature selection method to further improve the model performance. All models were assessed using weighted F1 scores (1 = best) and Brier scores (smaller is better) to select the best performing model with the highest confidence. Preliminary findings show the best performance is achieved by using a Random Forest approach resulting in good average F1 scores of 0.731. Based on a balanced assessment considering the prediction accuracy (F1 = 0.755) as well as model confidence (Brier score = 0.366) a model was selected to be initially deployed to the app. This initial model will be further assessed under supervision of experienced clinicians to ensure its safety. It is estimated that with this new patient-centred technology, the number of patient contacts could be reduced by as much as 50-70% and will have a significant positive impact on the HCP workload.

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OC6.5

Thyroid hormones promote mammary metabolic pathways required for milk synthesis: Relevance to the onset of lactation

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Increased mammary metabolism is critical for initiating lactation during postpartum days 1-4. We utilised clinical and cellular approaches to investigate whether thyroid hormones, which promote lactation in rodents, are involved in initiating human lactation and regulating mammary metabolism. We recruited $n = 30$ pregnant women following informed consent and measured serum thyroid hormones (free T4 and TSH) at 36 weeks' gestation and on postpartum day 4. Free T4 increased from 10.4 ± 0.2pmol/l at 36 weeks' gestation to 11.7 ± 0.2pmol/l on postpartum day 4 ($P < 0.01$) whilst no change was detected in TSH. We hypothesised that thyroid hormones increase mammary metabolism to promote milk synthesis and assessed this in human mammary epithelial cells (HMECs). Reverse transcription-quantitative PCR (RT-qPCR) of thyroid hormone receptor alpha and beta (THRA and THRB) genes showed that THRB has ~7-fold greater expression than THRA ($P < 0.0001$, $n = 4$). THRB phosphorylates Akt, which is required for initiating lactation. Consistent with this, HMECs stimulated with 10nM T3, the most potent thyroid hormone, for 15min showed an ~2-fold increase in Akt phosphorylation ($P < 0.0001$, $n = 4$). Akt regulates oxidative phosphorylation, which we assessed by measuring oxygen consumption rate (OCR) and ATP synthesis. HMECs treated with 10nM T3 for $\leq$8hrs showed a 2-fold increase in OCR ($P < 0.05$, $n = 4$) without any change in cellular ATP. These findings suggested that T3 uncoupled mitochondrial respiration from ATP synthesis. Consistent with this, RT-qPCR of HMECs stimulated with 10nM T3 showed increased expression of genes encoding uncoupling proteins 2 and 3 ($\geq$2-fold, $P < 0.01$, $n = 4$), which also function to divert substrates away from mitochondrial catabolism; and >20-fold increased expression of PPARGC1A ($P < 0.0001$, $n = 4$), which promotes mitochondrial biogenesis. In summary, these findings demonstrate that serum free T4 is increased at lactation onset. Moreover, our cellular studies indicate that thyroid hormones promote mammary mitochondrial biogenesis and may divert substrates used for ATP generation towards milk synthesis.

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OC6.6

Can systemic cytokines predict relapse of graves' disease?

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Background and Aims
Relapse in Graves' disease (GD) often occurs after antithyroid drugs (ATD) are withdrawn, however there is a lack of robust predictive biomarkers for relapse and little mechanistic insight into its pathophysiology. B-cell related cytokines and chemokines may reflect humoral immune activity and therefore be predictive of outcome. The purpose of this study was to evaluate serum B-cell activating factor (BAFF), Chemokine ligand 13 (CXCL13), A-proliferating inducing ligand (APRIL) and soluble B-cell maturation antigen (sBCMA) concentrations as prognostic markers for predicting relapse in GD.
Methods
This observational cohort study included 65 patients with GD who were followed-up for 12 months after ATD cessation. BAFF, CXCL13, APRIL and sBCMA were investigated when stopping ATD and 8-10 weeks later. Correlation between cytokine levels and the association with clinical outcome were analysed. Flow cytometry was used to investigate the association of cytokines and B cell subpopulations.
Results
In multivariate analysis, sBCMA at the end of ATD treatment was an independent prognostic factor for relapse ($P = 0.019$; OR 1.03,95%CI 1.005-1.06) in GD patients after adjusting for age, sex, goitre, smoking status, and thyrotropin receptor antibody titre. sBCMA fell significantly after stopping ATD only in remission patients ($P = 0.004$). BAFF was positively correlated to CXCL13 ($P = 0.02$) and negatively correlated to sBCMA ($P = 0.02$). There was a significant positive correlation between the frequencies of transitional B cells (CD19+CD24hiCD38hi) with sBCMA ($P = 0.02$) and BAFF ($P = 0.02$), and an inverse correlation between B regulatory cells (CD19+CD27+CD24hi) and BAFF ($P = 0.01$).
Conclusions
BCMA is predominantly expressed on the plasma cell surface and shed sBCMA is a good surrogate marker for disease activity in systemic lupus erythematosus. sBCMA may also represent a prognostic biomarker for predicting relapse in GD that is independent of TRAb concentration. The association of sBCMA with the transitional B cell subpopulation may provide mechanistic insight into GD relapse.

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Poster Oral Presentations

Thyroid

OP1.1

The 'real-world' outcomes of immunosuppression for Graves' orbitopathy (GO) in a single centre multi-ethnic cohort

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Background
Success of Graves' orbitopathy (GO) immunosuppression treatment is highly variable; patients relapse and a debilitating residual disease burden often remains with current therapies. This study describes the outcomes of immunosuppression in a multi-ethnic GO cohort treated in accordance with pre-2021 European Group on GO (EUGOGO) guidelines with first-line intravenous-methylprednisolone (IVMP). This study aims: (1) To evaluate the effect of first-line and additional immunosuppression on GO outcomes; (2) To assess the effect of immunosuppression on Graves-Orbitopathy-Quality-of-Life (GOQOL); (3) To determine the incidence of GO-relapse and predictive factors of relapse.
Methods
A retrospective study of patients who received IVMP first-line therapy at three MDT clinics between 2011-2021. Data was collected at the first, and most recent, appointment. This included: (1) demographics; (2) endocrine parameters; (3) MDT-clinic data (Clinical Activity Score [CAS], Gorman Diplopia, GOQOL, GO-treatment, relapse). First-clinic appointment data was compared between relapse and non-relapse patients.
Results
146/438 (33%) patients were included; median-age 50 (18-59) years. 77.4% were female; 42.8% Afro-Caribbean or Asian ethnicity. Fifty-four patients received IVMP alone; eighty-seven patients had additional immunosuppression with MMF or orbital radiotherapy (ORT). Median CAS was significantly reduced from 3(2.5-4.0) to 0(0.0-1.0)($P<0.0001$). Mean Gorman demonstrated an insignificant decrease from 1.2($\pm$1.1) to 0.9($\pm$1.1); twenty-seven (36.5%) patients achieved a clinically-significant diplopia response. Mean GOQOL visual-function and appearance scores increased by 8.3 and 9.2 ($P=0.03$) respectively. Thirty-eight (26.0%) patients relapsed. Baseline thyroid-stimulating hormone receptor antibodies (TRAb) levels were significantly higher with GO-relapse ($P=0.0039$). An antibody titre cut-off of 5.25 iu/l yielded 73% sensitivity and 67% specificity to detect GO-relapse.
Conclusions
Our study shows that the pre-2021 EUGOGO immunosuppression regimen is effective in reducing orbital inflammation but limited in improving subjective diplopia and appearance, which is likely to hinder QOL improvement. Our study found higher TRAb levels were associated with disease relapse.

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OP1.2

Long-term mortality and cardiometabolic effects of treatment for hyperthyroidism: EGRET study

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Hyperthyroidism has been linked to long-term cardiovascular and metabolic morbidity and increased mortality. We aimed to assess differences in mortality and cardiometabolic outcomes depending on treatment modality to better inform patient-clinician decision-making.
Methods
We identified 62,474 patients with newly diagnosed hyperthyroidism, treated with antithyroid drugs (ATD), radioiodine or thyroidectomy from a UK population-based GP database (>16M patients). Health records were linked with Hospital Episode Statistics, Office for National Statistics mortality data, and Index of Multiple Deprivation. All-cause mortality, major cardiovascular events (MACE: cardiovascular death, heart failure or stroke) and post-treatment obesity diagnosis were studied. A "target trial" approach was used to elucidate causal effects. Average treatment effects (ATE) were estimated using inverse-probability weights with regression adjustment. Mortality was assessed as time-to-event; other outcomes were modelled as binary (funding: NIHR RfPB, NIHR200772).
Results
Patients treated with ATD comprised 73.4% of the cohort; 19.5% were treated with radioiodine, and 7.1% with thyroidectomy. Patients were followed for a median of 10 years (IQR: 6-15). Estimated mean survival was 11.7 years with ATD treatment. Definitive treatment increased survival: radioiodine by 1.7y. (95%CI: 1.1-2.4; $P<0.001$) and thyroidectomy by 1.4y. (0.5-2.4; $P=0.003$). The estimated risk of MACE if the population were treated with ATD was 9.9% (9.6-10.3), which increased by an additional 0.7% (0.1-1.3; $P=0.02$) with radioiodine but not with thyroidectomy (0.02% [(-0.8)-1.2], $P=0.7$). The estimated risk of post-treatment obesity was 7.6%, which increased by 0.9% (0.3-1.6, $P=0.005$) with radioiodine and 1.7% (0.5-2.8, $P=0.003$) with thyroidectomy.
Conclusion
EGRET is the first large study using population-based linked community and hospital data to elucidate the long-term consequences of treatment modalities for hyperthyroidism. We confirmed a decreased mortality in patients undergoing definitive treatment whereas a slightly increased risk of obesity was found in patients treated with radioiodine and surgery. Compared to medical treatment, a small increase in cardiovascular events was noted with radioiodine.

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OP1.3

Levothyroxine absorption test: a therapeutic strategy for improving medication adherence

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Introduction
Low adherence to levothyroxine replacement therapy can be up to 27% in some population. Suboptimal levothyroxine replacement in the community is primarily due to medication non-adherence. The Levothyroxine Absorption Test (LAT) is a well-described intervention at confirming medication non-adherence or malabsorption. We audited the short-term and long-term clinical outcomes of patients undergoing LAT at our Centre since 2016.
Methods
LAT: Patients receive a weekly observed oral levothyroxine dose calculated at 1.6 mg x weight x 7 or adjusted based on clinician's clinical judgment for a total of 4 weeks. Thyroid function tests (TFTs) are measured hourly for 6 hours after the first dose and then weekly thereafter.
Results
16 patients underwent LAT: 12 patients with persistently raised TSH on levothyroxine replacement (Suboptimal Replacement Group) and four patients who were agreeable to transition off Liothyronine therapy (Transition Group). Suboptimal Replacement Group: Mean referral TSH was 58 mIU/l (range 20.6 to >100). Weekly Levothyroxine dose varied from 700 to 3500 mg. No patient had evidence of malabsorption on day 1 serial TFTs measurements. All patients demonstrated a decrement in TSH levels on weekly TSH monitoring. 9/12 (75%) were discharged back to GP care after LAT. For 10 patients with available follow-up TSH results, euthyroidism (TSH <10 mIU/l) was maintained in 80%, after a mean duration of 2.8 years (range 1-6) since LAT. Transition Group: Three patients were transitioned off Liothyronine therapy and one patient was established on a significantly reduced dose of Liothyronine in combination with Levothyroxine therapy.
Conclusion
The Levothyroxine Absorption Test offers a successful non-confrontational long-term therapeutic option for the majority of patients with persistently low adherence to daily Levothyroxine replacement therapy for Primary Hypothyroidism. For patients agreeable to transitioning off Liothyronine therapy, LAT offers a useful adjunct at achieving an individualised patient-centred clinical outcome.

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OP1.4

The role of oxidative stress in differentiated thyroid cancer risk stratification

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Differentiated thyroid cancer (DTC) is the most common malignant neoplasm arising from the thyroid parenchymal cells. DTC risk stratification is a multi-stage process based on investigated histopathological features and ultrasound test outcomes combined with biochemical test results. Thus, searching for novel diagnostic indicators useful in cancer risk stratification are still needed. Recent studies revealed that oxidative and epigenetic alterations in DTC represent the

signature of the disease that could be useful in early detection and diagnosis. Moreover, it was proved that nuclear factor kappa B (NF-kB), forkhead box protein 01 (FOXO), interleukin 6 (IL-6) and oxidative stress play a crucial role in DTC progression. Therefore, the determination of their role may be useful in DTC personalized clinical management. In this case, we analyzed the level of oxidative stress-related proteins, such as total oxidative stress capacity (TOC), total antioxidant capacity (TAC), NF-kB, FOXO and IL-6 to determine their role in DTC risk stratification particularly in intermediate-risk DTC progression detection. For this study 80 patients diagnosed with different stages of DTC after total thyroidectomy were enrolled. All patients were diagnosed as having papillary DTC based on laboratory tests and ultrasound imaging, and confirmed by FNAB, followed by histopathological examination. The study group consisted of DTC patients with intermediate risk based on American Thyroid Association (ATA) stratification. For the reference group low risk DTC patients were enrolled. The TAC, NF-kB, FOXO and IL-6 demonstrated increased levels among DTC intermediate risk group comparing to low risk DTC reference group (all $P<0.05$). Moreover, these measurements could be implicated as additional tools in intermediate DTC risk stratification (AUC= 0.68; AUC=0.67; AUC=0.7; AUC=0.69; all $P<0.05$ respectively). Our study suggested the utility of all studied parameters during DTC risk stratification, where FOXO and IL-6 assessments were characterized by the highest diagnostic utility.

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Adrenal and Cardiovascular

OP2.1

Novel radiolabeled ligand, Para-chloro-2-[^{18}F]fluoroethyletomidate (CETO) compared to [^{11}C]metomidate-PET (MTO) for the lateralisation of primary aldosteronism (PA)

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Introduction
Our MATCH study demonstrated 11-C ligand MTO was non-inferior to adrenal vein sampling in predicting surgical outcomes of adrenalectomy in patients with PA. The 20-min half-life of 11-C imposes logistic constraints. We investigated an 18-F ligand, CETO; its 2h half-life permits use in any facility with fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan capability.
Objective
To compare the detection of aldosterone-producing adenoma (APA), lateralisation ratio and biodistribution by CETO and MTO in PA patients.
Methods
32 patients were scanned twice, separately, once each with MTO and CETO, each after 72 hours preparatory dexamethasone, in an extension study of MATCH. The uptake of the tracers was compared in nodules, normal adrenal and liver.
Results
There was no significant difference in the number of APAs detected by CETO ($n=53$) and MTO ($n=58$) ($P=0.344$). The radiologist's interpretation of the likelihood of a unilateral APA (high, medium or low) was congruent in 30/32 scans. The average maximum standardised uptake value, by time of flight (SUVmaxTOF), in nodules was 14.4 and 16.4 in CETO and MTO respectively ($P=<0.0001$). CETO agreed with the lateralisation in all 20 scans identified to have high probability of unilateral APA by MTO. Of those scored with medium probability, only one disagreed on laterality, reporting a lateralisation ratio by MTO of 1.01 to the right and by CETO 1.06 to the left. Low probability outcomes of both scans were in agreement in all 6 subjects. SUVmaxTOF in the liver was significantly lower with CETO compared to MTO 3.95 and 14.47 respectively ($P<0.0001$).
Conclusions
CETO and MTO are strikingly similar in their ability to lateralise PA. CETO is the more favourable ligand, for clinical use, due to its longer half-life, and consequent potential for greater geographical distribution. 18-F CETO PET-CT imaging has the potential to increase lateralisation rates in PA.

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OP2.2

Can serum and urine Fludrocortisone measurements guide mineralocorticoid replacement therapy in primary adrenal insufficiency?

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Background
There is currently no agreed consensus for the optimization and titration of mineralocorticoid (MC) therapy in patients with primary adrenal insufficiency (PAI).
Objective
To explore the relationship between serum (sFC) and urine (uFC) fludrocortisone levels and biochemically and clinically important variables, and to assess their utility in guiding and titrating MC replacement.
Methods
Multi-centre, observational, cross-sectional study on 40 patients (mean age 43 ± 19 years) with PAI on MC replacement therapy (median dose 125 mg/d, range 50-400). sFC and uFC levels (measured by LC-MS/MS), plasma renin concentration (PRC), electrolytes (Na+, K+), systolic (SBP) and diastolic (DBP) blood pressure, total daily Glucocorticoid dose (dGC, hydrocortisone equivalents) and anthropometric parameters were incorporated into statistical models to determine their relative importance in guiding MC dose.
Results
We observed a close relationship between sFC and uFC ($r=0.434$, $P=0.005$) as well as between sFC and the time from the last FC dose ($r=-0.355$, $P=0.023$). Total daily MC dose was related to dGC dose ($r=0.556$, $P<0.001$), K+ ($r=-0.388$, $P=0.013$) as well as sFC ($r=0.356$, $P=0.022$) and uFC ($r=0.531$, $P<0.001$) levels. PRC was related to Na+ levels ($r=0.517$, $P<0.001$) and SBP ($r=-0.485$, $P=0.002$), but not to MC dose, sFC or uFC. Principal component analysis and multiple linear regression analyses confirmed Na+, K+ and SBP as important variable to guide MC total daily dose titration, but did not support a role for sFC, uFC or PRC measurements.
Conclusions
Our data suggest that sFC and uFC levels are not helpful in MC dose titration in PAI. Clinicians should continue to rely on clinical and biochemical important variables including electrolytes, blood pressures and symptoms to guide their decisions on MC dose adjustment.

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OP2.3

Complete clinical cure of primary aldosteronism (PA) is predictable and sustained for at least two years

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Introduction
In a prospective within-patient study (MATCH) 11C-metomidate PET-CT (MTO) was an accurate non-invasive alternative to adrenal vein sampling in the detection of unilateral PA[1]. Post-adrenalectomy (ADX), 24/78 (30%) patients achieved complete clinical success (PASO consensus) at 6 months, but 75% achieved reduction in B-type natriuretic peptide (BNP).

Aim
To determine: 1. the number of patients who sustain complete clinical success, and reduction in BNP, at 2 years, 2. whether tumour genotype associates with likelihood of sustained cure, and can be predicted from the baseline urinary 18-OH cortisol/cortisol ('hybrid steroid') ratio.
Results
63/78 ADX patients have completed 2-year follow-up. 20 of the 24 patients (83%) with complete clinical success at 6 months continue to have an average home BP $<$135/85mmHg, off treatment, at 2 years. In 18/78 patients, the aldosterone-producing-adenoma had a KCNJ5 (K$+$-channel) mutation; 14 achieved complete clinical success at both 6 and 24 months. Two patients with a double-mutation of CTNNB1/GNAQ also showed complete clinical success at 6 and 24 months. By contrast, 20/78 ADX patients had a CACNA1D (Ca$++$-channel) mutation, of whom 3 and 1 patients, respectively, were clinically cured at 6 and 24 months. The hybrid steroid ratio at baseline, measured in 66/78 patients, separated patients with KCNJ5 mutations (6.4($>$SD2.7)) from other genotypes (1.3($>$SD0.7)). Plasma BNP, available in 44/78 ADX patients, decreased in 36/44 (mean ($>$SD) reduction 27%, from 164 (248) to 84 (122) ng/l).
Conclusion
Complete cure of hypertension, achieved in a minority of ADX patients, is likely to be sustained for at least 2 years. Most complete cures are of patients with a KCNJ5 mutation, who are potentially predicted by their urine hybrid-steroid ratio. The majority of ADX patients have a substantial reduction in BNP, indicating the benefits, beyond cure of hypertension, of suppressing autonomous aldosterone production.
Reference
1. Wu *et al*. DOI:10.21203/rs.3.rs-1179128/v1.2021.

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OP2.4

Delta-like non-canonical notch ligand 1 (DLK1)-expressing adrenocortical progenitor cells: role in adrenal turnover, remodeling and tumorigenesis in mice

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The adrenal cortex is a dynamic organ that undergoes self-renewal. In the mouse it is divided into two concentric layers, the outer zona glomerulosa (ZG) and the inner zona fasciculata (ZF), that secrete aldosterone and corticosterone, respectively. Capsular and subcapsular stem/progenitor cells differentiate and migrate in a centripetal fashion to repopulate the gland until they reach the juxtamedullary region where they undergo senescence and apoptosis. Our lab has previously shown that Delta like non-canonical Notch ligand 1 (Dlk1) is expressed in partially undifferentiated cells of the subcapsular region in rat and human adrenals. Dlk1 is expressed in Steroidogenic Factor-1 (Sf1)-negative capsular cells throughout life, but, differently from Gli-1 capsular cells, its expression decreases significantly both postnatally and with aging. Genetic lineage tracing analyses using a tamoxifen inducible Dlk1CreERT2 mouse model carrying the R26tdTom reporter showed that capsular Dlk1 cells are indeed steroidogenic progenitors; these cells are particularly active during the embryonic life, whilst being near dormant postnatally, especially in males. However, in postnatal life, Dlk1 cells can be re-activated to regenerate the ZF after dexamethasone treatment, demonstrating their plasticity during adrenal remodelling treatment mimicking pharmacological interventions in humans. Finally, we present preliminary data on the potential role of Dlk1 cells in the pathogenesis of adrenocortical tumorigenesis and carcinogenesis using appropriate transgenic mouse models.

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Reproductive and Neuroendocrinology

OP3.1

Kisspeptin enhances penile tumescence and sexual brain processing in men with low sexual desire

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Background
Hypoactive Sexual Desire Disorder (HSDD) is associated with a deficiency of sexual desire with marked distress. It affects up to 8% of men, but has no licensed treatments. The reproductive neuropeptide kisspeptin offers a putative therapeutic target owing to its emerging role in modulating reproductive behaviour in animal models and healthy men. However, there are no studies examining its effects in HSDD. To address this, we performed the first clinical study of kisspeptin in men with HSDD.
Methods
We examined the effects of kisspeptin administration (vs placebo) on brain activity during short and long erotic video tasks using functional MRI in 32 men with HSDD (mean $\pm$ $>$SEM age 37.9 $\pm$ 1.5 y, BMI 24.9 $\pm$ 1.0 kg/m2). To provide functional relevance for the fMRI brain responses during the long erotic video, simultaneous penile tumescence and subjective arousal were recorded. Participants also completed psychometric questionnaires. Standard analysis methods were used for fMRI data from the short videos task, and the long videos task used regressors derived from the subjective arousal and penile tumescence data.
Results
In response to visual erotic stimuli, kisspeptin significantly increased penile tumescence during the long video task compared to placebo, with kisspeptin increasing penile tumescence by 56% ($P=0.02$). Kisspeptin also increased participant-reported happiness about sex ($P=0.02$). During both video tasks, kisspeptin significantly modulated brain activity, compared to placebo, in key structures of the sexual-processing network ($P<0.05$). Additionally, we observed positive correlations between kisspeptin's effects on aforementioned brain activity and psychometric parameters of sexual desire and arousal (all $P<0.01$).
Conclusion
Collectively, we demonstrate for the first time that kisspeptin in men with HSDD increases penile tumescence and psychometric measures of sexual desire and arousal by modulating sexual brain processing. Our data suggest that kisspeptin-based therapeutics may offer a novel, effective and much-needed clinical strategy for men with HSDD.

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OP3.2

Identification of differentially activated pathways in recurrent non-functioning pituitary tumours using quantitative proteomics and bioinformatics analysis

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Background
No predictive biomarkers have been identified for clinically nonfunctioning pituitary tumour (NFPT) recurrence, with Ki67 being controversial. We employed quantitative mass spectrometry-based analyses to examine the differential expression of proteins in NFPTs.
Methods
NFPTs were sub-grouped: non-invasive/non-recurrent group (NI/NR-G, $n=5$), invasive group (I-G, $n=10$) and recurrent group (R-G, $n=5$). Invasiveness was determined Knosp classification 3,4; histopathological invasion (bone/dura/mucosa) and intraoperative findings. Mean follow-up was 17.4 ($>$SD $\pm$ 7.5), 13.4 ($>$SD $\pm$ 3.8), and 17.8 ($>$SD $\pm$ 3.9) months for NI/NR-G, I-G and R-G respectively (no significant difference, $P=0.19$). High-throughput tandem mass tags-based LC-MS/MS was performed. To calculate fold-change, NI/NR-G was considered as baseline. Upstream regulators analysis (URA) and causal network

analysis (CNA) was performed using ingenuity pathway analysis (IPA); -log (P-value) > 1.3 and Z-score > 2 was considered as threshold of significant activation.
Results
Out of 5903 identified proteins, 441 were differentially expressed in I-G (339 overexpressed, 102 underexpressed) and 683 in R-G (628 overexpressed, 55 underexpressed). In invasive tumours, IL-8 signalling (DEFA1, GNAI3, ITGAM, ITGB3, MPO) (-log p-value, Z-score:1.4,2.2) and RGS12, a regulator of GPCR signalling, with its 13 downstream members were enriched (9.0E-07,2.5). Recurrent tumours had significantly activated actin cytoskeleton (6.8,3.0) and Integrin-linked kinase (ILK) signalling (5.6,3.0). GATA1 was activated in R-G (2.5E-12,2.2) together with overexpression of further 24 downstream proteins involving actin cytoskeleton and ILK signalling. Members of the interleukin pathway were overexpressed in R-G (IL17RA receptor (1.28E-12,5.5) as well as IL6, IL6R, IL4, IL17A, IL1B, IL22, IL1A, IL23A and IL1. IL6 is most significantly upregulated protein (Z-score,4.6). Cytoskeleton pathway member PRDM1, a transcription factor, was upregulated in both I-G and R-G.
Conclusions
This study provides in-depth proteomics analysis of NFPTs. Actin cytoskeleton was upregulated in both I-G and R-G, with stronger effect in R-G, while ILK signalling, especially IL6, showed specifically high levels in recurrent NFPTs.

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OP3.3

Acetate restores hypothalamic-adipose kisspeptin status in a rat model of PCOS by suppression of NLRP3/PROKR1 immunoreactivity

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Background
Polycystic ovary syndrome (PCOS) is a complex reproductive event that is delineated by endocrine and metabolic disorders. Alteration of kisspeptin status in the hypothalamus and adipose tissue is critical to increased endocrine/metabolic derangements in PCOS individuals, aggravating the clinical manifestation of PCOS and its complications. Short chain fatty acids (SCFAs) are crucial modulators of metabolic homeostasis. However, the role of SCFAs, in particular, acetate on hypothalamic-adipose kisspeptin status (HAKS) in PCOS model is unknown. The present study hypothesized acetate as a key player in restoration of deranged HAKS associated with experimental rat model of PCOS.
Materials and Methods
Three groups ($n=6$/group) of female Wistar rats (8 weeks old) were used. The groups were treated (po) for 21 days with vehicle, letrozole (1 mg/kg) with or without acetate (200 mg/kg) respectively.
Results
Animals that received letrozole only had impaired glucose homeostasis, elevated testosterone/leptin and LH/FSH ratio and decreased GnRH/adiponectin with ovarian tissues largely characterized with degenerated follicles and disrupted morphology. In addition, these animals also showed increased hypothalamic lipid and decreased adipose lipid with a corresponding increase in hypothalamic/adipose malondialdehyde, NF-κB/TNF-α and decreased GSH/G6PD and hypothalamic but not adipose kisspeptin. Immunohistochemical analysis revealed the expression of inflammasome (NLRP3) and PROKR1 in the hypothalamic and adipose tissue. Altogether, the present results demonstrate that PCOS is characterized with hypothalamic-adipose inflammation, accompanied by immunohistochemical expression of NLRP3/PROKR1 with consequent alteration of hypothalamic but not adipose kisspeptin.

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OP3.4

Identification and characterisation of novel follicle-stimulating hormone receptor antagonists

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Follicle-stimulating hormone receptor (FSHR) is a Class A G protein-coupled receptor (GCPR) that is essential in reproduction. Interactions with its heterodimeric glycoprotein hormone, FSH, activates the cAMP/PKA signalling pathway, which induces steroidogenic activity and granulosa cell proliferation to support ovarian follicle growth and survival. Moreover, a number of ageing-related extragonadal roles of FSH/FSHR have been proposed, with menopausal elevation in FSH linked to bone loss, deposition/changes in adipose tissue depots, and Alzheimer's disease. Thus, targeted inhibition of FSH/FSHR is an attractive approach to combat these menopause-related co-morbidities, furthermore, would present a non-steroidal mechanism of contraception. Therefore, we aimed to screen and identify novel FSHR antagonists and investigate their effects on FSHR-induced second messenger pathway activation. Using human embryonic kidney 293 (HEK293) cells transiently expressing the FSHR, 84 AI-generated small molecule compounds (provided by Atomwise, San Francisco) were screened for the ability to inhibit FSH-dependent cAMP-production. 3 inhibitors were identified, showing <90% inhibition at high FSH concentration, with an IC50 value ranging between 35-65μM. Next, concentration-dependent assessment of the inhibitors (0-100μM) on FSH-dependent cAMP-production was analysed. Analysis suggested that these inhibitors displayed non-competitive antagonism, as there were no obvious changes in potency. Our findings present 4 new small molecule pharmacological non-competitive FSHR inhibitors, which may present new pathways for non-steroidal contraceptives or treatment of menopause-related co-morbidities.

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Metabolism, Obesity and Diabetes

OP4.1

The effects of a tripeptide hormonal infusion on sweet taste function and eating behaviour

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Background
Roux-en-Y Gastric Bypass (RYGB) results in sustained weight loss. Changes in food preferences and eating behaviour are postulated as possible contributing mechanisms. Post-RYGB, patients consume less sugary and fatty food. Sweet taste detection and sensitivity have been reported to be enhanced post-surgery and this may account for changes in the palatability of food. Underlying mechanisms for the changes in sweet taste function and eating behaviour are unclear.
Aims
We investigated whether the elevation in the post-prandial concentrations of the gut hormones Glucagon-Like Peptide-1 (GLP-1), Oxyntomodulin (OXM) and Peptide YY (PYY), account for the beneficial changes in sweet taste function and eating behaviour post-RYGB.
Methods
We infused GLP-1, OXM, PYY (GOP) or 0.9% Saline subcutaneously for 4 weeks in 26 obese subjects with pre-diabetes/diabetes, in a randomised single-blinded study. We reproduced the peak post-prandial concentrations of the gut hormones, as measured at 1-month in a matched RYGB cohort. A sweet taste study using the constant stimuli method of sucrose detection was carried out. Corrected hit rates for sucrose identification and sweet taste detection thresholds were recorded. The intensity and consummatory reward of sweet taste were assessed using Visual Analogue Scales (VAS) and eating behaviour was evaluated using validated eating behaviour questionnaires.
Results
We found no change in detection thresholds or corrected hit rates for sucrose detection following GOP. The intensity and palatability of sweet taste also remained unchanged on GOP. There was a significant reduction in restraint eating on GOP, comparable to the RYGB group. A trend to diminished external eating was observed with GOP while the saline group demonstrated no change in any aspect of eating behaviour.
Conclusion
Our findings suggest that the elevation in GOP concentrations after RYGB, are unlikely to account for the changes in sweet taste function after surgery but may promote restraint eating.

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OP4.2

Differential effects of L- and D-lactate on HCAR1 signalling

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Lactate is a metabolite that activates the G-protein coupled receptor, Hydroxycarboxylic acid Receptor 1 (HCAR1) to regulate physiological processes

such as lipolysis, cancer cell survival, and neuroprotection. Lactate exists in two forms, L+ and D-, with the L isoform predominant in the human body. Interestingly, both isoforms are only found together in the gastrointestinal tract. L-lactate is synthesised as a by-product of anaerobic respiration, whereas D-lactate, is a product of fermentation by microbiota. To understand the different physiological roles of HCAR1 following activation by each form of lactate, our aim was to characterise the potential differential effects of L- and D-lactate on HCAR1 activity. HCAR1 mediates its signalling by coupling to Gαi to inhibit adenylate cyclase and reduce intracellular cAMP levels. Using HEK293 cells stably expressing FLAG-tagged HCAR1, we first investigated lactate-dependent differences in Gαi, Gαs and Gαq-protein activation. We confirmed HCAR1 activated only Gαi signalling, with L-lactate exhibiting a significantly higher potency than D-lactate (IC50 L-lactate: 23.67 mM, IC50 D-lactate: 61.84 mM, $P<0.0001$, T-test). In addition, two distinct HCAR1-selective ligands (HTL60092 and HTL61461) activated Gαi signalling with a higher potency than lactate (IC50 HTL60092: 245.9 nM, IC50 HTL61461: 18.6 nM, $P<0.0001$, T-test). Unexpectedly, measurement of intracellular calcium levels identified L- but not D-lactate could inhibit ATP-mediated calcium signalling without impacting ATP-mediated IP1 levels, suggesting possible crosstalk with a purinergic receptor downstream of Gαq/PLC activation. Analysis of HCAR1 trafficking via confocal microscopy indicates that HCAR1 undergoes both constitutive and lactate-induced internalisation, to an endosomal compartment that poorly co-localises with early endosomal markers. Preliminary data suggests that pre-treatment with ATP may promote D-Lactate-induced HCAR1 trafficking to the early endosome. Together, these results emphasise that L- and D-lactate activate HCAR1 in unique ways and both isomers must be considered to gain a better understanding of HCAR1 action in physiological settings.

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OP4.3

miR-10b is an essential regulator of adipogenesis

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Determining the sequence of events controlling preadipocyte commitment and subsequent terminal differentiation into adipocytes is critical to gain insight into brown and white fat physiology and metabolic dysfunction. MicroRNAs (miRNAs) are important regulators of gene expression and emerging evidence supports their involvement in adipogenesis and adipose metabolism. The aim of this study is to 1) identify miRNAs that modulate differentiation or function of white and brown adipocytes, and 2) define miRNA action in a stem cell model of adipogenesis. Small RNAseq analysis of primary mouse brown and white adipocytes identified enriched miRNAs in mature adipocytes and pre-adipocytes. miR-10b was upregulated in brown adipocytes and CRISPR/Cas9 was used to generate its functional knockout (KO) in E14 mouse embryonic stem cells (ES). Wild type (WT) and KO cells were assessed for proliferation and self-renewal and differentiated to mature adipocytes using an optimized protocol. The expression of key genes associated with pluripotency, adipogenesis and brown adipose tissue were determined. Samples were collected at different time points for qRT-PCR and RNA-sequencing. MiR-10b expression was significantly increased during ES adipocyte differentiation. Knockout of miR-10b severely compromised differentiation into adipocytes as judged by lack of lipid droplet accumulation and low expression of white and brown adipocyte marker genes (aP2 and CIDEA) as well as preadipocyte markers (Pref-1). In contrast, stem cell markers (OCT4, Nanog) were upregulated in KO clones. KO clones showed similar self-renewal and proliferation compared to WT. Transcriptomic analysis revealed that key pathways regulating ES commitment to the adipocyte lineage appear to be affected in the KO clones. This study shows that the process of differentiating mature adipocytes from stem cells is dependent on the presence of miR-10b. Understanding the miR-10b-mediated regulatory mechanism during adipocyte commitment and differentiation may help to generate adipose tissue-engineering strategies for cellular therapies for lipodystrophy and obesity.

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OP4.4

iPSC-derived hepatocytes as a novel tool for glycogen storage disease 1A (GSD1A) modelling and drug screening

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Glycogen storage disease 1A (GSD1A) is an inherited metabolic disorder caused by glucose-6-phosphatase (G6PC) deficiency. Patients with GSD1A present disturbed glucose homeostasis and exhibit glycogen accumulation accompanied by hepatomegaly, hypoglycemia, lactic acidosis and hyperlipidemia. However, there are currently no licensed treatments for GSD1A, and human *in vitro* systems for disease modelling and drug screening are lacking. We aimed to develop a human hepatocyte model recapitulating the GSD1A phenotype in-a-dish. Healthy and GSD1A patient-derived (R83C) induced pluripotent stem cells (iPSCs), alongside isogenic controls, were differentiated towards hepatocyte-like cells (HLCs). Successful differentiation was confirmed by expression of the hepatocyte markers Albumin, Alpha-1-antitrypsin, Alpha-fetoprotein and HNF4alpha using qPCR and immunocytochemistry. Mutation correction (C83R) in G6PC was performed by CRISPR/Cas9 mediated gene editing, and iPSC genotyping was confirmed by Sanger sequencing. Media glucose secretion and intracellular glycogen levels were measured by colorimetric assays. Intracellular glycogen levels were significantly reduced in healthy HLCs following 1h glucagon stimulation under starvation. However, no differences in GSD1A-derived HLCs were observed. In line with this, media glucose levels were elevated in healthy glucagon-stimulated HLCs compared to vehicle-treated ones, but not in GSD1A-HLCs, suggesting impaired glycogen breakdown towards glucose formation. In contrast, correction of disease mutation in GSD1A-HLCs reduced glycogen levels in a time dependent manner, alongside enhanced glucagon-stimulated glycogen breakdown. Finally, to confirm that the observed effects were the result of corrected G6Pase activity, transient over-expression of G6PC in unedited GSD1A-HLCs similarly resulted in increased glucose secretion, suggestive of restored glycogen mobilization. We have developed an iPSC-derived hepatocyte model that recapitulates human GSD1A phenotype *in vitro*. This technology provides a framework for the development of human liver disease models from patients of varied genetic disease backgrounds. Crucially, it highlights the advantage of iPSCs as an effective platform for liver disease modelling and hit-lead drug screening.

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Bone and Calcium

OP5.1

3' UTR structural elements are associated with *CYP24A1*-mediated abnormal calcium handling

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Hypomorphic *CYP24A1* protein coding mutations causing inappropriate $1,25(OH)_2D$ concentrations are associated with idiopathic infantile hypercalcemia and adult-onset hypercalciuria and nephrolithiasis. It is unclear why some cases present with *CYP24A1*-mediated abnormal calcium handling lack protein-coding *CYP24A1* mutations. Non-coding region mutations, e.g. the 3' UTR, impacting messenger RNA (mRNA) structure have rarely been studied in patients. RNAs fold into complex structures critical for their function and regulation including post-transcriptional modifications, localisation, translation and degradation. Non-coding variants altering *CYP24A1* mRNA structure may be the fundamental mechanism behind cases with absent protein coding pathogenic mutations. Biochemical profiling, next generation sequencing, bioinformatics, proteomic and molecular cytogenetic approaches were used to examine *CYP24A1* in a patient cohort of four adults with hypercalciuria and nephrolithiasis and two infants with nephrocalcinosis. We identified inappropriate $1,25(OH)_2D$ concentrations (mean ± > SD = 247.3 ± 189.3pmol/l [range = 55-139 pmol/l]) in our cohort, associated with elevated 25OHD:$24,25(OH)_2D$ (32 [range 7-23]) in one adult and both 25OHD:$24,25(OH)_2D$ (35) and $1,25(OH)_2D$:$24,25(OH)_2D$ (176 [range = 11-62]) in one infant. *CYP24A1* direct sequencing revealed single nucleotide variants located in the 3' UTR of each patient (c.1993C > T, c.2083T > C, c.2512T > A, c.2658C > G and c.2691G > A) causing mRNA misfolding in silico. These mRNA structural abnormalities are associated with significant increase in CYP24A1 retention ($P<0.05$), while biochemical profiles suggest compromised functionality. We generated a CRISPR-Cas 9 model cell line containing *CYP24A1* 3' UTR mRNA structural alterations for *in vitro* investigations into non-canonical *CYP24A1* pathogenesis. Single molecule fluorescence *in situ* hybridisation (smFISH) in this model revealed no significant effect on *CYP24A1* mRNA cellular localisation and abundance. We present insights into novel non-coding 3'UTR *CYP24A1* hypomorphic variants that alter mRNA folding, associated with CYP24A1 biological function. These results will

improve knowledge of structure-function relationships affecting RNA translation and protein expression, expanding our understanding of the molecular basis of disease pathogenesis in patients lacking protein coding abnormalities.

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OP5.2

Hyperparathyroidism jaw tumour syndrome due to a novel familial CDC73 germline mutation

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Introduction
Approximately 5-10% of PHPT cases are hereditary. One such hereditary cause of PHPT is Hyperparathyroidism-jaw Tumour Syndrome (HPT-JT) caused by an autosomal dominant mutation in cell division cycle 73 (CDC73) that impairs parafibromin, a protein with antiproliferative activity. HPT-JT is characterised by parathyroid tumours, ossifying jaw fibromas, renal tumours and uterine tumours. We report a familial case of HPT-JT caused by a novel CDC73 mutation.
Case presentation
A 52-year-old female with a biochemistry consistent with PHPT (aCa 2.65 mmol/l, PTH 21.2 pmol/l, Vit D 88.5 nmol/l) was referred to our Endocrine Bone Unit. Of note, she previously had a 2-gland parathyroidectomy at the age of 30 at a different institution, hysterectomy for fibroids/polyps in her 40's and previous renal calculi. Ultrasound and nuclear medicine imaging of the neck suggested a left-sided parathyroid adenoma. Her bone mineral density was normal and there was no evidence of nephrolithiasis/nephrocalcinosis on imaging. A detailed family history revealed that her 37-year-old daughter underwent parathyroidectomy at the age of 24 for PHPT and consequently developed hypoparathyroidism as a complication. An x-ray orthopantomogram showed a cemento-fibro-osseous lesion in the daughter only. Genetic testing was carried out in both mother and daughter and revealed a novel heterozygous CDC73 missense variant in GRCh37 (hg19) (Chr1: g.193091353T>G). This variant has not been reported in the gnomAD database (~125,000 individuals) and may represent a de novo mutation. Additional family members have been diagnosed with PHPT and therefore family segregation analysis is underway. Our patient was managed conservatively, with close monitoring of her biochemistry and for potential dental and renal complications.
Conclusions
Screening for CDC73 germline mutations is important in patients with early-age onset PHPT and a family history of PHPT as well as in patients uncured by surgery.

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OP5.3

Lower bone mineral density is associated with primary hyperparathyroidism patients with abnormal vitamin D metabolite ratio (VMR): A case-control study

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Introduction
The role of vitamin D and calcium metabolism has long been implicated in the clinical manifestation of primary hyperparathyroidism (PHPT). The skeletal response to the overproduction of PTH is less predictable, and the effect on bone loss can be greater in some patients. In this study, we established associations between vitamin D metabolism, vitamin D metabolite ratio (VMR) 1,25OH2D:24,25OH2D with rates of bone loss in PHPT patients who did not undergo surgery.
Methods
An audit was conducted from the electronic health records of PHPT patients from the Endocrinology clinic at the NNUH during 2017-2019. The search identified patient cases $n=13$(age mean (range): female ($n=9$)70.6(50-94)yrs, male $n=473$(63-79) yrs, VMR ≥ 51), with age/gender matched controls (VMR <51) Excluded were those who had parathyroid surgery. Serum 25OHD, adjusted calcium, phosphate and PTH were retrieved with bone mineral density (BMD) T-score values (lumbar, left hip and left femoral neck) from DEXA scans carried out ± 1 month of biochemical measurements.
Results
We observed a significantly lower Lumbar Spine T-score in the cases, mean(95%CI) -1.85(-0.9 to -2.77) than in the controls -0.2(0.30 to -0.79), $P<0.001$. Whilst the left hip and left femoral neck T-scores in the cases were lower but not statistically significant. 25OHD and 24,25OH2D were significantly lower in the cases than controls; mean(>SEM) 42.9(6.6)/69.4(3.9) nmol/l, $P<0.01$ and 2.0(0.44)/5.0(0.38) nmol/l, $P<0.001$, respectively. In contrast, the 25OHD:24,25OH2D VMR in the cases were higher 27(2.0)/15(0.8), $P<0.001$.
Conclusion
Our cohort of non-surgically managed PHPT patients presented with elevated 1,25OH2D:24,25OH2D VMR were strongly associated with lower Lumbar Spine T-score. By using VMR we demonstrated an imbalance between the active and catabolic forms of vitamin D metabolites, that may play a role in altering the responsiveness to PTH and accelerating bone loss.

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OP5.4

Prospective clinical trial of a novel, reusable, pocket size Point of Care device to measure ionized calcium in venous and capillary blood and saliva

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Background
Patients with hypoparathyroidism require frequent calcium measurements and currently there is no point of care device allowing this to be done at home by patients themselves.
The aim
Of our study was to evaluate whether ionized calcium(iCa) can be accurately measured in venous and capillary blood and saliva by a repurposed device LAQUA.(R&D Ref 18/0058– IRAS 236079)
Methods
Patients undergoing thyroid and parathyroid surgery underwent daily measurements of venous blood adjusted calcium(adjCa, Roche-Cobas-Gen.2,) and ionized calcium (iCa, Blood Gas Analyser-ABL90) as "gold standard" and iCa in venous and capillary blood using LAQUA. Calcium was also measured in saliva in the main laboratory (Roche-Cobas-Gen.2) and LAQUA.
Results
67 sets of measurements were obtained from 30 patients. We observed strong correlation between venous adjCa and BGA iCa. ($r=0.95$, $P<0.001$) with minimal average difference between measurements 0.03mmol/l (95%CI-0.11-0.05). Strong positive correlation was seen between BGA iCa and LAQUA iCa ($r=0.75$, $P=<0.001$) with average difference between measurements of 0.14mmol/l (95%CI:-0.11-0.41). A similar relationship was observed between venous BGA iCa and LAQUA capillary iCa($r=0.68$, $P=<0.001$) with average difference of 0.22mmol/l (95%CI:-0.02-0.46). There was a positive correlation between saliva LAQUA iCa and saliva calcium Roche-Cobas-Gen.2 ($r=0.76$, $P=<0.001$) with average difference between measurements of -1.34mmol/l (95%CI:-3.67-0.99). No correlation between saliva calcium (Roche-Cobas-Gen.2) and blood adjCa(Roche-Cobas-Gen.2) was observed($r=0.17$, $P=0.2$).
Conclusion
iCa could replace adjCa for monitoring hypocalcaemia and LAQUA is a promising device which might allow calcium measurements to be done at home by patients themselves.

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Endocrine Cancer and Late Effects

OP6.1

Post-Transcriptional regulation of wild-type and variant androgen receptors during prostate cancer progression

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A key mechanism of persistent cell survival under testosterone suppression in advanced prostate cancer (PC) is continued Androgen Receptor (AR) activation. This results from AR mutation, overexpression, hyper-activation, and/or expression of constitutively-active AR transcript variants (AR-Vs). AR has an unusually long 3' untranslated region (3'UTR), which performs vital regulatory roles but is remarkably understudied. Its contribution to continued AR activation under androgen-depletion, and to disease progression, has not been investigated. Indeed, its associations with RNA-binding proteins and non-coding RNAs (e.g. microRNAs – AR is the most commonly microRNA-targeted oncogene in PC) have dramatic effects on transcript stability and translational efficiency. Further,

shortening of oncogene 3'UTRs, via alternative polyadenylation (APA), avoids repression by microRNAs and is a widespread feature of cancer associated with poor outcome. Opposingly, 3'UTR circularisation is linked to mRNA stabilisation and increased translation. We identified mechanistically-undescribed APA sites within AR in prostate tissue. We used *in silico* approaches to examine 3'UTR length of AR and other cancer-implicated transcripts in a cohort of >5000 PC patients (Decipher Biosciences), assessing their association with disease progression and patient outcome. AR transcript-length was significantly increased in high *vs* low Gleason grade tumours (in contrast to the majority of oncogenes showing transcript shortening), and is the most significantly length-altered transcript. This is consistent with reduced AR 3'UTR splicing observed in cancerous *vs* non-cancerous prostate, and may increase AR activity through retention of binding sites for miRs shown to stabilise AR transcript. We present novel findings from long-read RNA-sequencing from 22RV1 cells and patient-derived xenografts treated $\pm$anti-androgen, Enzalutamide, revealing novel cancer-associated transcript isoforms and length alterations that may contribute to maintenance of AR activity in advanced disease. These hitherto under-investigated AR-regulatory mechanisms could be exploited in the design of new therapies, particularly for scenarios driving resistance to current therapeutics

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OP6.2

Investigating the utility of microRNA signatures as a tumour biomarker in patients with succinate dehydrogenase deficient phaeochromocytoma, paraganglioma and GIST

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Background
International consensus supports interval biochemical and imaging surveillance for all asymptomatic carriers of succinate dehydrogenase (SDHx) gene mutations and patients with a history of SDH deficient tumours. There is growing awareness that the life time penetrance of the SDHx genes is much lower than that originally estimated and that long term radiological surveillance carries a significant risk including ionizing radiation exposure and incidental findings. There is a need to consider alternative biomarkers for long-term clinical surveillance of SDHx mutation carriers and to identify new therapeutic targets. MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression at the post-transcriptional level and alterations can promote cancer specific molecular mechanisms. Fluctuations in specific miRNA's have been identified as sensitive biomarkers in a number of cancers.
Aims
To identify specific miRNA signatures in SDH deficient tumours compared to control tumours.
Results
Small RNA sequencing was performed on 44 tumour samples including; 13 SDH preserved (pSDH) PPGL, 11 SDH deficient (dSDH) PPGL, 15 pSDH and 15 dSDH GIST. Principle component analysis (PCA) demonstrated that differential miRNA signatures separated PPGL from GIST and within the tumour groups, unbiased PCA of miRNAs clustered tumours according to their underlying molecular drivers. Top miRNAs separating dSDH from pSDH PPGL included miR-183-5p, miR-182-5p and miR-96-5p, previously suggested as SDHx specific miRNA's, and associated with pro metastatic features *in vitro*. Novel findings include increased expression of miR-338-5p in dSDH vs pSDH GIST. Preferential miR-338-5p expression has been identified in colorectal cancel tissue and associated with an increased tendency towards migration and invasion through inhibition or repression of PI3KC mediated authophagy. MiR424-5p was also preferentially expressed in dSDH vs pSDH GIST. miR-424-5p targets genes responsible for cell division, and regulation of cell migration in a number of tumour types.

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OP6.3

Knockout mouse embryonic fibroblasts reveal a physiological role for the proto-oncogene PBF in cell adhesion and motility

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The proto-oncogene pituitary tumor-transforming gene-binding factor (PBF) is upregulated in multiple tumours including thyroid cancer. PBF overexpression mediates tumorigenic processes such as cell motility and accelerates thyroid cancer cell invasion. We have recently shown that both PBF phosphorylation at tyrosine 174 (Y174) and PBF endocytosis are required for PBF-stimulated thyroid and breast cancer cell migration and invasion. This prompted further investigation into a physiological role for PBF in cell motility. We utilised a novel Pbf knockout (Pbf-/-) mouse model to determine the impact of Pbf deletion on cell motility. Mouse embryonic fibroblasts (MEFs) were isolated at embryonic day 13.5 and used as primary cultures within 3 passages. Pbf-/- MEFs showed a significant reduction in migration compared with wild-type (Pbf+/+) MEFs. Interestingly, the loss of one functional copy of Pbf in heterozygote MEFs (Pbf+/-) resulted in an intermediate decrease in migration suggesting a gene-dosage effect. Immunofluorescent studies of Pbf-/- MEFs identified alterations in focal adhesions (FAs). FAs are structures that link the extracellular matrix with the intracellular actin cytoskeleton, and the turnover of FAs plays a crucial role in cell motility. In Pbf+/+ MEFs focal adhesion kinase (FAK) and paxillin staining highlighted FA structures that were normally elongated and aligned with actin stress fibres. In contrast, Pbf-/- MEFs demonstrated a significant reduction in FAK and paxillin staining with smaller, punctate, and more radially distributed FAs. These studies demonstrate a physiological role for PBF in cell adhesion and migration and further elucidate the mechanism by which PBF induces cell motility in tumour progression.

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OP6.4

Endocrinopathies in cancer patients receiving immune checkpoint inhibitors are associated with an improved overall survival

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Background
Immune checkpoint inhibitors (ICIs) including programmed-death cell-1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) re-activate T lymphocytes and promote cancer cell death. Immune-related adverse events (irAEs) are common in cancer patients receiving ICIs. Endocrine irAEs include primary thyroid dysfunction, hypophysitis, type 1 diabetes mellitus (T1DM) and primary adrenal insufficiency. These endocrinopathies may require a treatment break until toxicity resolves.
Methods
A retrospective analysis was performed at our centre in all cancer patients receiving PD1, PDL1 and CTLA4 inhibitors. Data collection included treatment details, characteristics of acute endocrine manifestations, history of autoimmune disease and overall survival, defined as the time between treatment initiation to death or 1st March 2022 when data collection ceased.
Results
400 cancer patients (249 male, 62.2%; 151 female, 37.8%) were identified. 15% ($n=60$) of these developed an endocrine irAE: 64.1% primary thyroid dysfunction ($n=41$), 15.6% primary adrenal insufficiency ($n=10$), 12.5% hypophysitis ($n=8$). 7.8% type 1 diabetes mellitus ($n=5$). All cases of new onset diabetes mellitus presented acutely with diabetic ketoacidosis, were not associated with adjuvant glucocorticoid use and developed late in treatment. By multiple logistic regression, men were less likely to develop an irAE (OR = 2.73, 95% CI [1.7, 5.8]) ($P<0.001$). A history of autoimmune disease or non-endocrine irAEs were not associated with developing an endocrine irAE. Overall survival was higher in patients developing combined endocrine and non-endocrine irAEs ($P<0.001$) and in patients developing an endocrine irAE($P<0.01$).
Conclusion
Endocrine complications from immunotherapy may present acutely and late in treatment. Women receiving ICIs are at higher risk of ICI-induced endocrinopathies. Interestingly, this study shows that development of endocrine irAEs alone or in combination with non-endocrine irAEs are associated with a favourable overall cancer survival. Future prospective studies are needed to further elucidate the links between endocrine manifestations of ICI treatment and cancer survival.

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Featured Clinical Case Posters

CC1

Case report: a rare case of hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome due to heterozygous pathogenic GATA3 alteration

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Introduction
Hypoparathyroidism may be an isolated or a component of a complex syndrome. Although genetic disorders are not the most common cause, molecular analyses have identified a growing number of genes that when defective result in impaired formation of the parathyroid glands, disordered synthesis or secretion of parathyroid hormone.
Case presentation
We are reporting a 37-year-old gentleman, who is the first adult case diagnosed at our University Teaching Hospital. He was initially seen in the Genetics Clinic after his son was referred for assessment of congenital hearing loss, identified on new-born screening. Family history revealed the baby's paternal family had several individuals with hearing loss and renal anomalies. Subsequent testing revealed that both patient and his son had a heterozygous likely pathogenic alteration for the GATA3 gene (c.815_816delinsTA p.Thr272Ile) consistent with a diagnosis of Hypoparathyroidism, Deafness and Renal Dysplasia (HDR) syndrome. Biochemistry confirmed asymptomatic hypoparathyroidism in our case and he was commenced on calcium supplementation.
Discussion
HDR syndrome, also known Barakat Syndrome is a rare genetic syndrome characterized by hypoparathyroidism, sensorineural deafness, and renal disease. Hypoparathyroidism leads to symptoms such as muscle pain, muscle spasms, seizures, and rarely, cardiomyopathy. Hearing loss is the most consistent feature of HDR syndrome. It is usually bilateral and can range from moderate to profound. The renal involvement includes structural renal anomalies and reflux however penetrance is reduced. HDR is inherited as an autosomal dominant disorder and is associated with genetic alterations involving the GATA3 gene, a zinc-finger transcription factor.
Conclusion
Taking a thorough clinical and family history is important when assessing patients to identify possible genetic clinical syndromes. The combination of hearing loss and hypoparathyroidism should prompt assessment for HDR syndrome, with cascade testing of family members following on and general genetic screening should be considered in young patients with sporadic hypoparathyroidism.

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CC2

Coexistence of cranial diabetes insipidous and heart failure with reduced ejection fraction: a case report presenting challenges and unique therapeutic opportunities

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History
We present the case of a 47-year-old man with heart failure (HF) and cranial diabetes insipidus (CDI) secondary to Langerhans-cell-histiocytosis. In the context of worsening HF with increasing shortness of breath and fluid retention, careful desmopressin dose reduction provided adequate aquaresis to restore euvolemia, obviating the need for usual diuretic treatments.
Investigations
Echocardiography and a cardiac MRI revealed a non-dilated but severely impaired left ventricle (ejection-fraction 35%). His right ventricle was impaired but non- dilated. Sodium, paired osmolarities were within reference range throughout follow-up.
Treatment
Careful reduction of desmopressin from maintenance dose of 200 mg thrice-daily to 200 mg twice-daily allowed for adequate aquaresis and resolution of worsening HF symptoms. Iatrogenic diuresis was not indicated. Desmopressin adjustment manoeuvres were adequate to restore euvolemia, with urine output averaging 2-2.5 litres. After resolution of HF symptoms, desmopressin was switched back to 200 mg thrice-daily. Maximum tolerated Losartan dose was 50 mg. Beta-blockade, mineralocorticoid-receptor or angiotensin-receptor- neprilysin inhibition were not tolerated. SGLT-2 inhibition has not been trialled yet.
Conclusions
The co-existence of CDI and HF presents both challenges and unique therapeutic opportunities. Desmopressin dose manoeuvres produced adequate aquaresis, leading to restoration of euvolemia and rapid symptomatic relief. Dizziness, polyuria, thirst limited tolerability of HF prognostication drugs. Close endocrinology and cardiology co-operation was key in avoiding admissions with decompensated HF. This case provides insights for novel drug development targets. Our patient has complete absence of V1a-receptor activity (absent endogenous vasopressin). V2-receptor activity is dose-dependent based on desmopressin manipulation. Inducing a similarly balanced V1a/V2-receptor activity state pharmacologically could translate to clinically meaningful aquaresis, obviating V1a-receptor induced deleterious vasoconstriction and cardiac remodelling. This could represent a novel HF treatment target, potentially more effective than selective V2- receptor antagonism (tolvaptan) associated with toxic V1a-receptor activation via rebound endogenous vasopressin release. Pecavaptan, a novel balanced oral V1a/V2-receptor antagonist is under development.

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CC3

Transient hypophosphatemia secondary to iron infusion

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Hypophosphatemia is commonly missed due to nonspecific signs and symptoms. It can cause muscle weakness, confusion, white blood cell dysfunction and disrupt cardiopulmonary systems. Three main mechanisms of hypophosphatemia are shifts from the extracellular to intracellular compartment, increased renal excretion and decreased intestinal absorption. Here we report a case of symptomatic hypophosphatemia post ferric carboxymaltose (Ferrinject) infusion. A 42 year old lady with longstanding ulcerative colitis on vedolizumab injection and mesalazine attended the Emergency department with palpitations, nausea and fatigue. She also suffered from iron deficiency anaemia secondary to menorrhagia and had received intravenous Ferrinject six days prior. Her blood tests were unremarkable apart from low phosphate level (0.39 mmol/l). Electrocardiogram revealed sinus rhythm with atrial ectopics. Over eight days, she required three IV phosphate infusions and oral phosphate replacement. Within two months, serum phosphate returned to normal (1.0 mmol/l) with resolution of symptoms. During this time, a 24-hour urine phosphate collection highlighted an inappropriately high level of 17.05 mmol/24hrs, with a high fractional phosphate excretion of 25.8%. Further investigations showed a low vitamin D (37.6 nmol/l), normal 1,25 OH Vitamin D (133 nmol/l), normal Fibroblast growth factor 23 (FGF-23) (51RU/ml) and normal Retinol binding protein/creatinine ratio (7.6ug/mmol). These tests exclude proximal renal tubular injury and tumour-induced osteomalacia as a cause and the normal FGF-23 indicated resolution of the transient pathology. It is suggested that iron infusions cause hypophosphatemia by increased FGF-23, which reduces phosphate reabsorption in the proximal tubules. Severe hypophosphatemia is infrequent, but a potentially serious and reported complication. It can occur five days post infusion and last up to five weeks which is significant given the increased use of iron infusions within ambulatory care. Further education and monitoring post infusion should be implemented, and assessment of renal tubular phosphate handling to identify the cause.

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CC4

Bilateral adrenalectomy for congenital adrenal hyperplasia: holygrail for infertility?

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This is the case of a now 37 years old female. She was diagnosed with classical salt wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency at 1 week after birth. She highlights the challenges of living with CAH. She struggled all through her childhood and adolescence with the burden of treatment, difficulties with compliance and the effects of the inadequate control of hyperandrogenism. In adulthood supraphysiological doses of exogenous steroids lead to a number of medical problems including raised BMI, osteoporosis, Type 2 Diabetes and sleep apnea. She suffered infertility and the patient, and her partner,

spent over a decade trying to conceive. The couple sought fertility treatments which were hindered by the patient's obesity and the struggle to lose weight while taking steroids. The only break from the vicious cycle came after the difficult decision to undergo bilateral adrenalectomy despite the significant risks involved. The outcome was physiological steroid replacement, weight loss and spontaneous conception. After a relatively uncomplicated pregnancy, monitored closely in the maternal medicine clinic, she delivered a healthy baby girl at 37 weeks gestation by elective C-Section. Bilateral adrenalectomy is not recommended in published guidelines for the management with patients with CAH due to the risks of surgery, subsequent adrenal crisis in a group of patients who often struggle with compliance with treatment, as well as adrenal rest tumours particularly in men. The literature does however report successful management of selected patients with this approach. Our case demonstrates that with careful selection, counselling and consideration adrenalectomy can benefit women with CAH to normalise biochemical control, reduce corticosteroid doses and side effects and improve the chances of conception and motherhood.

Year	Free Androgen Index
2005	21
2008	16
2009	29
2011	0
2015	0

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CC5

Insulinoma induced pseudo-remission of type 1 diabetes

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Insulinomas are neuro-endocrine tumours of the pancreas with an incidence of 0.7-4 cases per 1,000,000 population per year. Type 1 diabetes has an incidence of >20 cases per 100,000 per population per year. Cases of insulinoma with diabetes are lower than in the general population with a type 2 preponderance. This report is the seventh of insulinoma with type 1 diabetes suggesting the latter inhibits the development of the former. A 31 year old female with a 20 year history of type 1 diabetes presented with increased frequency and severity of hypoglycaemic episodes over 6 months. For 1 month daily pre-breakfast hypoglycaemic episodes had occurred despite nocturnal consumption of carbohydrate and withdrawal of insulin. The nature of the hypoglycaemic episodes and Covid restrictions necessitated a day case investigation protocol commencing non-fasted at 09:00 hours. Basal investigations confirmed glucose 3.9 mmol/l, insulin 19.6 mU/l, proinsulin 48 pmol/l, c-peptide 1097 pmol/l and cortisol 270 nmol/l. At 2 hours glucose 2.3 mmol/l, insulin 15.2 mU/l, proinsulin 51 pmol/l, c-peptide 1161 pmol/l and cortisol 528 nmol/l coincidental with neuroglycopenic and autonomic nervous system symptoms. IV dextrose corrected the hypoglycaemia with resolution of symptoms fulfilling Whipple's triad. CT imaging confirmed a 2.5 cm diameter head of pancreas mass. Treatment with diazoxide, prednisolone and octreotide was ineffective and a hypoglycaemic seizure necessitated urgent surgical intervention in the form of pylorus sparing pancreaticoduodenectomy. Insulin treatment was necessary post-surgery. Histology confirmed a well differentiated neuro-endocrine tumour grade 1 (Ki 67 index 1%). C-peptide was <50 pmol/l. The development of insulinomas in beta cell deplete type 1 diabetes remains an enigma. Benign and malignant insulinomas have occurred in the 7 cases now described suggesting the cells of both escape the immune processes that affected normal beta cells.

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CC6

A rare presentation of avascular necrosis of the femoral head and mild cardiomyopathy in a patient with 17-hydroxylase deficiency

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Introduction
Avascular necrosis of the femoral head (AVN) is most commonly a consequence of glucocorticoid excess and is believed to be due to osteocyte apoptosis. It can also be due to vascular occlusion or trauma. We describe a patient with congenital adrenal hyperplasia secondary to 17-hydroxylase deficiency who presented with osteoporotic vertebral fractures and atraumatic avascular necrosis of the femoral head. She was also found to have mild cardiomyopathy.
Case report
We report a case of a 38-year-old female who was referred to endocrinology outpatients with primary amenorrhea. She had a BMI of 30 and mild hypertension. Initial investigations showed low baseline cortisol of 19 nmol/l and 30-minute cortisol of 29 nmol/l on SST with a high ACTH of 192ng/l and corresponding low salivary cortisol/cortisone levels, confirming primary adrenal insufficiency. Further studies revealed low androgens, LH 30.4IU/l, FSH 56.9IU/l, oestradiol <91.8 pmol/l and high progesterone of 23.3 nmol/l. MRI pelvis showed a small uterus, no ovary identified, and early avascular necrosis of the right femoral head supported by severe osteoporosis on DXA scan. She was started on hydrocortisone, an intravenous bisphosphonate and continued on HRT. Following treatment, her BP improved. Her ECHO showed mild dilated cardiomyopathy. A urine steroids test confirmed the diagnosis of 17-hydroxylase deficiency with a high level of corticosterone metabolites and a high pregnanediol to pregnanetriol ratio. In addition, androstenedione, DHEA and cortisol metabolites were low. Genetic studies confirmed the diagnosis of autosomal recessive 17-hydroxylase deficiency – (pathogenic CYP17A1 variant c.753+1G>A).
Discussion
- AVN has never been reported previously as a complication of untreated 17-hydroxylase deficiency in the literature. The pathophysiology is unclear. Moreover, mild cardiomyopathy is an unusual finding.
- If untreated, 17-hydroxylase deficiency may lead to significant multi-organ long-term consequences such as osteoporosis complicated by vertebral fractures. We recommend early screening for osteoporosis in such patients.

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CC7

Cholestyramine as monotherapy for thyrotoxicosis: experience at a tertiary care centre during COVID-19 pandemic

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Introduction
Thionamides are the mainstay of management of thyrotoxicosis but can be associated with adverse effects like agranulocystosis, hepatitis and vasculitis. While radioactive iodine and thyroidectomy can be utilized in such scenarios, they were not timely available during the COVID pandemic. We present our experience of using cholestyramine as monotherapy.
Case Series
Our series consists of four females. Graves' disease was the underlying aetiology in all cases (three TSI antibody positive and one TSI antibody negative).The cholestyramine dose used varied between 2-4g bd and all patients achieved clinical and biochemical euthyroidism. Age at diagnosis, adverse effects with thionamides and treatment trajectory following cholestyramine therapy are summarized below:
Conclusion
Thyroid hormones undergo hepatic clearance by conjugation to glucuronides and sulphates, which are excreted into the intestine along with bile. The conjugated metabolites can then release free hormones which are reabsorbed, completing enterohepatic circulation of thyroid hormones. Cholestyramine, a bile acid sequestrant, binds to thyroid hormone in the intestine and enhances their clearance. Cholestyramine is usually prescribed as an adjunct to thionamides in patients with refractory thyrotoxicosis. Our experience however demonstrates that in selected patients it may be used as an effective monotherapy when other options are contraindicated or unavailable.

Case 1 (19years)	Nausea and vomiting with both carbimazole and propylthiouracil (patient lactose intolerant). Completed 10 months of treatment with cholestyramine and remains in remission
Case 2 (61 years)	Mild persistent neutropenia-resolved after carbimazole cessation. Underwent RAI 2 years after initial diagnosis and euthyroid currently.
Case 3 (74 years)	Rash with carbimazole, ALT elevation with propylthiouracil. RAI 6 months after initial diagnosis with post-therapy hypothyroidism.
Case 4 (19 years)	Mouth ulcers with carbimazole; rash and arthralgias with propylthiouracil. Cholestyramine discontinued 4 months after treatment due to discolouration of teeth. Restarted on low dose propylthiouracil and tolerating well.

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CC8

Pituitary pseudo-tumour in primary hypothyroidism: early recognition avoids unnecessary pituitary surgery

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Presentation
A 20 year old student was brought to the Emergency Department with a 13 day history of heavy menstrual bleeding. On the day of her admission she had collapsed. On admission, she was noted to be pale with severe postural drop (70 mm Hg).
Investigations
Haemogobin: 46 g/l. Blood film showed an iron-deficient picture. eGFR: 54ml/min/1.73m2. Creatinine: 124 μ mol/l. Free T4: <5.3 pmol/l. TSH: >500 mU/l. TPO antibodies positive (8.3 kU/l). HCG<1 IU/l. Prolactin: 1264 mIU/l. Short SynActhen test: normal response.
Progress
She was transfused 2 units of blood and commenced on tranexamic acid. Levothyroxine was started, initially 50 mg daily, increasing to 100 mg daily after 3 days. An MRI pelvis showed an unremarkable uterus. At thyroid ultrasonography, the parenchyma was atrophic, hypoechoic and heterogeneous consistent with a thyroiditis.
Follow-up
In view of the hyperprolactinaemia, an MRI pituitary scan was ordered. This showed a soft tissue mass 12 x 10 x 14 mm within the sella turcica with strong post contrast enhancement, displacing the optic chiasm thought likely to represent a pituitary macroadenoma. Ophthalmic assessment revealed full visual perimetry and normal acuities. An interval pituitary scan at 5 months, when her TSH was corrected (0.62mU/l), showed complete resolution of the pituitary enlargement.
Discussion
Pituitary hyperplasia manifesting as increased sella turica volume occurs in 25-81% of patients with primary hypothyroidism, due to lack of negative feedback, and correlates with the severity of the thyroid deficiency. It is important to be aware of this condition as the appearance on pituitary scan can mimic a pituitary macroadenoma. Patients may develop visual field defects if the hyperplastic pituitary compresses the optic chiasm. Early recognition is important to avoid unnecessary surgery as the pituitary mass will completely regress with levothyroxine treatment.

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CC9

A rare presentation of ovotesticular disorders

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Introduction
The prevalence of gynaecomastia ranges between 40-60% and the majority of cases are asymptomatic, commoner among obese and is due to excess circulating oestrogen. Ovo-testicular disorders of sex development (OT-DSD) is one of the rarest disorders of DSDs and commonly presents with bilateral intra-abdominal gonads and ambiguous external genitalia.
Case presentation
A 15 years old male presented with progressively worsening bilateral gynaecomastia over 2 years and delayed puberty leading to school absenteeism. His BMI was 19 kg/m2, height was within the mid-parental range with absent pubic, axillary and facial hair. There was bilateral gynaecomastia (Simon grade 3), normal male external genitalia but a 2 mL testicle in the right scrotum and an absent testicle in the left. No palpable gonad on abdominal examination. Oestradiol was elevated at 494 pmol/l (<102) with normal testosterone 18.5 nmol/l (0.95-21.5), gonadotrophin, prolactin, thyroid functions, alpha fetoprotein and beta human chorionic gonadotrophin. US-scan and CT-scan confirmed left testis (2.1́1.1 cm) in the groin and a right intra-scrotal testis (1.81 cm). The patient underwent left laparoscopic orchidectomy and bilateral subcutaneous mastectomy. Histopathology showed testicular tissue with atrophic seminiferous tubules admixed with normal ovarian tiss,,ue without evidence of malignancy. Six weeks post-surgically, both oestradiol (54 pmol/l) and testosterone (10.5 nmol/l) levels were normal. Intra-scrotal gonad was preserved in this patient in his best interest. The patient would be followed up with monitoring for pubertal characteristics, testosterone levels, tumour markers and US-scan of right scrotum.
Conclusions
To the best of our knowledge, all reported cases of OTDSDs had bilateral cryptorchidism. However, in this case, the patient had a significantly higher oestradiol concentration with unilateral cryptorchidism and otherwise normal male external genitalia. Although he has an intra-scrotal gonad, regular surveillance for malignancy would be prudent as the risk of testicular malignancy is much higher among patients with dysgenetic gonads.

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CC10

Percutaneous pulmonary valve intervention in severe metastatic mid gut neuroendocrine tumour with carcinoid heart disease (hedinger syndrome): a case report

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Introduction
Carcinoid heart disease can occur in up to 20 % of patients with carcinoid syndrome. It is a regarded as a rare complication and associated with high morbidity and mortality as a sequela of vasoactive peptides resulting in plaque formation on the valve leaflets classically tricuspid and pulmonary valves and causing right heart failure. Definitive treatment is surgical valve replacement, but percutaneous valve management is an attractive alternative for those deemed unsuitable for surgery.
Case
We describe a 56 year old lady, presented with diarrhea and flushing in 2015 diagnosed with NET of mid gut with multiple metastasis. Investigations revealed elevated Chromogranin A level 283 mg/ml and Urinary 5 HIAA 1321 mg/24 - hours (5 hydroxy indole acetic acid). Her octreotide scan with SPECT revealed right iliac fossa lesion with multiple liver metastasis, metastasis in abdominal lymph node, left femur, right pleura, left breast and bilateral orbits. She was treated with 4 cycles of Lutathera in 2016 and 2 cycles in 2020. She has developed carcinoid crisis in 2019. She was treated with Lanreotide autogel 120 mg deep sc every 2 weeks with rescue subcutaneous octreotide top-ups and denosumab for bone metastasis. Orbital metastasis treated with steroid injections in 2021. She has developed shortness of breath and bilateral ankle edema in 2021 and diagnosed with severe carcinoid heart disease. Her 2D-ECHO and CT cardiac angiogram revealed thickened right heart valves with pulmonary more significantly involved. She underwent percutaneous intervention of pulmonary valve in 2022 and currently her right heart failure is improved.
Conclusions
Hedinger syndrome is a challenging entity in cardiac surgery due to right sided valvular lesions and risk of open surgery. Percutaneous valve intervention or transcatheter valve repair of tricuspid and pulmonary valve has become a suitable entity over invasive surgical intervention in non-surgical candidates in recent years.

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Poster Presentations

Adrenal and Cardiovascular

P1

Replication of association at the LPP and UBASH3A loci in a UK autoimmune Addison's disease cohort

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Background
Autoimmune Addison's disease (AAD) is a rare endocrinopathy arising from a complex interplay between multiple genetic susceptibility polymorphisms and environmental factors. Several variants in immune pathways have been identified through hypothesis-driven candidate gene analysis, though these associations can prove difficult to replicate. The first genome wide association study (GWAS) with patients from Scandinavian Addison's registries identified association signals at four novel loci in the genes *LPP*, *SH2B3*, *SIGLEC5* and *UBASH3A*. To verify these novel risk loci, we studied five SNPs for association in our independent cohort of patients with AAD from the UK.
Methods
Genotypes at five SNPs [*rs4686484* (*LPP*), *rs12634152* (*LPP*), *rs4801888* (*SIGLEC5-SPACA6*), *rs11203203* (*UBASH3A*), *rs3184504* (*SH2B3*)] from 420 UK-based AAD patients were compared with either 544 healthy controls, or in the case of *rs3184504* (*SH2B3*) with 5154 healthy controls provided by the Wellcome Trust case-control consortium (WTCCC2). Chi-squared analysis was performed on allele and genotype frequencies and odds ratios were calculated for risk alleles. *P*-values of <0.012 were considered significant, reflecting Bonferroni correction for tests at four independent loci.
Results
We report significant association of variants in the *LPP* and *UBASH3A* genes (odds ratio [95% confidence intervals], 1.46 [1.21-1.75; $P=5.4\text{x}10^{-5}$] and 1.40 [1.16-1.68; $P=3.7\text{x}10^{-4}$], respectively) with AAD in the UK cohort. In addition, we report nominal association of AAD with *SH2B3* ($P=0.02$). No significant association was seen with the *SIGLEC5/SPACA6* locus.
Conclusion
Our study replicates that variants at the *LPP* and *UBASH3A* loci confer susceptibility to AAD for the first time, in an independent patient population. These loci have been implicated in coeliac disease, type 1 diabetes, Graves' disease and Hashimoto's thyroiditis, and thus contribute to the autoimmune comorbidity seen in AAD patients. Further studies with larger patient cohorts are required to robustly confirm the association of *SH2B3* and *SIGLEC5/SPACA6* alleles.

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P2

Radiological and biochemical assessment of adrenal incidentalomas need improving to prevent unnecessary follow up

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Background
Adrenal incidentalomas often pose a clinical conundrum when identified radiologically. The direction of management is often based on findings on imaging and biochemistry. To aid management, the European society for Endocrinology (ESE) recently published guidelines.
Aims and Methods
We conducted a retrospective analysis of 142 patients with identified adrenal incidentalomas between April 2020 and April 2021 in East Kent Hospitals University NHS Foundation Trust to assess whether the imaging modality and reporting, biochemical tests and follow up were in line with ESE guidelines.
Results
Of the 142 cases reviewed, 89 (62%) of cases were referred to the endocrinology department. Adenomas were identified in 122 (85.9%) of cases, with 95 (77.9%) of these adenomas being unilateral. 46.7% of patients had CT of the adrenals with the majority having MRI. Only 27 (47.4%) of CT scans had a Hounsfield Unit (HU) or CT washout indicated in the report. 36 (40.4%) had suspected clinical evidence of endocrinopathy. Majority of the referred cases 51 (57.3%) had biochemical tests with only 17 (11%) having positive results. Plasma metanephrines and 24hr urine free cortisol (UFC) continue to be the main biochemical screening tools with 47 (92.2%) and 37 (72.5%) respectively, and only 23 (45.1%) having an overnight dexamethasone suppression test (ONDST). Follow up biochemistry and imaging were unnecessary in 3.9% and 21.5% of these patients.
Discussion and Conclusion
We identified MRI scans as the main imaging modality and of those who had CT scans, the reporting fell far short of the reporting guidance. Plasma metanephrines and 24hr UFC still appear to be the main biochemical screening tools with only a minority performing ONDST. These results highlight the need to raise awareness of current guidance around imaging and biochemical work up. This has the potential to reduce inappropriate use of investigations for screening and follow up.

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P3

Identification and characterization of a receptor for N-terminal pro-opiomelanocortin peptide

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Background
Numerous studies have reported the role of the N-terminal of pro-opiomelanocortin (N-POMC1-76) and its smaller fragments; 1-28 and 1-49, in adrenal steroidogenesis and mitogenesis. A full understanding of this area will help to understand the pathophysiology of certain adrenal tumours but exactly how these peptides elicit this effect is unclear. We have recently identified an orphan G protein-coupled receptor (GPCR) as a possible N-POMC receptor. Preliminary data showed that overexpression of this receptor leads to its accumulation inside the cell so we hypothesised that the accessory protein MRAP (melanocortin 2 receptor accessory protein) might be needed to translocate the receptor to the plasma membrane.
Objective
To investigate the binding affinity and specificity of this GPCR to N-POMC and if the co-expression of MRAP is required for functionality.
Methods
GPCR was overexpressed in HEK-293 cells with or without co-expression of MRAP. Ligand specificity was determined by non-radioactive ligand binding assay and association of GPCR and MRAP was determined by immunocytochemistry (ICC) and co-immunoprecipitation (co-IPs).
Results
ICC showed that co-expression of MRAP increases cell surface expression of the GPCR and co-IPs showed that the two proteins associate with each other. Non-radioactive ligand binding assay using biotinylated N-POMC1-28 as a ligand showed significant binding to cells expressing both MRAP and the GPCR while competitive binding assays showed other N-POMC fragments 1-49 and 1-77 could compete with N-POMC1-28 although N-POMC1-77 was found to be around 10-fold lower affinity than either N-POMC1-28 or 1-49.
Conclusions
These results support the hypothesis that the identified GPCR is the receptor for N-POMC and MRAP is required for full functionality. The identification of a receptor for N-POMC is significant and might be a potential target in adrenocortical carcinomas.

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P4

Bone health optimisation and patient education in adult congenital adrenal hyperplasia patients

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Introduction
Decreased bone mineral density (BMD) is a concern in Congenital adrenal hyperplasia (CAH) given life-long glucocorticoid treatment. We undertook a quality improvement project (QIP) to optimise bone health for all adult CAH patients under our care in line with Endocrine Society CAH Guidelines.
Method
Retrospective case notes and electronic records' review was undertaken to identify CAH patients in University Hospitals of Leicester (UHL). Following actions were undertaken as part of QIP: 1) CAH education (website information, CAH leaflet) 2) Steroid safety education (Glucocorticoids stress dosing, emergency Hydrocortisone, sick day rules, medic alert bracelet, Emergency

steroid card) 3) CAH biochemistry 4) Bone health assessment (Bone profile, Vitamin D, DEXA) 5) Osteoporosis education (smoking cessation, exercise, Vitamin D) 6) Quality-of-life assessment (SF-36 questionnaire) 7) FRAX tool patient questionnaire to estimate fracture risk. 8) Genital examination for testicular adrenal rest tumors (TART)
Results
$n=92$ CAH patients treated in UHL until June 2022; $n=76$ patients (46F;20M) information was available; $n=41$ patients currently under follow-up. Mean age: 39 years; Mean BMI 28.1 kg/m^2. 33/41 (80%) had prior DEXA but only 42% in preceding 3 years: 16% treated osteoporosis, 25% osteopenia, 59% normal BMD. Of the invited 41 patients to attend CAH education clinic, 15/41 (11F: 4M) have attended so far. 12/41 (30%) are on supra-physiological glucocorticoid dose. 4/11 females menopausal; 3/11 primary amenorrhea. 3/15 had fragility. 12/15 (80%) are on Calcium and vitamin D supplements, rest were commenced on Vitamin D replenishment regimen. All 15 of them admitted to be compliant with steroids as evidenced by stable androgens.
Learning points
1. Bone health evaluation, treatment & patient education is a vital aspect of CAH management
2. DEXA scan should be undertaken every 3 years
3. Preventive measures for Glucocorticoid-induced osteoporosis should be educated.
4. Optimising steroid dose should be considered.

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P5

Abstract Unavailable

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P6

Evaluation of fracture risk in patients with mild autonomous cortisol secretion and adrenal incidentaloma

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Background
Patients with adrenal incidentaloma (AI) and cortisol levels of 50-138 nmol/l on overnight dexamethasone suppression tests (ONDST) may have "mild autonomous cortisol secretion" (MACS). MACS is associated with increased morbidity, including osteoporosis, but this is infrequently systematically evaluated. We compared fracture risk and fracture prevalence in patients with AI, both with and without MACS.
Methods
Data were collected retrospectively on patients with an AI and ONDST. Demographic data, biochemistry and fracture prevalence were recorded. FRAX risk and corresponding National Osteoporosis Guidance Group (NOGG) risk category were calculated. Statistical analysis was conducted using PRISMv9.3.1.
Results
498 patients with AI were evaluated (49.3% male), mean age 65.6$\pm$11 (SD) years. 202 patients had evidence of MACS, the remainder had a suppressed cortisol. Patients with MACS had a mean age of 69.3$\pm$11.2 years vs 62.7$\pm$10.8 in those without MACS. There were no other significant differences between the groups. 15.6% of MACS patients had a previous fragility fracture vs 9.8% of patients without MACS ($P=0.055$). 33.8% of patients with MACS were classified as medium, high or very high-risk according to NOGG vs 24.4% of patients without MACS ($P=0.022$). Mean FRAX risk of major osteoporotic fracture over the next 10 years in patients with MACS was 9.4$\pm$8.5% compared with 6.8$\pm$5.2% in those without MACS, ($P<0.0001$). Mean FRAX risk of hip fracture was 3$\pm$3.4% in the patients with MACS vs 1.8$\pm$2.6% in those without MACS ($P<0.0001$).
Conclusion
One third of patients with MACS warranted further bone health evaluation. Patients with AI and MACS had higher risk of fracture and trend to increased fracture prevalence, compared to patients with AI and no evidence of MACS, although age may be a confounder. Therefore, we recommend routine FRAX evaluation in all patients with AI and MACS to guide further bone management.

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P7

Adrenalectomy for unilateral primary aldosteronism improves quality of life: prospective analyses in the MATCH trial

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Background
After adrenalectomy (ADX) for primary aldosteronism (PA), approximately 30% of patients achieve clinical success (normalisation of home BP); many additional patients report feeling subjectively better. We used the non-randomised MATCH study1 to further assess quality of life (QoL) changes in participants.
Objective
Assess QoL using the 36-item Short Form Health Survey (SF-36) after surgical treatment of unilateral PA and medical treatment of (mainly) bilateral PA (MRA group).
Method
Prospective analysis of SF-36 in MATCH, measured at baseline and 6 months after treatment. Summary scores (physical component summary (PCS) and mental component summary (MCS)) of 8 subscales were calculated for completed questionnaires. PCS and MCS range from 0-100, with population mean of 50.
Results
At baseline, all SF-36 subscales were lower in patients with PA ($n=71$), with PCS 20% lower (SE 1.3), and MCS 13% lower (SE 1.3) vs the general population. At 6 months, ADX ($n=44$) conferred notable benefit, with PCS improved by 8.9 points ($P<0.0001$) MCS by 6.29 ($P<0.0001$), compared to MRA ($n=23$), where there was decrease in PCS -4.41 ($P<0.0001$) and MCS -4.8 ($P<0.0001$). The greatest subscale improvements with ADX were in "emotional wellbeing" and "physical health limitations". Post-treatment difference in QoL between groups was 10.14 in PCS (SE 1.4) ($P<0.0001$) and 7.56 in MCS (SE 1.3) ($P<0.0001$) in favour of ADX.
Conclusion
Patients with PA have a lower QoL than the population average. ADX markedly improves QoL in patients with unilateral PA. Lack of improvement in the patients treated with MRA may reflect difference in pathogenesis, in treatment, or sub-optimal titration of MRA within a surgical study.
Reference
1. X.Wu, R. Senanayake, E. Goodchild *et al*. 11C-metomidate PET CT vs Adrenal Vein Sampling for diagnosing surgically curable primary aldosteronism: prospective test validation, and impact of somatic genotype and ethnicity on outcomes, 29 December 2021, PREPRINT Research Square [https://doi.org/10.21203/rs.3.rs-1179128/v1z

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P8

Gender-Related Analytical Bias in Biochemistry - Under-Recovery in a Serum Cortisol Immunoassay

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Background
The displacement of cortisol from its binding globulin (CBG) in the Abbott Alinity immunoassay assumes an average concentration of CBG in all individuals. Displacement buffer volume, and/or composition, is frequently insufficient to displace cortisol where higher concentrations of CBG are present (e.g. with higher oestrogen concentrations). To address this bias, the Eastern

Pathology Alliance (EPA) introduced a 1:2 dilution step on all serum cortisol specimens in December 2021. Diluting the specimen, prior to the displacement step, markedly improved the recovery seen in neat specimens.
Methods
External quality assessment (EQA) specimens, with known concentrations of cortisol (established via liquid chromatography-mass spectrometry (LC-MS)), were used to examine the impact of automatic dilution on expected results, irrespective of gender. Serum EQA pools (8 males, 6 females, and 3 pregnant females) were analysed, in duplicate, neat and diluted (1:2), and compared with the LC-MS target concentrations. Patient specimens (106 males, 95 females, and 106 pregnant females) were analysed neat and diluted to assess any potential clinical impact of this change.
Results
Post-dilution step patient specimen recovery, compared to the neat result, for males, females and pregnant females was 108%, 110% and 116% respectively. Recovery was concentration-dependent, with little change seen in patient samples at cortisol concentrations <200 nmol/l.
Conclusions
Introduction of an automatic dilution step to the Abbott Alinity immunoassay for serum cortisol analysis has corrected an inherent gender-related bias in the assay design. The concentration-dependence of the recovery ensures that patients at risk of adrenal insufficiency are investigated appropriately. Therefore, the change averts potential over-investigation, without compromising the clinical utility of the analysis.

EQA pools (n)	Results bias – Neat	Results bias – Dilution
Male (8)	+0.5%	+8%
Female (6)	-7%	+2%
Pregnant Female (3)	-18%	-5%
Combined EQA results (neat 56; dilution 25)	-15% (intercept +17 nmol/l)	+2% (no intercept)

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P9

Inflammation-Based Scores as Predictors of Treatment Response in Advanced Adrenocortical Carcinoma

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Background
Standard treatment for advanced adrenocortical carcinoma (ACC) is mitotane in monotherapy or combined with etoposide, doxorubicin and cisplatin (EDP), yet biomarkers predictive of treatment response are lacking. Inflammation-based scores were proposed as predictors for gemcitabine + capecitabine efficacy, used as second-line in progressive ACC. We investigated the role of inflammation-based scores in predicting response to first-line treatment in advanced ACC.
Methods
Retrospective analysis of patients with advanced ACC treated with mitotane monotherapy or EDP ± mitotane. We investigated clinical parameters (ENSAT stage at diagnosis, Ki67, resection-status, time from diagnosis to start treatment, ECOG performance status, plasma mitotane levels and time in mitotane target $\geq$80%) and pretreatment inflammation-based scores [neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR), monocyte-to-lymphocyte-ratio (MLR)]. Primary endpoints were time-to-progression (TTP) and overall-survival (OS) from treatment initiation.
Results
We included 64 patients (58% women, median age 52 years); 35 treated with mitotane and 29 with EDP ± mitotane. Median TTP was 4 months (range 1-96) and 3 months (1-6), while OS was 14 months (3-133) and 9 months (1-39), respectively. In the mitotane cohort, NLR $\geq$ 5 predicted significantly shorter TTP (HR 2.86, 95%CI 1.33-6.14) and OS (HR 4.99, 95%CI 2.15-11.61), while PLR $\geq$ 190 correlated with shorter OS (HR 4.31, 95%CI 1.83-10.19). These findings remained significant at multivariable analysis including Ki67, resection-status, ENSAT stage, ECOG status, time-to-treatment and time in mitotane target (HR 66.55, $P=0.02$). In the EDP cohort, NLR $\geq$ 5 and PLR $\geq$ 190 predicted significantly shorter OS (HR 2.98, 95%CI 1.25-7.09; HR 2.30, 95%CI 1.01-5.25, respectively). Moreover, MLR $\geq$ 0.4 was associated with worse TTP (HR 3.28, 95%CI 1.17-9.18). However, trends in the EDP cohort were no longer observed at multivariable analyses.
Conclusion
Inflammation-based scores are readily available in clinical practice and may be useful to predict response to first-line pharmacotherapy in patients with advanced ACC. These findings will be validated in larger cohorts.

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P10

Practices in perioperative management of patients with pheochromocytoma and paraganglioma: a Scoping Review

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Introduction
There is variation in practice with regards to preoperative optimization protocols and postoperative management in pheocromocytoma and related paraganglioma (PPGL). We aimed to review the literature on perioperative strategies to reduce morbidity and mortality following surgery for PPGL and enhance understanding of optimal approaches.
Methods
Two databases were systematically searched in January 2020 for terms related to perioperative management of PPGL. Articles were screened and included if they described preoperative strategies, intraoperative manoeuvres or interventions and postoperative regimens, both pharmacological and non-pharmacological.
Results
The initial search identified 625 articles, of which 89 studies met the inclusion criteria, including 5387 patients, of which 91% were observational, and 21% evaluated the impact of preoperative interventions by including a control group; 48% were published in the last decade. Alpha-blockade was mentioned in 90% of studies: phenoxybenzamine (66%), doxazosin (26%), prazosin (26%). 40% of studies mentioned either use of preoperative high fluid intake, intravenous fluids and/or high-sodium diet. Eleven studies reported hypoglycemia episodes, which occurred mainly in the first 24 hours after surgery, but ranged between 60 min and 162 hours after surgery. Postoperative vasopressors were usually used for sustained hypotension which was not corrected by intravenous saline replacement. In 11 studies, only 14.6% of 895 patients required postoperative vasopressors for sustained hypotension.
Conclusions
The variation of practices described in this paper underlines the lack of consensus on the optimal strategy in practices of perioperative management of pheocromocytoma. These practices are based largely on local experiences and retrospective studies with the inherent biases they carry thus resulting in poor strength of recommendations in current guidelines.

		No. of studies
Intraoperative monitoring	Intraarterial catheter	32
	Central venous catheter placement	21
	Pulmonary artery catheter	9
Intraoperative management	Hypertensive surges	Most common: sodium nitroprusside (22)
	Hypotension	Intravenous fluids use (37) Colloids use (22) Vasopressors use (23)

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P11

Development of novel immunoassays for pro-opiomelanocortin (POMC)-derived peptides as surrogate markers of adrenocorticotrophin levels for use in the diagnosis of Cushing's syndrome

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Plasma adrenocorticotrophin (ACTH) is extremely labile and far from an ideal analyte for use in the diagnosis of Cushing's syndrome. Processing of ACTH by some ectopic tumours releases high levels of smaller ACTH-like fragments, α-MSH and CLIP, which can interfere with individual antibodies in current

diagnostic immunoassays. Furthermore, cross-reactivity with the precursor of ACTH, pro-opiomelanocortin (POMC), increases the likelihood of erroneous interpretations and unreliable results. Here we explore the use of other co-secreted POMC-derived peptides, pro-y-MSH and the POMC joining peptide (JP), as more robust surrogate measures of secreted ACTH levels. For detection of pro-y-MSH, a two-site immunoassay was constructed using antiserum raised in rabbits and sheep against N-POMC (1-28) and y_1-MSH, respectively. For detection of the POMC JP, antiserum was raised in sheep against the full-length peptide, and N- and C-terminal-specific antibodies were affinity purified and subsequently used to develop a two-site immunoassay. Both ELISAs were optimised for the direct measurement of endogenous pro-y-MSH and POMC JP in unextracted human plasma. The sensitivity of the pro-y-MSH assay was 12 $\pm$ 0.3 ng/l ($n=10$) and the JP assay was 10 $\pm$ 0.5 ng/l ($n=8$). Initial experiments show that endogenous pro-y-MSH and JP remain stable *in vitro* at room temperature for far longer than ACTH, which has a half-life in plasma of <30 minutes. The analytical performance of the assays will be assessed, along with a comparison of endogenous pro-y-MSH and JP levels in normal subjects and patients with disorders of the hypothalamic-pituitary-adrenal axis. The assays are now being evaluated in patients with Cushing's disease, ectopic Cushing's syndrome and small-cell lung carcinomas. To conclude, the two-site ELISAs for pro-y-MSH and POMC JP in unextracted plasma could offer reliable surrogate assays for clinical purposes.

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P12

Phaeochromocytomas Most Commonly Present As Adrenal Incidentalomas – A Large Tertiary Centre Experience

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Background

The detection of phaeochromocytomas evolved from autopsy finding to presentation in symptomatic/hypertensive, and genetically-predisposed individuals. Increasingly, phaeochromocytomas are diagnosed in incidental adrenal masses and the impact on the clinical, biochemical, and radiological features is unclear.

Methods

Retrospective review of patients with phaeochromocytomas seen at a large tertiary referral centre between January 2010 and May 2022. Diagnosis was confirmed histologically or with positive combination of indeterminate adrenal mass, unambiguously increased plasma and/or urinary metanephrines/normetanephrines (MN/NMN), and MIBG findings.

Results

We identified 149 patients with phaeochromocytoma; 131 (88.0%) underwent adrenalectomy, for 18 (12.0%) surgery was either awaited, carried high operative-risk, or declined by patients. Women represented 59.1% ($n=88$). Median age at diagnosis was 52 years (range = 12-86). After excluding phaeochromocytomas diagnosed upon screening for genetic predisposition, patients presented with: 77 of 115 (67.0%), incidental; 20 (17.4%), adrenergic symptoms (e.g., palpitations); 18 (15.7%), hypertension. Presentation with bilateral phaeochromocytomas was in 8.7% ($n=13$). Three patients presented with metastatic disease. Median size of phaeochromocytomas was: overall, 47 mm (range = 10-215 mm); diagnosed upon screening for genetic predisposition, 30 mm (range = 10-75 mm); incidental, 42 mm (range = 10-180 mm); symptomatic/hypertensive patients, 56 mm (range = 15-215 mm) (all P-values = <0.05). Unenhanced CT was performed pre-operatively in 71 patients, all had tumour density ≥ 10 Hu or tumour was heterogeneous. Median MN/NMN increase was 5-10-fold (range = normal-95-fold), which was lower in patients with incidental phaeochromocytoma compared to symptomatic/hypertensive patients (P-value = <0.001). Phaeochromocytomas diameter positively correlated with fold increase in MN/NMN ($r=0.62$; P-value = <0.0001). MN/NMN production increased in incidental phaeochromocytomas with size: median size ≤ 20 mm ($n=6$), median MN/NMN ≤ 2-fold; size >20-30 mm ($n=11$), 2-3-fold; >30-40 mm ($n=16$), 3-4-fold; >40 mm ($n=43$), >10-fold (all P-values = <0.05).

Conclusion

Phaeochromocytomas most presented as adrenal incidentalomas. Small incidental phaeochromocytomas modestly increase MN/NMN and may represent a diagnostic challenge. Appropriate assessment of adrenal incidentalomas is crucial to avoid the adverse consequences of unrecognised phaeochromocytomas.

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P13

Counselling for adrenal insufficiency for patients on long term steroids amongst physicians and patients

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Patients with adrenal insufficiency (AI) should be informed about 'sick day rules' and risk of a life-threatening adrenal crisis if corticosteroids are abruptly stopped or if the steroid dose is inadequate.

Aims and Methods

To assess current practice with regard to steroid advice given across medical specialties at Oxford University Hospital Trust. To assess patient knowledge both in a specialist Endocrine department and in a medical specialty where steroids are commonly prescribed (Rheumatology). An online survey was used for the clinician survey and 5-point question survey for the patient survey.

Results

Forty-one doctors across training grades (37% IMT, 24% registrars, 39% consultants) from a range of specialties completed the survey. 56% of respondent medics stated they usually/always counselled regarding sick day rules when starting long term steroids; 20% of respondents said they rarely/never advised patients on steroid sick day rules. Only 34% of the doctors surveyed were providing the NHS steroid alert card. Sixty patients attending the endocrine clinic (34F,26M; 21 patients primary AI, 30 patients secondary AI and 9 patients with tertiary AI secondary to long-term steroid use) were surveyed and only one patient was not familiar with sick day rules. 83% (50/60) patients carried a steroid card and 70% (42/60) wore a medical alert. 25% reported a delay in receiving steroids when unwell in the past. By contrast, 0/20 Rheumatology patients had received a steroid alert card; and 40% (8/20) were unaware of steroid sick day rules; 10%(2/20)patients had experienced an adrenal crisis.

Conclusions

There is a need for patient steroid education training across the medical specialties so that all patients at risk of adrenal insufficiency are identified and educated appropriately about the risk of adrenal crisis. As Endocrinologists we should reach out to Trust colleagues in other specialties to help deliver this education.

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P14

Factors which contribute to LDL-C target attainment in familial hypercholesterolaemia

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Background

In the UK, NICE guidelines for familial hypercholesterolaemia (FH) recommend a greater than 50% reduction in low-density lipoprotein-cholesterol (LDL-C) as the therapeutic target. However, despite the availability of a range of lipid lowering medication, this target is often difficult to achieve and, more importantly, maintain life-long. Understanding factors that affect LDL-C target achievement is key to reducing cardiovascular disease (CVD) risk. Currently, there is a paucity of evidence regarding goal achievement among FH patients in the United Kingdom.

Methods

A retrospective longitudinal study was conducted using data from patients followed-up at a tertiary centre lipid-clinic. The primary outcome was attainment of a $\geq 50\%$ LDL-C reduction from their baseline LDL-C reading at the end of the follow-up. Contributing clinical factors which impact on target achievement were assessed.

Results

Seventy genetically diagnosed heterozygous FH patients were included (mean follow-up 28 ± 9.3 years), of which 75.6% of patients achieved $\geq 50\%$ LDL-C reduction by the end of the follow-up. Treatment with high intensity statins and combined therapy with statin and ezetimibe were significantly associated with a higher rate of $\geq 50\%$ LDL-C reduction. Patients who achieved the NICE LDL-C target had a significantly higher frequency of outpatient follow-up visits per year

compared to those who did not achieve their target (1.7 ± 0.4 vs 1.1 ± 0.3 visits per year $P < 0.0001$). There was a significant, negative correlation between frequency of follow-up and change in LDL-C from baseline (rs = -0.50, $P < 0.0001$).

Conclusions

The more frequently FH patients are followed-up at a specialised centre, the more likely they are to achieve the NICE LDL-C target. Cost benefit analyses are needed to determine whether following patients up more frequently is economically beneficial. Additionally, future works could explore the impact of increased follow-up in primary care on LDL-C goal achievement.

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P15

Involvement of the adrenal gland in post-bariatric surgery Type 2 Diabetes remission

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Currently, most Type 2 Diabetes (T2D) treatments are targeted for the mitigation of the disease rather than remission. It has been previously demonstrated that T2D remission post-bariatric surgery in mice is independent of weight loss, indicating a metabolic mechanism. One avenue that remains largely unexplored is the role of cortisol, a hormone secreted from the adrenal cortex, dysregulation of which is linked to insulin resistance and obesity. The enzyme 11β-Hydroxysteroid Dehydrogenase 1 (11β-HSD1) is responsible for converting cortisone from the adrenal gland, into cortisol in the liver. We have previously shown that hepatic 11β-HSD1 expression significantly decreases post-Vertical Sleeve Gastrectomy (VSG), indicating the involvement of the adrenal gland in T2D remission. The aim of this study is to determine this metabolic involvement of the adrenal gland by analysing changes in 11β-HSD1 expression. Inflammation is a known highly predominant factor in T2D; therefore, it was hypothesised that inflammatory cytokines would have the largest affect in 11β-HSD1 expression. HepG2 human hepatoblastoma cells were treated with a variety of inflammatory cytokines and hormones (insulin, leptin, IL-6, and TNF-α) and 11β-HSD1 gene and protein expression were measured. Additionally, we performed VSG on high-fat diet fed C57BL/6J mice in order to investigate changes in adipokine and 11β-HSD1 expression levels in liver and adipose biopsies collected post-operatively. We found a statistically significant increase in 11β-HSD1 expression in cells treated with high concentrations of IL-6, mimicking the conditions observed in T2D. A difference in 11β-HSD1 expression was not observed with other treatments, further highlighting the significance of the correlation between IL-6 and 11β-HSD1 expression. To corroborate these results, IL-6 expression was significantly inhibited in the liver, and 11β-HSD1 was significantly inhibited in liver and adipose tissue post-VSG. The results of this study reveal a novel angle on bariatric surgery euglycemic effects, that includes cytokine-controlled cortisol function.

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P16

Can we use swabs to collect samples for salivary androgen analysis?

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Salivary androgens (testosterone, androstenedione, 17-hydroxyprogesterone, 11-ketotestosterone and 11-hydroxyandrostenedione) are currently analysed on samples collected by passive drool. Other saliva analyses such as cortisol are often collected using swabs such as Sarstedt Salivettes, therefore multiple samples are required if both cortisol and androgen analysis is requested. The aim of this study was to determine whether salivary androgen analysis could be performed on samples collected using swabs. A total of 19 healthy volunteers were recruited to the study (10 female, 9 male). Each volunteer collected two saliva samples, one immediately after the other. One sample was collected by drooling into a plastic tube, the other by chewing a Salivette swab for 30 seconds. In addition, one male and one female volunteer also collected samples via passive drool and using a SalivaBio swab. Volunteers were not instructed as to which sample to collect first. Samples were centrifuged and frozen prior to analysis by LC-MS/MS. Statistical analysis showed that testosterone, androstenedione, 17-hydroxyprogesterone and 11-ketotestosterone concentrations were significantly different when collected using Salivettes compared to passive drool ($P < 0.05$). The Wilcoxon signed rank test showed the 11-hydroxyandrostenedione concentrations were the same when collected by Salivette or by passive drool ($P = 0.953$), however closer examination of the data revealed that although most of the paired samples agreed, there were large differences between some of the pairs, ranging from -341 to 42%. Large discrepancies in results were also noted between passive drool and SalivaBio samples for testosterone and 11-hydroxyandrostenedione, and there was interference in 17-hydroxprogesterone chromatography for one of the SalivaBio samples. Salivary androgen concentrations are significantly different when samples are collected on Salivettes compared to passive drool. Salivette samples are not suitable for salivary androgen analysis. Further work remains to be done to assess the suitability of SalivaBio swabs for androstenedione and 11-ketotestosterone analysis.

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P17

Adrenal insufficiency caused by herbal remedies - a case presentation

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Case Presentation

A 35-year-old Caucasian male presented to our endocrine clinic with a right pituitary lesion. This was found incidentally on MRI nine months previously after admission with head injury. He was asymptomatic apart from intermittent pain in his left wrist and right knee. He has a history of epilepsy. He was on paracetamol for analgesia, levetiracetam for epilepsy, and was not on any oral, topical, inhaled or injectable steroids. On assessment, he had central obesity with lower abdominal striae. He was otherwise euthyroid and eupituitary and did not complain of headaches or visual disturbances. Hormone profile revealed a low serum cortisol and ACTH. He was also found to have low testosterone but normal levels of gonadotrophins. These findings remained consistent on repeat testing.

Management

The patient was temporarily started on hydrocortisone replacement therapy. The case was then discussed at the endocrine MDT which gave the impression that the picture was consistent with exogenous steroid use and so hydrocortisone was stopped. However, no clear source of steroids could be identified. With further probing, the patient shared that he was using Thai herbal tea daily for analgesia and agreed to a trial off the tea. Serum cortisol and ACTH levels returned to normal thereafter on serial testing. As such the tea was suspected as the source of exogenous steroids.

Conclusion

Literature supports the steroid-like effects of traditional/natural remedies. It has been suggested that some natural products have innate steroid-like effects, whereas other products are in fact corticosteroids masquerading as 'natural' remedies. This case highlights a potentially interesting dietary source of steroids that clinicians may encounter in their practice. Additionally, if a patient presents with adrenal insufficiency or Cushingoid features alongside natural remedy use, it would be wise to investigate further.

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P18

Adrenal reserve and glucocorticoid requirements post unilateral adrenalectomy for primary aldosteronism

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Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension that can be cured by surgery. Mild autonomous cortisol co-secretion is a recognised feature of PA, which is associated with an increased cardiometabolic penalty and the possibility of adrenal insufficiency postoperatively. There have also been case reports of adrenal crisis post adrenalectomy for this patient subtype. We report our experience of adrenal insufficiency post adrenalectomy for primary aldosteronism.

Method
We audited all patients who underwent unilateral adrenalectomy with confirmed diagnosis of PA, performed in our tertiary centre from 2013-2021. We reviewed electronic charts with clinical data, documented biochemistry, results of overnight dexamethasone and post operative morning cortisol or short synacthen test (SST) if done.
Results
There were 28 unilateral adrenalectomy for PA performed in our centre during the eight-year period. Preoperative overnight dexamethasone suppression tests were available in 17 patients, of whom 12 demonstrated normal cortisol suppression (< 50 nmol/l), whilst five (17%) failed to suppress. No patient received pre or intra- operative hydrocortisone. Post-operative cortisol levels were available in 27 patients. Six patients were discharged with hydrocortisone replacement, and this was weaned between two weeks to a maximum of eight months after HPA reassessment of HPA axis with either 9 am cortisol or SST. No patients experienced episodes of adrenal crisis.
Conclusions
Cortisol co-secretion was seen in 17% of our PA patients with adrenalectomy. Our audit demonstrated the post adrenalectomy patients with cortisol co-secretion requiring initial hydrocortisone replacement, but no patient experienced life-threatening adrenal crisis. The hydrocortisone treated patients had transient adrenal insufficiency with treatment successfully weaned off with complete recovery of HPA axis.

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P19

An Audit of Adrenal Vein Sampling in a large teaching hospital in Leeds

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Introduction
Primary hyperaldosteronism (PA) can affect up to 10% of patients with hypertension. Adrenal vein sampling (AVS) is used to distinguish between unilateral and bilateral aldosterone production. However, it is invasive, technically challenging and is only performed in a limited number of centres. This audit aimed to evaluate the effectiveness of AVS in informing the management of PA in a large teaching hospital.
Methods
A retrospective audit of all AVS ($n=38$) performed in LTHT from 2011 to 2020 was conducted. Half of the cases were excluded due to limited access to data from regional referrals. Data collected included patients' age at time of sampling, biochemistry, radiological and histological findings and outcomes following AVS.
Results
Of the 19 patients who underwent AVS, the average age at time of sampling was 54.5 and 12 (63%) were males. All patients had hypertension and 16 (84%) had >1 episode of hypokalaemia. 15 (79%) patients had radiological evidence of unilateral disease. 8 (42%) patients underwent a saline infusion test prior which demonstrated failure to suppress aldosterone secretion. AVS was unsuccessful in 8 (42%) patients due to failure in cannulating the right adrenal vein. Lateralisation was demonstrated in 7 (64%) patients, of which 6 (86%) were concordant with radiology. Following AVS, 11 (58%) patients underwent unilateral adrenalectomy. Hypokalaemia resolved in all patients (9) following surgery and 9 patients (82%) had reduction in the number of antihypertensive medications. Histology demonstrated unilateral adenoma consistent with Conn's tumour in majority (80%) of the cases. AVS results informed decisions regarding conservative or surgical management in 13 (68%) patients.
Conclusion
Despite failure due to technical difficulty in a significant proportion of cases, AVS remained useful in informing the management of patients with PA. The vast majority of patients following successful AVS and subsequent surgery had positive outcomes and concordant histology.

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P20

Cortisol/cortisone measurement in sweat samples

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Introduction
Alternative biofluids such as sweat, which can be obtained non-invasively and present a simpler matrix composition than serum/plasma or urine, may be useful for monitoring biomarkers. The long-term sampling with patches either on the chest or back can be conveniently used under both rest and exercise conditions to provide an integrated response of free biomarkers over the course of a day. The smaller sample volumes generated by sweat collection can be conveniently handled using modern sensitive LC-MS/MS methods (1).
Methods
Sweat samples were collected using 5 x 5 cm non woven patches attached to the subject's back with Tegaderm patches and left in place for 24 hours. Sweat was extracted from the swab using centrifugation and the filtrate was extracted using liquid liquid extraction. The extract was analysed for cortisol and cortisone using LC-MS/MS. (Waters TQ-XS) and was based on our routine validated salivary cortisol/cortisone method.
Results
The weight of sweat collected ranged from 200-500 mg, in keeping with published sedentary sweat production rates. Cortisone exceeded cortisol concentration by at least 4:1 in agreement with typical results seen in saliva samples.
Conclusions
Sweat contains measurable concentrations of cortisol and cortisone and may provide a convenient non invasive means of monitoring these steroids.
Reference
(1) *Nunes MJ. Evaluation of Sweat-Sampling Procedures for Human Stress-Biomarker Detection. Analytica 2022, 3, 178–194.*

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P21

Adrenal function in patients with extrapulmonary tuberculosis using serum and salivary cortisol

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Background
Adrenal insufficiency has been well established in patients with pulmonary tuberculosis in Nigeria. It has however not been well documented in patients with extra pulmonary TB. This study compared the adrenal function in patients with pulmonary TB vs those with extra pulmonary TB.
Methods
We randomized 100 cases of pulmonary TB and 50 cases of diagnosed extra pulmonary TB, with the aim of assessing the adreno-cortical functions using both serum and salivary cortisol assay. Serum and salivary cortisol were measured after the administration of a low dose ACTH stimulation test using 1μg synacthen (synthetic ACTH analogue). The morning fasting basal serum and salivary cortisol levels were assayed, followed by the post-stimulation serum cortisol levels. Basal serum cortisol levels < 220 nmol/l or post-stimulation test serum cortisol level increment < 200 nmol/l or post-stimulation serum cortisol levels < 500 nmol/l were suggestive of adrenal insufficiency.
Result
Of the 100 cases of pulmonary TB, 13 had drug resistance. The mean age (yrs) of the study population was 34.3 PTB cases vs 32.6 in EPTB cases. There was no statistically significant difference in the basal serum cortisol or salivary cortisol of the PTB cases compared with the EPTB cases (243.21 vs 239.63 nmol/l, $P=0.713$) and (0.68 vs 0.65 nmol/l, $P=0.116$). The thirty-minute response to ACTH stimulation and increment was significantly lower in ETB than PTB in both serum and salivary cortisol. Adrenal insufficiency was reported in 36% of PTB cases and 21% of ETB cases respectively. The most consistent symptom of adrenal insufficiency were vomiting, salt craving and hyperpigmentation (73.2%, 66.8% and 63.7% respectively). The presence of HIV was a positive predictor for adrenal insufficiency.
Conclusions
This study showed that the prevalence of adrenal insufficiency in EPTB is similar to the prevalence in PTB. Salivary cortisol can be used to screen for AI in patients with TB (EPTB and PTB).

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P22

Hyperaldosteronism caused by sertraline

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Introduction
Antidepressants especially SSRI are widely used in all ages. Increase in serotonin level is not supposed to give side effects in other hormonal systems. Here we present a case with serotonergic like symptoms, elevated aldosterone levels and hypertension due to sertraline treatment.
Clinical Case
A 37-year-old woman with previous PCÓs was admitted due to hypertension and high aldosterone. She had undergone two pregnancies after letrozole treatment, with one living child and one miscarriage, and still wishing for pregnancy. Due to depression, she was medicated with sertraline 150 mg daily, starting at 50 mg. Aldosterone was 862 pmol/l (28-540 pmol/l), aldosterone/renin-ratio 66 ($<$23), saline infusion showed insufficient suppression of aldosterone while renal arteries, dexamethasone-suppression test, and 17-OH-progesterone were normal. CT adrenal scan and adrenal vein catheterization were not clearly conclusive but leaned towards dominance for right side. A unilateral adrenalectomy was performed. Histopathology was not possible due to destroyed tissue. Blood pressure and aldosterone levels normalized initially. After 6-8 months, the patient complained of tiredness, weakness, headache, sweating and diarrhea. Aldosterone rose to 1570 pmol/l and blood pressure to 145/95. Sertraline and desmetylsertraline were very high, 656 nmol/l (median 112; 10-90:e percentile 39-244) and 1450 nmol/l (median 201; 10-90:e percentile 32-407), respectively, despite normal dosage. CYP2C9 and CYP2D6, of importance for metabolizing sertraline, were found normal. Grape fruit was not consumed. Dexamethasone for two weeks did not decrease aldosterone levels. Serotonergt syndrome was suspected, and sertraline was gradually decreased. Blood pressure and aldosterone levels slowly normalized. IVF treatment succeeded.
Clinical message
The high plasma level of sertraline in this patient is still unexplained. Sertraline in recommended dose can significantly increase the level of aldosterone leading to hypertension. The stimulation of aldosterone is probably mediated by serotonin with a direct effect on zona glomerulosa.

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P23

Endocrine Complications and Metabolic Risk in Sleep Apnoea

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Introduction
Within our single centre, the referral rate from the endocrine hypertension clinic to the sleep clinic is high. We have also observed a particular metabolic profile of those patients including raised normetanephrines which subsequently improve after treatment for sleep apnoea.
Illustrative cases
56 year old man with a BMI of 33 kg/m^2 and multiple complications of obesity including NAFLD, gallstones and loss of libido. He was rarely refreshed after sleep and his partner confirmed loud snoring. His 24 hour urinary normetanephrines were raised at 11.2umol/24h (NR0-3.8) on one sample. Sleep apnoea was confirmed by the respiratory team and after treatment his normetanephrines normalised becoming normotensive on single agent therapy. 34 year old man with a BMI 42.4 kg/m^2 seen in clinic with headaches, hypertension, hypogonadotropic hypogonadism, raised urinary normetanephrine (peak of 12.3umol/24h) and plasma normetanephrine (1250 pmol/l NR $<$1180). His partner had witnessed many concerning apnoeas overnight and reported significant daytime somnolence. He was reviewed by the respiratory team who started CPAP and his plasma normetanephrines returning to within the normal reference range.
Discussion
The current theory is that the relationship between metabolic profile and the intermittent hypoxia experienced during sleep apnoea is bidirectional. Elevated sympathoadrenal activity may explain the increased cardiovascular morbidity associated with obstructive sleep apnoea.
Conclusion
We are currently in discussion with our respiratory, biochemistry and statistician colleagues to help design a feasibility study to investigate:

- Metabolic status assessment of patients seen in the sleep clinic at diagnosis and after establishment of appropriate treatment.
- We would like to assess 24 hour blood pressure, urinary/plasma metanephrines, fasting glucose/HbA1C, markers of inflammation (CRP, TNF-alpha, IL-6), an anterior pituitary profile, lipid profile and renin/aldosterone.
- Ideally, we would also like to assess pulse wave velocity and 24 hour ECGs.

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P24

A Case of Pheochromocytoma with Haematuria

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Introduction
Pheochromocytomas are rare neuroendocrine tumours from catecholamine producing chromaffin tissue of adrenal medulla that typically present with headache, palpitations, diaphoresis, and paroxysmal hypertension. Here we describe a case of pheochromocytoma presenting as haematuria. There are case reports of paraganglioma of urinary bladder with haematuria. In our case no bladder lesion was identified but close follow up is needed for recurrence and bladder involvement.
Case report
A 74-year-old male with history of myotonic dystonia was investigated by Urologist for haematuria and CT abdomen pelvis showed a 2.4 cm left adrenal nodule with density 25HU. No other cause of haematuria was found. He did not have hypertension or other classic symptoms of pheochromocytoma. Further biochemical studies showed raised plasma metanephrine (1521 pmol/l), normetanephrine (1601 pmol/l), and 24H urinarymetanephrines(3.94µmol/24hr) with normal Chromogranin A levels(3ng/ml).24-hour BP monitoring showed maximum systolic BP of 169 and maximum diastolic of 97 mmHg.MIBG scan confirmed left adrenal pheochromocytoma. Laparoscopic adrenalectomy was done after adequate alpha and beta blockade. The histology is consistent with pheochromocytoma with PASS score of 3. He needs close follow up and monitoring for any local or metastatic recurrence particularly for recurrence in bladder. He is referred for genetic testing as well.
Discussion
This is a case of pheochromocytoma as incidental adrenal nodule in a normotensive patient who presented with haematuria. A close follow up is needed for patients after surgery for at least 10years to look for recurrences or new tumours. Plasma or urinary metanephrines and normetanephrines to be checked every year. Those with syndromic disease like VHL, MEN2, NF-1 may develop renal cancer, Medullary cancer of thyroid. European Society of Endocrinology recommends all patients with PPGL to be considered for genetic testing as around 40% of cases carry a mutation and identifying the mutation type helps to deliver an individualised patient management plan.

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P25

Coincidence of Primary Adrenocortical Carcinoma and Melanoma: Three Case Reports

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy. ACC may rarely occur as part of familial cancer syndromes, but the majority of the cases occur sporadically. A significant proportion of sporadic ACC cases may be preceded by other malignancies and adrenal metastasis from these primary tumours may frequently occur. Herein we present three cases where sporadic ACC was identified in patients with coexistent or previous history of melanoma.
Case description
Patient 1 - A progressively enlarging left adrenal mass was found in a 37 year old man with a superficial spreading BRAF-positive melanoma. Initially, adrenal metastasis was suspected, but histology after adrenalectomy diagnosed ACC. Patient 2 – A rapidly enlarging left adrenal mass was found in a 68-year-old man with a history of recurrent BRAF-positive disseminated melanoma. Consequently, he underwent left adrenalectomy, and histology showed a diagnosis of ACC. Patient 3 – A 50-year-old man with a background of pT1 melanoma was referred with histological diagnosis of metastatic ACC. Germline TP53 variants (Li-Fraumeni syndrome) were excluded in all cases. Targeted DNA sequencing of ACC tissue samples was performed in all cases. Somatic variants were observed in the known driver genes CTNNB1 (Patient 1), APC and KMT2D (Patient 2),

and APC and TP53 (Patient 3). The retrospective review of the patient cohort referred for adrenal masses during the last 21 years revealed that 1.6% of patients with histologically confirmed ACC had a previous history of melanoma. Only 0.5% of our patients had histologically proven adrenal metastasis.
Conclusion
sporadic ACC can occur in the background of melanoma, even if adrenal metastasis might appear to be the most likely diagnosis. Coexistent primary adrenal malignancy should be considered in all patients with a history of melanoma with suspicious adrenal lesions.

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P26

Primary adrenal lymphoma as the culprit of fever of unknown origin and adrenal insufficiency

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Introduction
Primary adrenal lymphoma is a rare cause of adrenal insufficiency, with most cases being of B-cell lymphoma.
Case report
We present the case of a 51 yo man with a 1.5-month history of recurrent fever, nausea, vomiting, anorexia, weight loss of 12 kg, fatigue, polyarthalgia, hypotensive episodes (70/40 mmHg) and singultus. Before admission in our clinic he had a thoracic CT scan, which showed a 5.5 cm right adrenal mass and hyperplasia of the left adrenal, followed by plasmatic measurement of cortisol and ACTH, consistent with primary adrenal insufficiency: plasmatic cortisol = 22.6 nmol/l (172-497), ACTH = 729.5 pg/ml (7.2-63.3). Consequently, 3 days prior to admission in our clinic, his GP recommended daily 4 mg Dexamethasone iv treatment, with significant improvement of symptoms. On physical examination he had hyperpigmentation of the palmar creases, buccal mucosa and gums. Further work-up revealed mild leukocytosis [11.14 *103/µl (4.9-10.2)] with lymphocytosis [4.12 *103/µl (0.6-3.4)], elevated inflammatory markers [ESr = 71 mm/h (0-15), CRP = 19.9 mg/dl (<10)], mild hypercalcemia [10.6 mg/dl (8.4-10.2)] with low-normal PTH [15.8 pg/ml (15-65)]. An infectious cause of the fever was excluded by performing cardiac ultrasound, urine culture, nasal, rectal, inguinal swabs, respiratory pathogens panel test, blood cultures. Abdomen CT scan revealed an inhomogenous right adrenal gland of 7/3.3/4.7 cm and a left adrenal adenoma of 1.5/1 cm. Screening for primary hyperaldosteronism and pheochromocytoma was negative. We started glucocorticoid and mineralocorticoid replacement therapy and referred the patient to the Surgery department where tumor debulking was performed. Histopathological report described undifferentiated malignant tumor and immunohistochemistry analysis was consistent with anaplastic large cell lymphoma, ALK-negative, an aggressive neoplasm of T-cell lineage.
Conclusions
Primary adrenal T-cell lymphoma is an extremely rare cause of adrenal insufficiency. Our patient is currently receiving glucocorticoid and mineralocorticoid replacement therapy and combination chemotherapy (epirubicin + etoposide).

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P27

Sulfasalazine as a cause of false positive elevation of normetanephrine in patients with adrenal mass – A diagnostic challenge

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In clinical settings, when biochemical screening revealed grossly elevated urinary normetanephrine and metanephrine in the presence of an adrenal mass, there is a high clinical suspicion of a pheochromocytoma. However, sulfasalazine, an anti-inflammatory drug can cause analytical drug interference, leading to falsely positive elevation of urinary normetanephrine and a misdiagnosis of phantom pheochromocytoma. This report illustrates two patients with adrenal mass who had false positive elevation of normetanephrine due to sulfasalazine, one of whom underwent adrenalectomy and another one did not.

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P152

Utility of point of care ultrasound (POCUS) as an adjunct investigation for guiding fluid management in severe hyponatraemia

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Background
The main dilemma in hyponatraemia management is that of fluid restriction vs fluid administration. Inappropriate fluid management may result in either cerebral oedema/death or permanent neurologic disability due to rapid sodium correction.
Objective
We explore the utility of point of care ultrasound (POCUS) as an adjunct tool for assessing 3-volume groups (Hypovolaemia, Euvolaemia & Hypervolaemia) in severe hyponatraemia (Na < 120 mmol/l).
Methodology
Patients underwent POCUS1 at admission when Na < 120, POCUS 2 when Na > 130. US parameters: 1) > 50% Inferior Venacava(IVC) compressibility 2)Left Ventricular contractility 3)Pulmonary oedema 4)Pleural effusion 5)Ascites. Hyponatraemia panel requested : U&E, Albumin, Cortisol, TSH, BNP, paired osmolalities & Urine Na. Clinician vs POCUS volume status assessments were compared(UHL QIP No:11408).
Results
n = 18; Mean admission Na 112(106-118); Mean discharge Na 129(122-137). 11/18 on diuretics and 4/18 CKD, rendering urine lab measurements uninterpretable in 13/18. Clinician's assessment: Hypovolaemia 12, Euvolaemia 4, Hypervolaemia 3, Indeterminate 1. POCUS1 assessment: Hypovolaemia 7, Euvolaemia 5, Hypervolaemia 3, Indeterminate 3. POCUS1 reliably guided fluid management in 14/18(78%) as evidenced by subsequent Na correction. 6/15(40%) of Clinician's assessment did not correlate with POCUS1. POCUS1 was inaccurate in1/15(7%). POCUS1 findings normalised in 4/6 after Na correction in POCUS2. Discussion: At admission, POCUS guided better fluid management in 78% compared to Clinician's assessment (55%). Advantages: a) Simple procedure (US probe and gel), b) Safe (lack of irradiation), c) Performed at bed side d) Quick (5- 8 minutes). Limitations: a) Requires expertise & b) Inter-user variability.
Conclusion
1) POCUS is a useful adjunct to physical examination and biochemistry to guide fluid management in hyponatraemia patients. 2) Integrating Venous Excess Doppler Ultrasound (VEXUS) for portal vein flow & Velocity Tegral Index (VTI) (stroke volume) to IVC compressibility may enhance sensitivity & specificity in accurate fluid status assessment.

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P153

Preliminary data from FABULAS: a Feasibility study of Radio-Frequency endoscopic ABlation, with ULtrasound guidance, as a non-surgical, Adrenal Sparing treatment for aldosterone producing adenomas

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Primary aldosteronism (PA) is the potentially curable cause of high-risk hypertension in 5-10% of unselected patients. Diagnosis and lateralisation of PA is challenging and complex. Outcomes post total adrenalectomy, the standard treatment for unilateral aldosterone producing adenomas (APAs), are variable. Between 30-60% are cured (1), but prediction of outcome is unreliable, and some patients are reluctant to have abdominal surgery to remove a whole adrenal gland. Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) is an alternative treatment to surgery for epigastric malignancies but has rarely been attempted for adrenal lesions. Given the proximity of the left adrenal gland to the stomach, we conducted a multicentre pilot study of EUS-RFA for left-sided APAs and present here our preliminary results The primary outcome was a safety assessment of this procedure: the objective being to establish that rare events such as perforation, haemorrhage and infarction of major organs did not occur within the first 48 hours. 30 patients with a definite or probable

left-sided APA were recruited: 24 males and 6 females. Patients had an average age of 56 years and either comorbidities dictating surgical caution; or had declined surgery (personal preference). Four clinically significant events occurred: hypokalaemia-induced-atrial fibrillation (AF) during the procedure in a patient with known paroxysmal AF; hospital acquired pneumonia; an ischaemic cerebral event 6 months post ablation; and a non-ST elevation myocardial infarction from occult atherosclerotic disease exacerbated by undergoing a general anaesthetic. An independent safety committee reviewed all events and considered all to be unrelated to the trans-gastric puncture. Clinical and biochemical outcomes (PASO) are being recorded at 6 months post-procedure. Preliminary evidence suggests EUS-RFA is a safe alternative to complete adrenalectomy for left-sided APAs.

Reference
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P154

HLA-DRB1*0404 is associated with the deletion of the 21-hydroxylase pseudogene in AAD patients

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Background
HLA-DRB1*04 is one of the MHC alleles which is associated with several autoimmune endocrinopathies, including autoimmune Addison's disease (AAD). The two versions of the gene which encodes the main target of the autoimmune attack in AAD, steroid 21-hydroxylase, are encoded in a gene cluster, called RCCX module, which is a copy number variation located in the MHC class III locus. Previous data from our group showed that AAD patients are more likely to have no copies of the defective version of the steroid 21-hydroxylase gene, CYP21A1P, compared to healthy individuals.
Aim
We examined whether patients in our UK AAD cohort carry the DRB1*04:01 and DRB1*04:04 alleles, and if there is association with the CYP21A1P deletion status.
Methods
Genomic DNA was isolated from the whole blood of AAD patients. We typed 264 AAD individuals for the DRB1*04:01 and DRB1*04:04 alleles by genotyping two SNPs (rs3817964A and rs2736157G, respectively) that tag them in Northern Europeans (CEU). Pearson chi-square test was performed for the testing of the association between the allele frequencies and the CYP21A1P deletion.
Results
Significant results for allele and genotype frequencies were observed for the rs2736157, but not for the rs3817964. The strongest association was seen in case of the rs2736157G, with a significantly higher frequency of G allele in individuals who carry no copies of the CYP21A1P relative to patients who carry copies of the gene (87.5% vs 30%, $P=5.8801$x10-38) and a calculated allelic odds ratio (OR) of 16.6923 ($P<0.0001$). No association was observed in case of the rs3817964A, with calculated OR of 0.3259 ($P=0.0656$).
Conclusion
The results of this study indicate an association between CYP21A1P absence and HLA-DRB1*04:04 allele in a UK AAD cohort. Lack of CYP21A1P could contribute to the breakdown of immune tolerance to steroid 21-hydroxylase in AAD.

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P155

Glucocorticoid Excess Disrupts the NAD+ Metabolome Within Skeletal Muscle in Male and Female C57BL/6J Mice

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Introduction
Glucocorticoid excess (GE) causes severe metabolic dysfunction within skeletal muscle (SM) which includes reduced muscle accrual and increased proteolysis. The NAD+ metabolome is crucial for SM health and metabolic function, however, whether this is disrupted by GE remains unknown.
Methods
Male and female C57BL/6J mice ($n=12$) were treated with a vehicle control or corticosterone (100 mg/l) ad libitum via drinking water for 3 weeks to induce a phenotype typical of GE. SM samples were analysed using NMR and qPCR to assess the impact on the NAD+ metabolome.
Results
Corticosterone treatment reduced SM accrual as assessed by tissue weight. Corticosterone treatment decreased SM NAD+ in both males and females (-78.7±3.1% and -8.8±2.3%), as assessed by NMR. The NAD+ breakdown product and precursor, nicotinamide (NAM) was similarly decreased in males and females (-73.3±1.8% and -56.7±1.3%). The gene expression of some of the enzymes involved in SM NAD+ biosynthesis was altered, as assessed by qPCR. Corticosterone increased expression of the rate-limiting enzyme nicotinamide phosphoribosyltransferase (NAMPT) (16.0±11.3% and 18.3±13.0%) and decreased expression of nicotinamide riboside kinase 2 (-50.7±35.8% and -7.63±19.5%) in males and females. In males only it decreased nicotinamide nucleotide adenylyltransferase 1 (NMNAT1) expression (-6.2±4.4%). No other alterations to gene expression were observed.
Conclusion
These findings provide evidence that the SM NAD+ metabolome is disrupted by GE in male and female C57BL/6J mice. This includes a decrease in NAD+ and NAM content, as well as some alterations to the gene expression of enzymes involved in SM NAD+ biosynthesis. Whether this is a contributing factor to SM dysfunction associated with glucocorticoid excess remains to be determined. Further analysis of the NAD+ metabolome is required, including assessment of the reduced form of NAD+, NADH, and the NAD+/NADH ratio, both of which are metabolically important.

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P156

Whole genome sequencing and Sanger sequencing to identify novel mutations in adrenal tumours from cats with primary hyperaldosteronism

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Primary Hyperaldosteronism (PA) is caused by adrenal tumours or bilateral adrenal hyperplasia (Djajadiningrat-Laanen *et al*., 2011) causing constitutive aldosterone production. Both germline and somatic mutations have been identified in human PA (Scholl, 2022). The commonest somatic mutations in benign tumours causing PA in humans include KCNJ5, CACNA1D, ATP1A1 and ATP2B3 (Williams *et al*., 2015). It is hypothesized that analogous somatic mutations arise in feline adrenal tumours. DNA was extracted from adrenal tumours and normal tissue (adjacent adrenal, blood, or pancreas) from eight cats diagnosed with primary hyperaldosteronism. Four cases underwent whole genome sequencing (WGS), with one sample having paired normal and tumour tissue. Variant calling was used to identify single nucleotide substitutions arising within the tumours, these were filtered using SIFT to leave variants with a predicted effect on protein function. Variants of interest were confirmed using Sanger sequencing. All cases underwent polymerase chain reactions followed by targeted Sanger sequencing for CTNNB1, KCNJ5, ATP1A1, ATP2B3, GNA11, PCHD15, SLC35F1. WGS revealed numerous variants with predicted significant effects on protein function. In the case with paired germline DNA, somatic single-nucleotide substitutions were identified in PCDH15 and exon 3 of CTNNB1. A different exon 3 mutation of CTNNB1 was identified in a tumour that did not undergo WGS. GNA11 pg48V was identified in a single tumour. No mutations were identified in KCNJ5, CACNA1D, ATP1A1 or ATP2B3. WGS on 4 further paired samples is pending. The genes most commonly mutated in human aldosterone producing adenomas were not mutated in feline PA. Functional exon 3 mutations of CTNNB1 are however common both in human adrenal adenocarcinomas, and a distinctive subset of APAs alongside pQ209 mutations of GNA11 (Zhou *et al*., 2021). Protocadherin-related-15 (PCDH15) is one of several plasma membrane proteins essential to hearing and vision, expressed in cochlear, retinal and adrenal aldosterone-producing cells.

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P157

Depleting NAD+ pools specifically in the endoplasmic reticulum lumen impairs 11β-hydroxysteroid dehydrogenase activity

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Introduction
The endoplasmic reticulum (ER) lumen enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) obtains NADPH from hexose-6-phosphate dehydrogenase to reduce cortisone to the active glucocorticoid cortisol. Cells depleted in NAD+ (parent molecule of NADPH) have impaired 11β -HSD1 activity, which can be rapidly rescued with supplementation of the NAD+ precursor nicotinamide riboside. This suggests the existence of an ER-specific pathway to NAD(P)(H). Here we begin to use the poly-ADP-ribose assisted protein localization assay to study ER-specific NAD+ metabolism using 11β-HSD1 as a readout.
Methods
HepG2 human liver cells and C2C12 mouse muscle cells were transfected with ER targeted constructs containing the catalytic unit of poly-ADP-ribose polymerase 1 (ER-PARP1-EGFP which utilises NAD+ to produce a polymer of poly-ADP-ribose (PAR-ylation) in a NAD+ concentration dependent manner), and control ER-EGFP only (all experiments $n=3$, in triplicate). 48 hrs after transfection cells were analysed by fluorescence microscopy for target localisation, PAR-ylation levels assessed by western blotting, and 11β-HSD1 activity measured by assaying cortisone to cortisol conversion.
Results
Fluorescence microscopy for eGFP confirmed successful targeting of PARP1 to the ER with minimal effect on cell viability. Western blotting confirmed elevated ER PAR-ylation which was not seen in EGFP only controls, suggesting increased rates of NAD+ depletion. In HepG2 and C2C12 cells 11β-HSD1 activity was lower by $12\pm2\%$ and $10\pm2\%$ respectively in ER-PARP1-EGFP cells compared to ER-EGFP control cells which was not a result of altered expression of the 11β-HSD1 enzyme.
Conclusion
ER NAD(P)(H) availability and maintenance impacts upon redox sensitive enzymes is poorly understood. Here we show preliminary evidence that depleting ER NAD+ through targeted PARP1 activity can impair NADPH dependent 11β-HSD1 activity. Further experiments are fully evaluating the potential of a dynamic NAD(P)(H) pathway in the ER compartment.

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P158

Salivary dexamethasone and 11-dehydrodexamethasone analysis post overnight dexamethasone suppression test

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Background
The 1 mg overnight dexamethasone suppression test (ONDST) is recommended as a first-line test for the investigation of Cushing Syndrome. Measurement of dexamethasone alongside cortisol in a 9am serum sample has been credited with improving diagnostic sensitivity of the test. Previous studies have also looked at the utility of salivary dexamethasone and have observed poor correlation with serum dexamethasone. Herein we introduce the concept of measuring 11-dehydrodexamethasone: a dexamethasone metabolite produced in the salivary duct through metabolism with 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2).
Methods
Paired 9am serum and saliva samples ($n=44$) were collected post ONDST. The saliva samples were analysed utilising a novel in-house LC-MS/MS assay which measured cortisol, cortisone, dexamethasone and 11-dehydrodexamethasone. Serum cortisol and dexamethasone had previously been analysed separately by LC-MS/MS. Results were compared and correlations were assessed using Pearson regression.
Results
Serum and salivary dexamethasone exhibited poor correlation (R-squared = 0.16), supporting what has been observed previously. Salivary dexamethasone and 11-dehydrodexamethasone also showed poor correlation (R-squared = 0.19). Serum dexamethasone and salivary 11-dehydrodexamethasone yielded a positive correlation with an R-squared of 0.65. However, at higher concentrations the correlation appeared non-linear.
Conclusion
Correlation of serum dexamethasone with 11-dehydrodexamethasone is a novel finding, which to the author's knowledge, has not been previously established or investigated. It is hypothesised that the non-linear correlation might be due to saturation kinetics of the enzyme 11B-HSD2 in the salivary duct, a similar relationship was observed when comparison of salivary cortisol and cortisone was assessed. The development of this LC-MS/MS assay for salivary measurement of 11-dehydrodexamethasone opens the possibility for a fully remote DST, whereby patients could administer the drug and take a 9am saliva sample. Further sample comparisons are required to develop a 11-dehydrodexamethasone cut-off which equates to a serum dexamethasone concentration of 3.3 nmol/l.

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P159

An audit of the clinical utility of urine steroid profiling for endocrine disorder diagnosis in a routine clinical laboratory in 2021

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Measurement of steroid metabolites in urine by gas chromatography-mass spectrometry remains the gold standard for biochemical diagnosis of steroidogenic disorders. In the UK, three laboratories offer steroid profiling for routine clinical testing, with the Supraregional Assay Service at King's College Hospital being the largest and experiencing increased demand year-on-year for testing. In this study, we used our profiling database to audit 2021 workload. By direct comparison to 2011 data, trends in sample volumes, clinical indications for testing and diagnostic utility of results provided were reviewed. In 2021, 3227 requests were received from 153 hospitals across the UK and Ireland, a significant increase from 2011 (1539 requests, 135 hospitals). 92.2% of reports were returned within stated turnaround of 21 days (2011, 67.2%), with 72 requests processed urgently (2011, 33). Requesting on random vs. 24 hour urines has increased (2021, 81% of requests vs. 2011, 67%). The commonest indication for testing overall remains precocious adrenarche/puberty (2021, 29.3% of requests vs. 2011, 27.5%). In neonates, the commonest indications were ambiguous genitalia (41.2% of requests), ?CAH (15.9%) and salt-wasting (8.1%). In adults, requesting as part of adrenal tumour work-up shows clear increase (2021, 38.2% of adult requests vs. 2011, 26.1%). Review of final diagnoses showed the service contributes valuable information across a spectrum of endocrine and non-endocrine diseases. Inborn errors of steroidogenesis ($n=7$) were identified in 2.9% of cases, with 21-hydroxylase deficiency predominating (2021, 56 cases vs. 2011, 45 cases). Diagnosis of adrenocortical carcinoma was made in 25 patients (2011, 9 patients). Even in the absence of an underlying disorder, profiling still provided useful information. For example, positive evidence for precocious adrenarche/puberty was found in 36.0% of cases in which it was suspected clinically. In conclusion, this audit shows the service provides an adaptable, responsive and clinically useful service to users.

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P160

Mapping the chromatin-associated-lncRNAs and their enhancer regions between lymphatic and endothelial cells

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Blood vessels supply nutrients, oxygen and other key molecules necessary for the function of all organs in the body. The endothelial cell (EC) repair and response to injury or hypoxia is also regulated by the interplay of chromatin-modifying enzymes. Likewise, dysregulation of the lymphatic system underlies the development of the metabolic syndrome. New technologies using omics approaches have now allowed the detection of chromatin and RNA molecules that directly interact in normoxic or disease states. We utilised such approaches to explore the chromatin remodelling in maintenance of two types of primary ECs. We compared the epigenetic landscape as well as chromatin bound RNA:RNA species between the cultured human primary dermal lymphatic and blood vascular ECs. We generated a comprehensive database of human long non-coding RNAs (lncRNAs) that regulate functionality and genome structure through association with chromatin, and the particular enhancer regions specific to each

cell types. Thus, our study provides molecular framework for therapeutic targeting of RNA-associted genomic regions in individual vascular beds that associate with various metabolic conditions.

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P161

Prednisolone replacement therapy in Adrenal Insufficiency: Defining target ranges and timing for optimum Prednisolone level sampling

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Introduction

Glucocorticoid replacement in adrenal insufficiency may be achieved by administering thrice- daily hydrocortisone or once-daily very low dose (2-4 mg) prednisolone. Prednisolone's longer half-life enables once-daily dosing, improving patient satisfaction and compliance. At very low doses, it has shown no difference in most markers of metabolic risk when compared with hydrocortisone. At Imperial College Healthcare NHS Trust (ICHNT), use of an eight-hour trough prednisolone level enables individual dose titration with a target of 15-25μg/l indicating adequate replacement. However, the optimum timing of prednisolone level sampling and concurrent target ranges remain unexplored. This knowledge is vital in mitigating the adverse effects of under-replacement/over-replacement with prednisolone.

Methods

Data from individuals receiving established prednisolone therapy were retrospectively analysed. All had prednisolone day curves performed between August 2013–May 2021 at ICHNT. Data was derived from prednisolone assay results and electronic medical records. Spearman's rank correlation coefficient was used to determine the strength and direction of the relationship between 8-hour prednisolone levels vs. 6-hour and 4-hour levels. Target ranges were obtained using Passing-Bablok regression.

Results

108 prednisolone day curves were analysed from 76 individuals (61% female; mean($\pm$SD) age 61($\pm$13) years; secondary adrenal insufficiency (81.6%)) on a median (range) once-daily prednisolone dose of 4 (2-5) mg. There was strong correlation between 8-hour vs. 6-hour prednisolone levels ($r=0.9530$, $p\leq0.0001$) and 8-hour vs. 4-hour prednisolone levels ($r=0.8829$, $p\leq0.0001$). Proposed target ranges: 6-hour prednisolone level of 28-42μg/l and 4-hour prednisolone level of 48-65μg/l. 90% ($n=88/98$) of individuals with 6-hour levels and 87% ($n=85/98$) with 4-hour levels within these ranges were 'well' on their prednisolone dose at time of sampling.

Conclusions

There is a strong correlation between 8-hour vs. 6-hour and 4-hour prednisolone levels. Sampling at earlier time points allows greater flexibility for patients and clinicians, enabling optimisation of prednisolone dose titration.

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P162

5mg of Prednisolone results in over-replacement in individuals with Adrenal Insufficiency

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Introduction

Liberal glucocorticoid replacement therapy prevents Addisonian crises in individuals with adrenal insufficiency (AI). Prednisolone is six to eight times more potent than hydrocortisone. There is inter-individual variation in glucocorticoid metabolism wherein 5 mg prednisolone once-daily may result in over-replacement in most individuals, with subsequent long-term morbidity and mortality.

Methods

Data from individuals on established prednisolone replacement therapy at a dose of 5 mg was analysed. All had prednisolone day curves performed between August 2013–May 2021 at Imperial College Healthcare NHS Trust. Pharmacokinetic parameters were assessed. Demographic data and clinical outcomes were obtained using electronic medical records. Data is presented as mean ($\pm$SD) and median (IQR) for parametric and non-parametric parameters respectively.

Results

Twenty-six prednisolone day curves were analysed from twenty-six individuals. There were 16 females (62%) and 10 males (38%). Individuals were 54 ($\pm$15) years old, with 84.6% diagnosed with secondary adrenal insufficiency. A 5 mg replacement prednisolone dose corresponded to a serum maximal concentration (C_{max}), of 130.4 (80) μg/l, achieved at T_{max} 1.7 ($\pm$1) hours after administration. The median 8-hour (C_{8h}) prednisolone level was 31.8 (22.2) μg/l. The half-life of individuals that were 'well' on 5 mg replacement was 2.7 (1.4) hours vs. 4.3 (1.1) hours in individuals that were 'unwell'. 80.8% of individuals had C_{8h} level greater than the established target range of 15-25 μg/l. 92.3% ($n=24/26$) of individuals felt 'well' on a replacement dose of 5 mg. Of these, 33.3% ($n=8/24$) had successful subsequent reduction of prednisolone dose. 7.7% ($n=2/26$) reported symptoms of AI despite adequate replacement demonstrated by $C_{8h} > 25$ μg/l.

Conclusion

Our results demonstrate the inter-individual variability in prednisolone metabolism on a single given dose. For the vast majority of individuals within our cohort, 5 mg was supra-therapeutic. Use of 8-hour prednisolone levels enabled dose reduction, thereby reducing the adverse effects associated with excess glucocorticoid replacement.

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P163

Validating the cholesterol-year-score as a predictor of major cardiovascular events in familial hypercholesterolaemia

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Background

Cardiovascular disease (CVD) risk in familial hypercholesterolaemia (FH) is driven by cumulative exposure to high low-density lipoprotein cholesterol (LDL-C) levels. Previously, LDL-C burden has been loosely approximated using the cholesterol year score (CYS) based on two LDL-C readings only. We aimed to determine whether a more sophisticated LDL-C burden score based on serial LDL-C measurements, could more accurately predict major atherosclerotic cardiovascular events (MACE) in FH patients.

Methods

A retrospective longitudinal study was conducting using data from patients followed-up at a tertiary-centre lipid clinic. Area under the curve (AUC) was determined to represent cumulative LDL-C burden using all available LDL-C values for individual patients. The primary outcome was MACE. $AUC_{[LDL\text{-}C\ burden]}$, CYS and other clinical factors were investigated for their role in predicting MACE using receiver operator characteristics (ROC) and Kaplan-Meier analyses. Sub-analyses were performed among subgroups based on age.

Results

Seventy patients (male 55.7%, mean age 56.8$\pm$17.7) were included, of which 14 suffered a MACE during the follow-up period. Patients with MACE had significantly higher $AUC_{[LDL\text{-}C\ burden]}$ compared to those without MACE ($P<0.05$). However, this was only the case for younger patients ($P<0.01$ for patients <60 yr vs $P=0.27$ for patients >60 yr). This pattern was supported by Kaplan-Meier analysis. Area under the ROC curve analysis showed that the CYS tool (AUC = 0.696) is as valid at predicting MACE as $AUC_{[LDL\text{-}C\ burden]}$ (AUC = 0.685).

Conclusions

Cumulative LDL-C burden is associated with MACE development in FH patients, particularly in patients under the age of 60. The CYS tool is as effective at predicting CVD as using serial LDL-C values after diagnosis to represent LDL-C burden.

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P164

Review of clinical and biochemical characteristics, perioperative management and surgical outcomes in patients undergoing surgery for primary hyperaldosteronism (PHA) at The University Hospital Southampton NHSFT (UHS)

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Objective
We reviewed clinical and biochemical characteristics and post-operative outcomes in patients undergoing surgery for PHA in UHS between January 2014 and June 2022 (8.5-year period).
Results
17 patients (41% female, mean age 45y) underwent adrenalectomy for PHA during this period. 5/17 (29%) required admissions related to PHA, 7/17 had blood pressure (BP) of $\geq$ 200 mmol/Hg, 11/17 (65%) potassium $\leq$3 mmol/l, 5/17 required $\geq$ 4 BP agents. 3/17 (18%) described significant nocturnal polyuria. All had unilateral disease radiologically. Confirmatory testing was performed in 12/17 (70%), adrenal venous sampling (AVS) in 11/17 (65%) of which 6/11 had successful bilateral cannulation. 10/17 (59%) had 1 mg ODST, of which 3/10 had co-secreting lesions.
Histology
13/17 (76%) had single adenoma. 1/17 had normal histology and 3/17 a dominant nodule with background adrenal hyperplasia all of whom lateralised with AVS and experienced full BP and potassium normalisation.
Post-operative outcomes
All achieved normokalaemia. 12/17 (70%) achieved full normalisation of BP. 3/17 developed post-operative hypotension. 5/17 had partial BP response with reduction in number of BP medications (mean pre-op:4.2, mean post-op:1.6) and no readmissions. All partial responders had single adenoma on histology and neither underwent AVS (3/5) or had unsuccessful AVS (2/5).
Conclusion
In this small cohort we observed higher rates of complete clinical response to that reported in literature, likely due to patient characteristics such as younger age, shorter duration of PHA and severe disease. None of the partial responders lateralised pre-operatively and increased availability of lateralisation investigations such as AVS and ^{11}C Metomidate PET-CT scanning can increase success rates. 1 mg ODST should be checked in all to help with peri-operative planning. Lack post-operative ARR testing precluded assessment of biochemical cure. The post operative ARR should be considered in all, especially in those with partial surgical response to help guide medical therapy.

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P165

Oral itraconazole augments iatrogenic Cushing's syndrome and adrenal insufficiency after medication withdrawal

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A 37-year-old woman was referred to the endocrine team for the assessment of her adrenal axis, as she had been taking high dose prednisolone (20-40 mg) for several years for the management of her brittle asthma. Drug history included inhaled Symbicort 200/6 (SMART regime), tiotropium and montelukast. Her respiratory symptoms improved with the introduction of theophylline, thus enabling her prednisolone to be switched to oral hydrocortisone, with appropriate 'sick- day' rules advice. In spite of cessation of her prednisolone, the patient paradoxically developed pronounced features of Cushing's syndrome (central obesity, wide purple striae, bruising and proximal myopathy) over the subsequent months. It was noted much later on review, that she had been concomitantly prescribed long-term oral itraconazole for a fungal skin infection. Biochemical evaluation (whilst taking itraconazole) revealed a morning cortisol of 393 nmol/l, after omitting her evening and morning hydrocortisone dose, with follow- on hydrocortisone day curve revealing similar cortisol values throughout, suggesting an increased hydrocortisone half-life. Her Itraconazole was subsequently stopped and the patient was also advised to reduce her Symbicort, whilst maintaining her usual hydrocortisone replacement. Further biochemical evaluation after six weeks demonstrated a suppressed ACTH level ($<$5.0ng/l) as well as failed SST (baseline morning cortisol $<$28 nmol/l, 30 minutes 64 nmol/l) indicating marked ongoing HPA-axis suppression from prolonged steroid therapy. Since cessation of itraconazole, her Cushing's associated morbidity has been partially ameliorated with central weight loss, improved wound healing, resolution of excessive bruising, restoration of menstrual cycles and improvement in mood. Itraconazole is a potent CYP3A4 enzyme inhibitor and since steroids are metabolised through this pathway, potentiation for steroid toxicity may occur, with simultaneous suppression of the HPA-axis. A medication review on each clinic visit is mandated in order to proactively identify such serious interactions, thereby attenuating the risk of long term morbidity.

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P166

Review of multidisciplinary perioperative management of functioning and non-functioning adrenal lesions at The University Hospital Southampton NHSFT (UHS)

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Objective
We reviewed perioperative management of patients undergoing adrenal surgery at UHS between 1/12/2020 to 1/6/2022 (19-month period) since formalisation of its regional adrenal MDT.
Results
45 adrenalectomies were performed during this period with all cases being discussed at the adrenal MDT, of which 24 (53%) were referred from peripheral hospitals. Laparoscopic surgery was performed in 35/45 (78%) (median length of stay (LOS): 3d), open in 10/45 (22%) (median LOS: 6d). 100 % of eligible patients had metanephrines checked and 96% had 1 mg overnight dexamethasone test. 36/45 (80%) were symptomatic lesions or adrenal metastases. 9/45 (20%) were incidentally discovered: 5xPheochromocytoma, 1xadrenocortical carcinoma (ACC), 1xMild Autonomous Cortisol Excess (MACE) 1xConn's, 1xNon-functioning. 21/45 (47%) had malignant histology (3xACC, 3xSarcoma, 4xRCC, 11xAdrenal metastases). Lesions $>$ 6 cm (13/45) were malignant in 77%. Full staging imaging in 12/13, FDG PET in 4/13, open surgery in 9/13. 24/45 (53%) were benign (1xPeriadrenal paraganglioma, 15xAdrenal adenoma, 8xPheochromocytoma). 22/45 (49%) were functioning lesions (1xAndrogens secreting adenoma, 5xConn's, 8xPheochromocytoma, 3xACC, 1xAdrenal Cushing's, 4xMACE adenoma). All pheochromocytomas received pre-operative preparation and MIBG. 3/5 patients with Conn's adenoma underwent lateralisation with AVS, 2/5 opted for surgery without AVS (1xco-secretory, 1xyoung patient). All achieved BP/potassium normalisation off medications. 19/45 were identified at risk for post-operative adrenal insufficiency of whom 89% had perioperative steroid plan documented in notes.
Conclusion
49% adrenalectomies for functioning and 47% for malignant disease (including rising numbers of tumours such as ACC and sarcomas), emphasise the role of the adrenal MDT and the importance of concentrating expertise of adrenal surgeons experienced in laparoscopic, open and oncological surgery, as well as adrenal oncologist with ACC and mitotane experience. MDT continues to ensure, that those at risk of post-surgical hypoadrenalism, suspected ACC and with functioning adrenal disease undergo full endocrine work-up and have a documented perioperative plan.

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P167

The Value of Baseline Cortisol in Predicting a Preserved Cortisol Response to Synacthen

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Background
Adrenal Insufficiency (AI) presents a diagnostic and clinical challenge. While short Synacthen Tests (SSTs) are most commonly utilised to diagnose AI, the value of a baseline cortisol is being explored. We aimed to review indications for performing an SST and to determine the baseline cortisol that predicted a preserved cortisol response to Synacthen.
Methods
Eight hundred and sixty SSTs performed in 621 individuals at a tertiary endocrinology unit were retrospectively reviewed (April 2017-December 2021, Abbott Architect i-2000 immunoassay analyser). Tests started at 09:00-10:00.

ROC curve analysis was used to determine the 0-minute cortisol threshold that predicted a subsequent adequate response to synacthen. The thresholds that have previously been determined by our Trust were used to define a preserved cortisol response: 30-minute value 370 nmol/l and 60-minute value 420 nmol/l.
Results
Mean (SD) age of the cohort was 53 ($\pm$16.0) years and mean (SD) body mass index measured 27.6 ($\pm$6.57) kg/m^2. Of the 860 SSTs, 30.2% (n=260) were conducted to investigate for primary, 51.4% (n=442) for secondary and 16.3% (n=141) for tertiary AI. Table 1 illustrates the 0-minute cortisol values that predicted a preserved adrenal axis according to type of AI investigated for.
Discussion and Conclusions
The type of adrenal insufficiency being investigated is associated with variations in baseline cortisol. In determining thresholds, the balance of missing a potentially serious condition against the risks of over-exposure to steroids needs to be considered. In this cohort, 0-minute cortisol has a limited ability to accurately predict a preserved cortisol response due to the low associated specificity.

0 min Cortisol Compared with	N	Basal(0 min) Cortisol Measurement (nmol/l) at Sensitivity=0.974	Specificity at Sensitivity=0.974
Primary 30 min	251	147	0.607
Primary 60 min	258	144	0.552
Secondary 30 min	422	135	0.556
Secondary 60 min	425	130	0.353
Tertiary 30 min	135	94	0.377

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P168

Inclisiran for the treatment of hypercholesterolemia in clinical settings

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Background
Inclisiran is the first clinically available small interfering RNA (siRNA)-based treatment, has been shown to reduce pro-atherogenic lipoproteins in patients with or without familial hypercholesterolemia (FH), diabetes mellitus (DM), or atherosclerotic cardiovascular disease (ASCVD), but has not been evaluated in Middle Eastern populations.
Methods
Retrospective review of patients initiating inclisiran treatment for any indication at our centre between 2021 and 2022. All individuals followed up for at least 90 days or with at least one lipid panel post-initiation were included. Participants subclassified into DLCN-diagnosed FH (n = 36) and non-FH (n = 56) groups.
Results
Inclisiran was initiated in 92 individuals, mean $\pm$ sd age 54.7 $\pm$ 11.6 years, 48 (52.2%) males, 70 (76.1%) with secondary prevention (prior history of ASCVD event) , 66.7% with DM and 25 (27.2%) with statin intolerance. At 90 days, substantial reductions in serum Low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol:HDL-C (TC:HDL-C) were observed in both primary and secondary prevention, and FH and non-FH individuals: FH; median (IQR) reduction in LDL-C was 61.4% (51.2%; 84.8%), TG 25% (7.5%; 45%), TC:HDL-C 42.2% (30.7%; 60.7%), non-FH; LDL-C 33.1% (3.2%; 59.4%), TG 13.5% (-14%; 32.1%), TC:HDL-C 22.9% (0.4%; 40.5%), all P-values $<$ 0.0001. American College of Cardiology / American Heart Association (ACCA/AHA) LDL-C targets were consistently achieved in 68 (73.9%) patients during a follow-up of 107 (27-237) days. Non-attainment of LDL-C target was attributed to non-adherence in 13 (54.2%), and discontinuation of treatment in 5 (20.8%) patients. New ASCVD hazard adjusted for age, sex, smoking status, diabetes, and FH was 0.66, $P<0.05$ in ACC/AHA LDL-C target achievers against non-achievers.
Conclusions
Clinically meaningful and sustained reductions in LDL-C, TG, and cholesterol ratios were observed after inclisiran initiation. Inclisiran is safe and effective in the management of hyperlipidemia and ASCVD in a predominantly Arabic population.

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P169

Adrenal Incidentaloma Service in a DGH; Role of an endocrine pharmacist

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An endocrine specialist pharmacist has been running an adrenal incidentaloma clinic since September 2020. As of Jun-22 258 patients have been seen in clinic and managed using a local protocol. Adrenal incidentaloma patient referrals are screened as per current guidelines on receipt; those measuring $<$1 cm are declined, suspected adrenocortical carcinomas are seen by a consultant and referred elsewhere if needed. All others are seen by the endocrine pharmacist within 4 weeks of referral. At the first appointment standard investigations are initiated – urine catecholamines and overnight dexamethasone suppression test (ODST) for everyone, aldosterone renin ratio (ARR) for anyone with a history of hypertension or has had episodes of hypertension in the past. All patients are followed up 3 monthly unless an alternative time frame is appropriate or their investigations are complete. Once results are back: Abnormal urine catecholamines: repeat sample requested and patient referred to adrenal MDT Abnormal ODST: 24 hour urine free cortisol arranged Abnormal ARR: interfering medications switched to suitable alternatives and test repeated; confirmatory tests are arranged as needed. Once the clinical picture is clearer the case is discussed at local adrenal MDT. The endocrine pharmacist manages the MDT list and decides which patients need discussing. After the MDT the pharmacist contacts all patients and the outcome conveyed. Patients with active nodules are transferred to consultant care or discussed with tertiary MDT. The endocrine pharmacist manages the list for presenting to the tertiary MDT ensuring all results and clinical information is available and imaging transferred. Since the endocrine pharmacist has been in post the service has been streamlined and managed efficiently. Patient outcomes: 52 active, 27 transferred to consultant care, 13 referred to tertiary care, 159 discharged, 3 died, 4 DNA discharged. Dynamic function testing is more efficient; improved relations with the day care team is assisting this.

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P170

Audit of adrenal lesions incidentally found on imaging in a London hospital: What is the clinical outcome?

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Background
We have seen an increased referrals to endocrinology because of adrenal lesions that are discovered on imaging performed for other clinical indications. This is largely driven by the increased use of, technological advancement in imaging modalities, and increasing prevalence of chronic disease. We performed an audit to determine the incidence of adrenal incidentalomas at a large general hospital and to assess management of adrenal incidentalomas in relation to the European Society of Endocrinology (ESE) guideline.
Method
We reviewed data of patients who were found to have adrenal lesions on imaging from December 2020 to December 2021. CT and MRI reports were reviewed, and relevant clinical data were reviewed on electronic patient records.
Results
Thirty-seven patients were identified to have adrenal lesions discovered incidentally on imaging. 15 males and 22 females with mean age 41.5 and 59.3 years respectively. Out of 37 patients, two patients passed away for other reasons before they could be referred. 35 patients were seen in endocrine clinic. Non-functioning benign lesions were diagnosed in 18 patients (51%). Remaining 17 patients: 2 (6%) had phaeochromocytoma, 1 (3%) had cortisol secreting adrenal adenoma and 3 (9%) had possible autonomous cortisol secretion. Eight (23%) with indeterminate adrenal masses and normal hormonal assessment underwent follow-up repeat imaging, these did not show any growth/change. 3 (9%) failed to attend for their investigations.
Conclusion
Our findings were in accordance with the ESE guideline. A multidisciplinary approach is required for effective management of adrenal nodules. The majority of adrenal incidentalomas were benign and non-functional and such patients can be reassured and discharged. Complete personalised endocrine workup and assessment of symptoms and signs is required for each patient, along with discussion in an adrenal MDT. We have established a nurse-led adrenal clinic to ensure referrals receive appropriate endocrine testing.

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P171

Myriad Complications of Cushing's syndrome

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Introduction
Ectopic Cushing's syndrome constitutes the second most common paraneoplastic syndrome and has been seen in 1-5 % of small cell lung cancers. It has a poor prognosis and can present with life-threatening complications.
Case
We present a 66-year-old lady who attended with peripheral oedema, bruising and visual blurring. Past medical history included bronchiectasis, oesophageal web, ischemic colitis, Ehlers Danlos syndrome, and hypoxic brain injury. For 2 years prior to presentation, she had used octreotide to manage diarrhoea associated with treatment for ischaemic colitis. She was also on long-term anticoagulation given history of thrombosis. On admission she was hypokalaemia (2.7 mmol/l) and hypertensive (171/85). Clinical examination was consistent with cushingoid features. Investigations showed cortisol >1750 nmol/l unsuppressed following dexamethasone with elevated ACTH 345ng/l and high urinary free cortisol: 20568 nmol/24 hour. She started metyrapone 250 mg QDS. Treatment was complicated by E coli urinary sepsis and then hypertensive crisis with posterior reversible encephalopathy (PRES). She and her family had previously refused level 2/3 care. MRI Pituitary showed no adenoma and CTPA revealed bilateral pulmonary nodules with a left upper lobe mass. Despite metyrapone 1.5g QDS alongside ketoconazole she remained hypercortisolemic and deteriorated. Palliative care was then offered.
Conclusion
Rapidity and severity of symptoms associated with hypercortisolism can be challenging to manage. Octreotide may have delayed her clinical presentation. Although the main causes of death with active Cushing's are infections, cardiovascular disease, and venous thromboembolism, it is important to remain mindful of the rarer complications. PRES is a serious complication associated with severe hypercortisolism which is reversible with aggressive treatment but usually associated with poor outcomes. Through this case we highlight the many options that can be used to treat active Cushing's syndrome alongside some of their limitations.

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P172

Silent clinical picture at diagnosis in incidentally discovered large pheochromocytomas

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Introduction
Pheochromocytoma is an adrenal medullary tumor which typically involves nonspecific symptoms like arterial blood hypertension, tachycardia, headache or sweating. In some cases, patients may be completely asymptomatic at onset and exceptionally develop symptoms after surgery.
Case presentation
We present two cases, first one of a 36 years old male, in which an MRI scan for evaluation of the spine revealed an oval, well-contoured heterogeneous mass of 10/9.6/11 mm in the right adrenal gland. At presentation, the patient was asymptomatic and the clinical evaluation was entirely normal. The diagnosis of pheochromocytoma was established based on extremely high levels of plasma cathecolamines. The patient was successfully operated and remained well. The second case, a 69 years old female, obese, presented for evaluation after a left adrenal mass was discovered on a routine abdominal ultrasound. Abdominal CT scan identified a 66/51/63 mm left adrenal mass. No signs or symptoms suggestive of overactive adrenals were present. She presented very high values of metanephrines and normetanephrines, which normalised after successful surgery. Despite that, she developed significant arterial hypertension few days postoperatively, which persisted and required specific treatment.
Conclusions
Widely variable clinical presentation may be present in patients with pheochromocytoma, before or after the surgery, possibly regardless of the tumor dimension. Hypertension developed after intervention could be explained by concomitant secretion of vasodilator agents from the tumor.

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P173

Adrenal adenomas: an atypical case

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Case Presentation
A 69-year-old female was found unconscious on the floor at her home. She was unable to provide a reliable history due to a GCS of 8. On examination there were no Cushingoid features and normal BMI (20 kg/m^2). She was previously fit and well with no significant history. Investigations revealed a hyperosmolar metabolic acidosis (pH 6.9) with a high serum sodium (174 mmol/l) and high glucose (70.5 mmol/l). Chest X-ray revealed left middle zone consolidation and imaging of the head revealed no abnormalities.
Management and Diagnosis
She received treatment for diabetic ketoacidosis (DKA) and further inquiry was conducted to investigate the cause of her DKA. Serum amylase was normal. CT of pancreas was performed to exclude pancreatic pathology as a cause but revealed a right adrenal mass and left adrenal nodule. Dexamethasone suppression tests failed to suppress cortisol with serum ACTH of less than 5 ng/l. Adrenal hormonal screen was otherwise normal. Further MRI measured the bilateral adenomas to be 46 mm and 18 mm on the right and left respectively. Patient was referred to adrenal MDT who deemed her unsuitable for surgery at this time and recommended further imaging. She was successfully managed on antihypertensives and basal insulin and metformin.
Conclusion
It is exceptionally rare for a functional adrenal adenoma to present with DKA as seen in this case. DKA is classically associated with type 1 diabetes. Yet this case highlights that, when it occurs in an older patient with no known history of diabetes, it is vital to investigate thoroughly for other causes.

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P174

Detection rate and management of adrenal incidentalomas at Gozo General Hospital (GGH)

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Background
Adrenal tumours are often benign and non-functioning. However, there can be underlying phaeochromocytoma, Conns, adrenal Cushing or even malignancy in some cases. It is therefore imperative that these incidentalomas are promptly investigated once detected and managed accordingly.
Aim
1. To determine the incidence of adrenal incidentaloma at Gozo General Hospital. 2. To determine the adherence of management of incidentalomas to guidelines recommended by the European Society of Endocrinology.
Methods
A cross-sectional study was performed in one centre during which all CT Trunk, CT Abdomen + Pelvis, CT abdomen and CT-KUB carried out between January 2021 and February 2022 were reviewed for presence of adrenal incidentalomas. Relevant information regarding management was collected, analysed and compared to the European Society of Endocrinology guidelines.
Results
A total of 1458 scans were reviewed and 54 adrenal incidentalomas were detected accounting for about 3.7% incidence. Of these, 47(87.04%) were unilateral and 7(12.96%) were bilateral. Overall, 50 were reported as benign, 1 indeterminate while 3 had malignant features. Only 18(33.3%) of the 54 cases were referred to endocrinology for further investigations. In total, 36 patients were not referred to endocrine clinic; However, 16 of these had a history of extra-adrenal malignancy or were over 80 years. The only case of indeterminate lesion had further adrenal imaging which showed possible phaeochromocytoma or ACC. Of the patients being seen at the endocrinology clinic, the investigation rate of 81-100% depending on indication and type of test appears to be of good performance.
Conclusion
1. There is a significant incidence of adrenal incidentalomas at 3.7%. 2. The low referral rate to Endocrinology at just 33.3% could be improved on. 3. Patients seen at endocrinology clinic were investigated in keeping with the guidelines of the European Society of Endocrinology.

Keywords: Adrenal, Incidentaloma, Benign
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P175

Neonatal salt wasting: A rare case of X-linked adrenal hypoplasia congenita

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Neonatal salt wasting can present in neonates with a life-threatening state of hyponatraemia, hyperkalaemia, dehydration and metabolic acidosis. The differential diagnosis of neonatal salt wasting includes congenital adrenal hyperplasia (CAH) most commonly due to 21-hydroxylase deficiency, pseudohypoaldosteronism (PHA), X-linked adrenal hypoplasia congenital (AHC) and aldosterone synthase defects. Diagnostic work up should include serum measurement of ACTH, Cortisol, 17OH-progesterone, androstenedione, aldosterone and renin. A term male neonate with a complex neonatal course including abdominal distention, meconium ilius, transient hypoglycaemia and vomiting episodes was found to be hyponatraemic and hyperkalaemic on day nine. NaCl supplements were administered. Electrolyte abnormalities persisted to D19 when a 10% weight loss from birth was reported. Further investigations showed a flat response to a short Synacthen test (Cortisol 138 to 137 nmol/l), after which the patient was commenced on NaCl, hydrocortisone and fludrocortisone. Serum androgen profile was suggestive of 11-beta-hydroxylase deficiency CAH (testosterone 16.4 nmol/l, androstenedione 9.1 nmol/l, 17OH progesterone 7.0 nmol/l, 11-deoxycortisol $>$53.5 nmol/l and 21-deoxycortisol $<$0.5 nmol/l). Elevated renin $>$550 mIU/l ($<$450) excluded PHA. ACTH and aldosterone were not available. A small dilute sample for urine steroid profile (USP) did not confirm a diagnosis of 11BOH deficiency. Further USP samples were consistent with hydrocortisone treatment but showed no evidence of 11BOH deficiency. No causative sequence variants in CYP11B1 were detected. Further genetic analysis of a 56 gene panel for disorders of sexual development identified a hemizygous pathogenic sequence variant c.106del p.(Asp36Ilefs*49) in NR0B1 gene. The patient was diagnosed with X-linked adrenal hypoplasia congenita, which can present with adrenal insufficiency and hypogonadotrophic hypogonadism. Raised 11-deoxycortisol in the first few weeks of life can lead to a misdiagnosis of 11BOH deficiency CAH. Increased 11-deoxycortisol is reported to return to normal levels in patients with AHC within a few months.

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P176

Type 1 Diabetes in remission following adrenalectomy for sporadic phaeochromocytoma

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Phaeochromocytoma is a rare adrenal tumour and patients usually present with palpitations, headaches, labile blood pressure and uncontrolled hypertension. Diabetes mellitus can occasionally be the presenting feature of pheochromocytoma due to catecholamine induced hyperglycaemia. We report a patient who presented with headaches and dizziness to the emergency department who was diagnosed with Type 1 diabetes incidentally following a random venous glucose of 41.6 mmol/l, capillary ketones of 2.1 mmol/l and positive GAD antibodies (101IU/ml). Following initiation of insulin, she experienced significant glucose variability and hypoglycaemia which led to further investigations and the diagnosis of sporadic phaeochromocytoma. The patient underwent laparoscopic adrenalectomy within 3 months of the diagnosis of Type 1 Diabetes. Following adrenalectomy, she continued to experience hypoglycaemia resulting in complete withdrawal of insulin. She continues to remain euglycaemic without any glucose lowering medications for more than 15 months following the adrenalectomy with a HBA1c of 37 mmol/mol and normal glucose readings indicative of remission Type 1 diabetes following the adrenalectomy.

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P177

A case of 17-alpha-hydroxylase deficiency congenital adrenal hyperplasia presenting with delayed puberty

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A 13 year old female presented with a two day history of abdominal pain and vomiting which responded to analgesia. Pelvic ultrasound showed complex ovarian cysts and a pre-pubertal uterus. Initial blood tests were consistent with hypergonadotrophic hypogonadism (LH 31.5 U/l, FSH 14.3 U/l and oestradiol $<$70 pmol/l) and karyotype was 46 XX. Bone age was slightly delayed (measured 12.4 years, chronological age 13.7 years). On referral to paediatric endocrinology, the patient reported primary amenorrhoea and on examination had some breast development, tanner stage B2. Blood tests showed undetectable androgens, testosterone $<$0.5 nmol/l, androstenedione $<$0.5 nmol/l, 17OH progesterone $<$0.5 nmol/l, DHEAS $<$0.5 nmol/l. Urine steroid profile showed elevated mineralocorticoid metabolites, undetectable cortisol metabolites and undetectable androgen metabolites consistent with a diagnosis of 17-alpha hydroxylase deficiency congenital adrenal hyperplasia (CAH). Genetic analysis using a 56 gene panel for disorders of sexual development detected an apparently homozygous likely pathogenic sequence variant in CYP17A1 gene (c.2T$>$C p.(Met1?)). Short Synacthen test showed a flat response, cortisol 38 nmol/l to 36 nmol/l with a significantly elevated ACTH 682 ng/l, consistent with adrenal insufficiency. Hydrocortisone therapy was commenced. Aldosterone was $<$130 pmol/l (130-600) and renin 8.5 mIU/l ($<$125). On review the patient had mild hypokalemia and intermittent hypertension. CAH due to 17-alpha hydroxylase deficiency is rare and can present with delayed puberty, hypertension, delayed bone age and the absence of secondary sexual characteristics. Adrenal crisis is unlikely due to the mild glucocorticoid activity from deoxycorticosterone. Treatment includes hydrocortisone and oestrogen replacement.

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P298

Mapping corticosteroids in mouse kidney following changes in dietary salt intake using mass spectrometry imaging

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Blood pressure homeostasis is regulated via renal sodium reabsorption by aldosterone and glucocorticoids, although the role of glucocorticoids is less clear. High-salt diets lead to suppression of aldosterone in plasma, but changes in available ligands for the mineralocorticoid and glucocorticoid receptors in kidney subregions are unknown. Hypothetically, high-salt intake modifies aldosterone and corticosterone amounts in specific kidney subregions. Kidney cryosections from male C57BL6/J mice (age = 2 weeks, n = 6) receiving different dietary salt (low = 0.03% vs normal = 0.3% vs high = 3%), under Home office guidance, were subject to mass spectrometry imaging analysis following derivatisation with Girard T. Steroid derivatives were detected in renal sections as ions with m/z 474.2957 (Δppm = 1.05), 460.3166 (Δppm = 0.65) and 458.3010 (Δppm = 0.65), in tissue sections, using matrix assisted laser desorption/ionisation (MALDI) coupled to Fourier Transform Ion cyclotron mass spectrometry. These represented aldosterone, corticosterone (active glucocorticoid) and 11-dehydrocorticosterone (inert glucocorticoid metabolite formed by 11β-hydroxysteroid dehydrogenase type 2) derivatives respectively. Steroids were quantified in plasma by liquid chromatography tandem mass spectrometry. Data are mean $\pm$ SEM compared by one way ANOVA with Dunnett's post-hoc test. * $P<0.05$ vs normal-salt. Plasma concentrations of corticosterone (228 $\pm$ 58 vs 251 $\pm$ 66 vs 312 $\pm$ 45nM; low-, normal-, high-salt respectively) were unaffected by dietary salt. 11-Dehydrocorticosterone was lower with low-salt (0.94* $\pm$ 0.13 vs 2.31 $\pm$ 0.55 vs 0.72* $\pm$ 0.14nM) and aldosterone lower with high-salt (0.91 $\pm$ 0.21 vs 0.41 $\pm$ 0.14 vs 0.01* $\pm$ 0.002nM). Within kidney tissue, under normal dietary conditions, corticosterone signal intensity was higher in inner cortex than the rest of the kidney. The highest levels of 11-dehydrocorticosterone were in the medulla. Aldosterone signal was similar in medulla and outer cortex. Corticosterone signal intensity increased in mice outer cortex on high-salt, while 11-dehydrocorticosterone and aldosterone were unaffected. The use of MSI highlights regions of the kidney susceptible to changes in mineralocorticoid and glucocorticoid signalling following changes in dietary salt.

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P299

Screening for adrenal insufficiency using home waking salivary cortisone is accurate and lowers NHS costs

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Introduction
The 250μg Short Synacthen test (SST) is the reference standard for a diagnosis of adrenal insufficiency (AI) in most endocrine centres. The test is expensive and time consuming, requiring clinic attendance. We hypothesised that a cheaper home waking salivary cortisone (WSC) is predictive of the SST 30-minute cortisol >430 nmol/l cut-off and carried out a diagnostic accuracy study to assess the predictive value of the WSC in diagnosing and excluding AI. We then carried out a cost analysis to compare two diagnostic strategies: the SST vs a two stage WSC $\pm$ SST.
Methods
We recruited 220 patients prospectively and all patients collected a WSC (measured by LC-MS/MS) and a SST was carried out on the same day. Using ROC curves we computed diagnostic accuracy and then estimated Positive (PPV) and Negative Predictive Value (NPV). A decision analytic model was developed to describe the costs and outcomes associated with the SST vs WSC $\pm$ SST. To obtain a societal perspective we also enquired about patient costs and time off work via questionnaire.
Results
The WSC was a strong predictor of the SST 30-minute serum cortisol >430 nmol/L: AuROC (95% CI), 95% (92,97%). Using a cut-off of ≥ 17 nmol/l one could exclude AI with a NPV 96% (90%,99%) and using a cut-off of <7 nmol/l one could confirm AI with a PPV 95% (87%,99%). Based on these values, using the WSC as a screening test would obviate the need for an SST in 70% of subjects. The economic results for the primary analysis show that a two-stage diagnostic strategy would save £102.83 in costs per patient. When using a societal perspective this strategy costs £126.99 less than current SST testing.
Conclusions
WSC is an accurate screening tool for AI and significantly reduces costs for the NHS. Home WSC should be introduced to clinical care.

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P300

Using mass spectrometry imaging to study the lipidome of atherosclerotic plaques

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Atherosclerotic cardiovascular disease (ASCVD) is a chronic inflammatory disorder characterised by the gradual build-up of plaques in the arterial wall. Unstable plaques are more dangerous than stable plaques as they are prone to rupture and obstruct blood flow, resulting in heart attacks and strokes. Lipids play a key role in plaque progression, yet their exact involvement remains elusive. We hypothesise that stable or unstable plaques will have distinct spatial lipid phenotypes. We sought to characterise the spatial lipid composition of atherosclerotic plaques. Matrix-assisted laser desorption/ionisation (MALDI) mass spectrometry imaging (MSI) was used for spatial lipidomic profiling of rabbit and human plaques. Rabbit aortic plaques were harvested from male New Zealand White rabbits (aged 6-9 months, $n=6$) following double-balloon injury to the abdominal aorta and maintained on a high-cholesterol diet (0.2%) to induce atherosclerosis under Home Office guidance. Carotid endarterectomy specimens were collected from symptomatic NHS Lothian patients (men aged 50-80y, $n=6$) with ethical approval. MS images were co-registered with histopathological images (hematoxylin and eosin, alizarin red, CD68, α-smooth muscle actin) to reveal the metabolic and spatial information associated with ASCVD. Unique histologically-discriminant lipids were identified in rabbit and human plaques, including sphingomyelins, phosphatidylcholines, cholesteryl esters, triglycerides, and oxidised phospholipids, among others. MSI enabled mapping of lipid/lipid classes that define histologically important regions such as the lipid-necrotic core, fibrous tissue and macrophage-rich regions. In both rabbit and human plaques, relatively high levels of sphingomyelins were observed in macrophage-rich regions, supporting their central role in promoting lesional inflammation, while glycerophosphocholines were among the lipids enriched in the lipid-necrotic core. The lipid profile in a rabbit model mimics that observed in human carotid plaques, serving as a good model for early-stage ASCVD. Important pathophysiological plaque features that define plaque (in)stability can be distinguished based on their lipid signatures using MSI.

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P301

Feasibility of primary aldosteronism screening in primary care – prevalence and concordance with secondary care assessment

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Background
Primary aldosteronism (PA) is the commonest cause of secondary hypertension. Reported prevalence is about 30% in hypertensive population. Success of screening for PA in general practice (GP) is unknown. Expected challenges include laboratory access, transport issues and interfering medications.
Aims
We aimed to report prevalence of PA in a large primary care cohort, the correlation between GP and in-hospital ARR and to assess if a change in renin assay affected rates of positive ARR detection.
Methods
A retrospective analysis of individuals who had aldosterone-renin ratio (ARR) checked by their GP (GP-ARR) between January2012-December2021 was conducted. Reasons for testing and outcomes were retrieved from electronic records. Samples were assayed for aldosterone concentration (pmol/l) and plasma renin activity (ng/ml/hour) before 2015 (positive if ARR $>$ 1000) and for aldosterone (ng/dL) and direct renin concentrations (mU/l) (positive if ARR $>$ 30) post-2015.
Results
In total 3408 samples from 2615 patients were received from GPs (13.5% rejected due to delayed transit time). Three hundred and thirty-two (12.7% of screened population) had positive GP-ARR (men 183 [55.1%]), median age 53 years [IQR 44-64]). Among positively screened, 232 (70%) were referred to secondary care. Among those referred to Endocrinology ($n=200$), 68% (60/88) had positive hospital-ARR and 33.5% (67/200) had confirmed PA and were treated with adrenalectomy ($n=22$) or mineralocorticoid antagonists ($n=45$). GP-ARR post-2015 renin assay change had higher positivity rate [16.7% (262/1568) vs 6.6% (70/1047), $P<0.001$].
Conclusions
Screening ARR for PA in primary care is feasible with low sample rejection rates and good concordance to in-hospital testing. Renin assay methods should be considered when analysing ARR outcomes. Over a quarter of patients with positive ARR results were not referred to secondary care highlighting the importance of increasing awareness of the benefit of investigation and treatment in PA to Primary Care colleagues.

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P302

The importance of questioning the ACTH result in Cushing's and potential need for a two-site assay

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This case shows the potential unreliability of a single ACTH assay in the context of Cushing's syndrome and need for better ways of measuring ACTH and precursors. A 35 year-old lady presented with severe abdominal pain and cushingoid features. CT scan showed a 2.9 cm right adrenal nodule. Investigations: 24-hour UFC 446 nmol/l, post-dexamethasone cortisol level of 572 nmol/l. The referring hospital found a suppressed ACTH $<$ 0.1ng/l consistent with ACTH-independent Cushing's but repeat testing showed elevated ACTH 20ng/l (2.2 – 13.3 pmol/l), which were repeatedly mildly elevated. CRH stimulation showed flat ACTH response. Urine steroid profile showed an elevation in cortisol metabolites relative to other adrenocortical steroid metabolites. Androgen levels were normal apart from suppressed DHEA $<$0.8umol/l. Despite the non-suppressed ACTH, the lack of correlation of ACTH with clinical features suggested assay interference. Failure of appropriate serial dilution of ACTH at dilutions 1, 2 and 4 suggesting a problem measuring ACTH. Roche Elecys assay in two other laboratories revealed ACTH $<$ 0.1ng/l confirming that this was ACTH-independent Cushing's. The patient underwent an uneventful laparoscopic adrenalectomy with post-operative cortisol $<$25mol/l, good resolution of cushingoid features and the histology showed a benign adrenal cortical adenoma. Current diagnostic tests for Cushing's syndrome measure

ACTH (1-39) which is unstable and has a short half-life. High stakes decisions can be made on a single laboratory result. ACTH fragments can interfere at high concentrations by saturating the capture antibody, leading to erroneous interpretation. A two-site assay including measurement of Joining Peptide (JP) secreted concomitantly with ACTH has the advantage of being more stable and may be more reliable. The development of further improved assays of ACTH and other POMC-precursors will help improve set the patient on the right diagnostic pathway and reduce the possibility of making high stakes surgical decisions based on erroneous ACTH results.

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P303

Prednisone is 100% converted to Prednisolone by first pass metabolism

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Prednisolone is widely prescribed in the UK, whereas prednisone is used instead for the same indications in the United States. Both have utility as anti-inflammatory agents and for use as glucocorticoid replacement therapy at lower doses. Oral prednisone is converted to prednisolone by first pass hepatic metabolism by 11 beta HSD-1. This study was undertaken to compare the bioavailability of prednisone against prednisolone. To determine the conversion of prednisone to prednisolone, two 'day curves' were completed in a healthy volunteer, given 10 mg oral prednisone (USP) and 10 mg oral prednisolone (BP) on two consecutive days. Serum prednisolone levels were checked by uPLC-LCMS/MS. The glucocorticoid dose was administered at 7am on both days. Subsequent blood sampling was completed at fixed time-points until 10 hours post-dose. Prednisone and prednisolone (10 mg) were rapidly absorbed achieving Tmax at 1 hour. The 8h levels were 37 mg/l and 35 mg/l for prednisone and prednisolone respectively. The area-under-the-curve for prednisone and prednisolone was 830.6 mg.h/l and 820.5 mg.h/l, equating to a bioavailability of 101.2%. Terminal half-life was comparable at 2.65h and 2.93h for prednisone and prednisolone respectively. There was no difference in the day curves between Prednisone and Prednisolone, indicating bioequivalence of both formulation. This should not be confused with METHYL prednisolone, which is 20% more potent than both prednisolone and prednisone. So 4 mg METHYL prednisolone is equivalent to 5 mg of prednisolone and 5 mg prednisone. In countries where prednisolone is not available, an equivalent dose of prednisone can be used.

Time (hours)	10 mg Prednisone (mg/l)	10 mg Prednisolone (mg/l)
1	173	190
1.5	161	161
2	146	146
6	64	64
8	37	35

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P304

Prolonged adrenal suppression does not always need additional glucocorticoid therapy

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A 53 year old female weighing 117 kg was thought to be slightly cushingoid by her GP who checked a morning cortisol. This was surprisingly undetectable (<28nM) on 13th June 2022. The patient was urgently referred for a medical opinion. A repeat cortisol in A&E was 29nM with an undetectable ACTH. Given the lack of clinical features of adrenal failure, further history was obtained. The patient appeared well on examination, and denied any inhaled, oral/ topical steroid use. Review of the radiology reports revealed that the patient had had a spinal injection of Tricamcinolone 40 mg 4 weeks previously in May 2022. When reminded of this, the patient agreed, and was discharged without steroids, given that she had recent depot of triamcinolone. The patients diabetic control deteriorated following the injection and additional steroid replacement was not deemed necessary. Given her diabetes and obesity, extra steroids may have been harmful. The patient remained well off steroids for several months. A synacthen test done in August, 3 months after the injection, revealed a baseline cortisol of 99nM, 30 minutes 232nM and 60 minutes 268nM. This confirms partial adrenal recovery. Given the complete lack of features of adrenal failure, we have elected to not give any extra steroids. The patient remains well. Patients given depot steroids for musculoskeletal pain lose their diurnal rhythm of cortisol, which is replaced by slow release of potent steroids for at least 3 months. The time for recovery of the HPA axis varies from a few weeks to several months. Endocrinologist do not routinely see these patients and no steroid cover are given following these procedures. When patients are found incidentally to have a low cortisol after injection of depot steroids, the reflexive prescription of steroid cover may cause more harm. Each case needs to be assessed clinically.

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P305

The utility value of genetic testing in endocrine syndromes

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A 51-year-old gentleman who has been diagnosed with bilateral pheochromocytoma at the age of 11 after developing classical symptoms of catecholamine excess and had bilateral adrenalectomy. At the age of 37, he underwent total thyroidectomy with preservation of the parathyroid glands for C-cell hyperplasia. Over the course of the years, it was presumed he had MEN2A syndrome, although no formal genetic testing was done. He does not have a family history of MEN syndrome and does not have children. Annual investigations have reported normal calcium and PTH, normal urine and catecholamines, and unrecordable calcitonin and CEA. He is taking medication hydrocortisone, fludrocortisone, and thyroxine replacement regularly Upon reviewing him in Endocrine clinic in 2021, the other diagnosis apart from MEN2A was re-investigated based on the absence of hyperparathyroidism and absence of medullary thyroid cancer in previous thyroid histology and noradrenalin producing bilateral pheochromocytoma. The Exeter Genomic Laboratory reported a genetic diagnosis of Von Hippel-Lindau syndrome subsequently. A series of screening for VHL including MRI head and MRI abdomen which reports no brain pathology, however, there is 4.2 x 2.8x 1.4 cm right adrenal solid mass which represents a right pheochromocytoma relapse and 4.2 x 3.6 x 3.9 cm solid pancreas mass consistent with NET tumour. Fasting gut hormone profiles, including chromogranin A and B and plasma seated metanephrines are normal. Ophthalmology screening shows Bilateral retina angioma He underwent Whipple's procedure in October 2021 and it is proved to be a well-differentiated grade 3 neuroendocrine tumour with Ki-67 proliferation index is 40.5% in hotspots with mitotic activity. Currently, he is ongoing adjuvant chemotherapy and clinically well. This case highlights the importance of genetic testing in endocrine syndromes which will establish an overlooked diagnosis. Moreover, it will enable surveillance for their manifestations that may not apparent clinically and initiation of early treatment.

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P306

Appropriateness of aldosterone renin ratio (ARR) testing: A retrospective multicentre audit

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Introduction
Clinical practice guidelines advocate testing the aldosterone-renin ratio (ARR) in specific circumstances only. Tests should be taken following abstinence from drugs associated with false results. We aimed to determine the appropriateness of testing locally and any associated wasted healthcare costs.
Methods
We retrospectively evaluated ARR requests taken July-October 2019 and July-October 2021 in Swansea Bay University Health Board to determine the indication, review of interfering medication and test outcome. We used clinical letters and request forms to determine these data.
Results
Sixty-three patients were included with a mean age 52.3 years and 34 (54.0%) were male. Endocrinology was the commonest requesting team (33.3%) followed by cardiology and general practice (15.9%). Indications for testing included adrenal adenoma plus hypertension (20.6%), hypertension with hypokalaemia (14.3%), hypertension aged <40 years (25.4%), resistant hypertension (4.8%) and 34.9% of requests were inappropriate. Table 1 summarises inappropriate testing by specialty. Twelve patients required medication to be held, evidenced in 3 (25.0%) patients. Three (4.8%) patients had a significantly high ARR, with 1

patient undergoing adrenalectomy and two patients managed medically for adrenal hyperplasia. In total 50.8% tests were either not indicated or taken without holding interfering medications, resulting in an estimated excess cost of £3,040 over 8-months (estimated annual cost £4,560).

Conclusions

Most ARR tests taken locally were for either an inappropriate indication or incorrectly carried out, resulting in significant excess laboratory costs. A third of endocrinology ARR testing was inappropriate, typically in those with adrenal adenoma without hypertension. Proposed changes to local requesting methods should improve ARR test requesting in future.

Specialty	Total tests	Inappropriate
Cardiology	10	3 (30%)
Elderly care	7	3 (42.9%)
Endocrinology	21	7 (33.3%)
Gastroenterology	2	0 (0%)
GP	10	1 (10%)
Nephrology	7	3 (42.9%)
Psychiatry	1	1 (100%)
Respiratory	1	1 (100%)
Stroke	4	3 (75%)

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P307

Pheochromocytoma in patient with Neurofibromatosis 1 (NF1) radiologically mimicking Neurofibroma

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Introduction

NF1 or Von-Recklinghausen's disease, an autosomal dominant neuro-cutaneous disorder results from NF1 (a tumour-suppressor gene) mutation, predisposing to neoplasms mainly affecting eye, skin and nervous system but rarely pheochromocytoma (0.1-5.7%). The incidence increases to 20-50% if NF1 is associated with hypertension.

Case history

30 years female, known NF1 since 2005 and multiple laparotomies for intra-abdominal neurofibromas presented with abdominal pain and vomiting. No palpitations, headache, flushing or sweating. She was systemically and hemodynamically stable with systolic blood pressure ranging between 109-139 mmHg and heart-rate 69-101 beats/minute. Baseline investigations were normal but computed tomography of chest-abdomen-pelvis (CT-CAP) revealed multiple lesions as outlined. She was conservatively managed and discharged with endocrine follow up.

Investigations

Full blood count, bone, liver, renal and coagulation profile, amylase, C-reactive protein and short synacthen test were normal. Plasma Normetanephrine: 4773 pmol/l (<1180), Metanephrines: 2120 (<510), 3-Methoxytyramine 228 pmol/l (<180). Repeat Plasma metanephrines were also raised. **CT-CAP:** 42x35x34 mm heterogeneous mass, inseparable from the right adrenal gland, with intra-lesional necrosis besides several small soft tissue masses adjacent to right internal iliac vessels consistent with neurofibromata, 38x28x58 mm left-sided pleural based mass, a 20x37x22 mm subcarinal mass/lymph node and 38x23x32 mm soft tissue axillary mass. **MRI Adrenals:** Well-defined rounded lesion arising from the right adrenal gland with a clear fluid level representing relatively recent haemorrhage into a well-defined, likely benign, adrenal tumour.

Results and treatment

Underwent right adrenlectomy, biopsy confirming pheochromocytoma and plasma metanephrines normalized post-operatively.

Conclusions

1. Pheochromocytoma with NF1 are rare but have significant morbidity and mortality if detected late therefore patients should be actively screened especially if associated with hypertension. 2. Pheochromocytoma can radiologically mimic intra-abdominal neurofibromas in patient with NF1 therefore caution must be considered. 3. Pheochromocytoma can present without classical symptoms of hypertension, tachycardia, flushing, sweating or headache so need high suspicion especially in NF1.

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P308

Severe Tiredness in patient treated with itraconazole in Aspergilloma and Type 1 Diabetes

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Introduction

Adrenal insufficiency is characterized by inadequate ¬glucocorticoid production owing to destruction of the adrenal cortex or lack of adrenocorticotropic hormone stimulation. Patients can present with an insidious onset of symptoms, or acutely in adrenal crisis, which requires prompt recognition and treatment. Chronic glucocorticoid therapy is the most common cause of adrenal insufficiency. We present a case with an adrenal insufficiency caused by Itraconazole.

Clinical case

A 48 year old lady presented with several weeks of tiredness, extreme fatigue and lethargy and these symptoms affecting her daily quality of life. She has Type 1 Diabetes and blood glucose control within target range with HbA1C of 55 mmol/mol and she also experienced frequent episodes of Hypoglycemia without changes in diet or Insulin regimen. Other health problems is bronchial asthma and aspergilloma on Itraconazole for several months. In view of her symptoms, we arranged early morning serum cortisol (14 nmol/l), Aldosterone (< 103 pmol/l) and plasma renin (15.2 mIU/l) and these results indicate adrenal failure. She was started on Hydrocortisone 10 mg + 5 mg + 5 mg, which showed significant improvement in her symptoms within few days and she noted significant improvement in her quality of life and she had no further hypoglycemic symptoms.

In Conclusion

This case indicates the potential side effects of Itraconazole in patients with aspergilloma causing adrenal suppression and early recognition of the symptoms of adrenal failure is extremely important to avoid patients suffering from such symptoms and to avoid delaying the diagnosis.

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P309

Case of herbal tea causing severe hypokalaemia and hypertension

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Liquorice intake is an uncommon but familiar cause of hypokalaemia and hypertension. Liquorice tea is available over the counter as herbal tea to promote general wellbeing. This case report describes a 64-year-old male patient who presented to hospital with severe hypokalaemia and hypertension. During the in-patient stay, patient was managed with potassium replacement and anti-hypertensives (avoiding medications that interfere with endocrine investigations), investigations were initiated for suspected primary hyperaldosteronism and cortisol excess and referred to Endocrine clinic. During the endocrine clinic review, it was noted the investigations for primary hyperaldosteronism and cortisol excess were normal. Renin and Aldosterone levels on two occasions were normal and there was no suggestion of secondary hyperaldosteronism or renovascular causes. Patient had metabolic alkalosis and was needing eight Sando K tablets per day to maintain normal serum potassium levels. Further detailed clinical history specifically about liquorice was asked and patient reported taking liquorice tea 2-3 times per day for the past year. Patient was advised to stop liquorice intake and over the next week, Sando K dose was reduced and stopped. Patient continued to maintain normal serum potassium levels. Anti-hypertensives were also tapered and stopped over next four weeks and blood pressure remained normal. Prolonged and regular use of liquorice can result in hypokalaemia and hypertension. Liquorice acts on aldosterone-responsive tissues and inhibits 11β-hydroxysteroid dehydrogenase, which converts cortisol to cortisone. This leads to high levels of cortisol which activates mineralocorticoid receptors. Many times, patients do not realise or report liquorice use unless specifically asked for it. In recent times, our Endocrine team has come across two other cases of hypokalaemia and hypertension secondary to liquorice intake. Therefore, detailed history and direct questioning regarding liquorice intake is advisable in all patients with hypertension and hypokalaemia and would help avoid unnecessary investigations.

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P310

Pheochromocytoma masquerading as acute coronary syndrome

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Pheochromocytoma is a rare catecholamine-secreting tumor. It is potentially curable but can cause life-threatening hypertension or cardiac arrhythmias. We report a 58-years- old woman with no significant past medical history who was admitted through the emergency department with complaints of chest pain, palpitation, and nausea. She reported six months history of episodic palpitation and throbbing headaches, sometimes associated with light-headedness and dizziness. Hence, she kept a meticulous diary of her blood pressure and heart rate, and indeed she had erratic blood pressure and heart rate during these episodes. She was anxious, tachycardic, had a systolic cardiac murmur and had no signs of decompensated heart failure on examination. Investigations revealed; Normal ECG with incrementally rising troponins at levels of 1577 Ng/l and 2577 Ng/l. She was initially managed for acute coronary syndrome (ACS); however, her presentation was atypical; hence she subsequently underwent a CT pulmonary angiography which ruled out pulmonary embolism but picked up an incidental 45 mm left adrenal mass. Later, an MRI adrenal was performed and confirmed the CTPA findings. Moreover, it showed a fluid level suggestive of possible recent intra-adrenal haemorrhage. Her Plasma metanephrines and normetanehrines were approximately 4 and 6 times the upper limit of the reference range, respectively, cortisol level and thyroid enzymes were within normal limits, Echocardiogram was normal. She was commenced on alpha-blockade followed by beta-blockade with good effect in controlling blood pressure and heart rate before she had left adrenalectomy.
Learning points: 1. Pheochromocytoma diagnosis needs a high index of suspicion as variable presentation 2. Pheochromocytoma, if not treated promptly, may lead to fatal cardiac complications.

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Bone and Calcium

P28

Is finger prick blood collection using Mitra® volumetric absorptive microsampling (VAMS) device a viable alternative to venous for testosterone, cortisol, 25 hydroxyvitamin D and bone resorption marker β-CTX measurements?

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Background
Volumetric absorbent microsampling (VAMS) provides a less intrusive alternative to venepuncture when collecting blood samples for diagnostic testing. A small, precisely determined amount of capillary blood from a single finger-prick is absorbed into a medium for storage, from which it can later be extracted and analysed. In this study, we developed methods to measure four commonly requested endocrine/bone biomarkers for finger-prick blood samples analysis, and investigate the difference in concentration values obtained from venous blood.
Methods
Paired capillary blood samples collected from finger prick using Mitra® VAMS devices (Neoteryx, Torrance, USA) and EDTA plasma from venepuncture (BD vacutainer) were obtained from 44 consented healthy adults from the British Army. LC-MSMS was used to measure 25OHD, testosterone and cortisol; the latter two were analysed by a newly developed Amplifex-keto derivatisation to enhance assay sensitivity. Carboxy-terminal cross-linking telopeptide of type I collagen (β-CTX) was determined by COBAS 6000 e601 using electro-chemiluminescence immunoassay (ECLIA) (Roche). VAMS results were adjusted by haematocrit measurements prior to comparison with plasma values.
Results
Our LC-MSMS method with derivatisation showed inter-and intra-assay precision (%CV) between 3.9-11.6% across testosterone range 0.1-39.9 nmol/L; cortisol was 3.9-8.9% across the range 10-806 nmol/l. Spiked recovery was 97-104%. Passing-Bablok regression showed correlation between the two sample types: cortisol ($y = 0.8828x + 63.004$, $r^2 = 0.85$), testosterone ($y = 1.1683x + 0.407$, $r^2 = 0.92$), 25OHD ($y = 1.1367x - 8.0091$, $r^2 = 0.83$), β-CTX ($y = 1.1367x - 8.0091$, $r^2 = 0.83$). Bland-Altman plots showed average bias(95%CI) against plasma; cortisol -0.91(-6.6 to +1.6)nmol/l, testosterone female +0.1(-0.13 to +0.3), male +4.3(-4.2 to +7.2) nmol/l, 25OHD +1.9(-1.6 to +6.9) nmol/l, β-CTX 0.05(-0.095 to +0.082)µg/l.
Conclusion
The capillary blood concentration of the analytes we tested showed correlation with venous samples. Our finding supports the use of finger prick bloods and Mitra® VAMS device has shown its potential to be an alternative to venepuncture.

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P29

The dangers of ward-based treatment of hypocalcaemia with intravenous calcium replacement

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A frail, long-term surgical inpatient, was under-nourished on TPN. He had a tendency towards hypocalcaemia and was under regular review by the surgical and nutrition team. It was noted on his routine monitoring that his Ca had fallen to 1.78 mmol/l (2.2-2.6 mmol/l). He was reviewed out-of-hours and prescribed 10mls of 10% Calcium Gluconate infused over 10 minutes, as per the hospital guidance for the treatment of hypocalcaemia. A further prescription of calcium gluconate 10% in 100mls (10x10 ampoules) in 1l of normal saline was written up following the initial infusion. Unfortunately the patient deteriorated and after further assessment, it was noted that his venous blood gas calcium was immeasurably high. A confirmatory plasma calcium was noted to be 6.4 mmol/l (and rechecked to confirm that the original sample had not be accessed from the PICC line, where the calcium infusion had been administered). An urgent endocrine opinion was sought which delineated the options of fluid hydration, haemofiltration or potential bisphosphonate infusion. An intensive care review was facilitated and the decision to continue with 'ward-based' care was made. Fluid infusion to facilitate calcium excretion was commenced and within 24 hours, the calcium had improved to 4.78 mmol/l. Ongoing fluid management was continued but sadly the patient deteriorated and died, with sepsis contributing to his demise. On review of his care, it was noted that Calcium Chloride (and not Calcium Gluconate) had been administered (despite dual nursing verification). This has ~3 times the calcium content. [Calcium chloride 10 mmol/10ml injection = 6.8 mmol/10ml whilst Calcium gluconate 10% injection = 2.2 mmol/10ml]. As a result of this incident, calcium chloride 10 mmol/10ml injection ampoules have been removed from all ward stock lists except critical care units, cardiac specialty wards and emergency departments and guidelines which currently recommend use of calcium chloride 10 mmol/10ml injection have been updated e.g. management of hyperkalaemia.

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P30

Recognition and acute management of parathyroid crisis; early localization and surgery

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Background
Parathyroid crisis is a rare presentation with high mortality if unrecognized. Early surgery is curative with rapid symptom resolution and improved outcomes.
Case Report
We describe a case of severe hypercalcaemia due to primary hyperparathyroidism in a 59 year old male who presented with symptoms of lethargy, confusion, reduced appetite, constipation, light headedness and vomiting. Clinical examination was unremarkable. He had normal inflammatory markers. Severe hypercalcaemia of 4. 44 mmol/l was detected with a Parathyroid hormone level of 480 nmol/l. A diagnosis of parathyroid crises was recognised and he was started on intravenous fluid and Pamidronate. He then had haemofiltration in ICU as calcium levels remained refractory to treatment. CT scans of the thorax and abdomen demonstrated an uncharacterized cyst immediately adjacent to the upper thoracic oesophagus with no evidence of malignancy. Ultrasound of the neck and a MIBI subtraction scan failed to localize a definite parathyroid adenoma, however a site of MIBI activity was noted around the area of the cyst, and this was identified with endobronchial ultrasound as a fluid-filled paraoesophagheal cyst, with PTH level >530 pmol/l in the cyst fluid. He was started on Cinacalcet as a bridge to surgery, which also stabilized his calcium levels. Immediate parathyroidectomy was carried out at the site identified on the EBUS. A benign, large cystic parathyroid gland 44 x 19 x 20 mm and weighing 6.04g was excised. His calcium levels remained stable post-operatively and his symptoms resolved.
Discussion
Parathyroid crisis was detected early in this patient and several modalities were employed to lower calcium level. Immediate tumor localization and surgery prevented multi-organ failure and adverse outcomes. We recommend that the BES should consider addition of guidelines to aid early recognition and management of parathyroid crises.

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P31

COVID-19 Induced Hypoparathyroidism

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Case history
A 55-year-old man presented to the Emergency Department with worsening breathlessness 11 days after testing positive for severe acute respiratory syndrome coronavirus 2 (SARS CoV 2). He reported ongoing diarrhoea, starting 1 week prior to the SARS CoV 2 infection. He was previously fit and well, on no regular medication. All clinical observations within normal limits and there were no significant examination findings.
Results and treatment
3 Months Later Parathyroid antibodies-Negative Adjusted Calcium-2.08 mmol/l Phosphate-1.4 mmol/l PTH-6 ng/l Magnesium-0.82 mmol/L
Final Diagnosis: SARS CoV 2 infection-induced hypoparathyroidism, complicated by campylobacter diarrhoea (resolved). Treatment: Adcal-D3 2 tablets daily and Alfacalcidol 1 microgram daily.
Conclusions
Hypocalcemia is a prevalent symptom of SARS CoV 2 infection, but is normally self-resolving. Several reports have shown SARS CoV 2 infection leading to autoimmune diseases but rarely involve the parathyroid gland. Three case studies have described SARS CoV 2 infection-induced hypoparathyroidism, but none with as profound hypocalcaemia requiring ongoing active vitamin D therapy.

	Day 1	**Day 2**	**Day 11**(discharged)
U&E	Sodium-127 mmol/l (133-146) Potassium-3 mmol/l (3.5-5.3) eGFR-58 ml/min		Sodium-Normal Potassium-Normal eGFR-$>$90 ml/min
Bone Profile		Adjusted Calcium-0.98 mmol/l (2.2-2.6) Phosphate-1.01 mmol/l (0.74-1.62) ALP-78 U/l (40-150) PTH-5 ng/l (15-68) Magnesium-0.52 mmol/l (0.7-1.0) Vitamin D-34 nmol/l (50-200)	Adjusted Calcium-1.96 mmol/L PTH-4 ng/L Magnesium-0.92 mmol/L
Other	CRP-41 mg/l (0-10) Serum osmolality-267 mosmol/kg (280-300)	Stool culture-Campylobacter sp. ECG-Prolonged QTc	
Provisional Diagnosis	Hypovolaemic hyponatraemia and hypokalaemia secondary to diarrhoea	Hypocalcaemia secondary to hypomagnesaemia (campylobacter diarrhoea)	Resolving electrolyte disturbances secondary to campylobacter diarrhoea
Treatment	Intravenous fluids	Intravenous replacement of calcium and magnesium	Cholecalciferol 20,000 units once weekly for 6 weeks, Adcal-D3 4 tablets daily, Alfacalcidol 0.5 micrograms once weekly

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P32

Medical optimisation and multidisciplinary approach to management of hyperparathyroid crisis in an elderly patient

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Primary hyperparathyroidism causing symptomatic hypercalcaemia is often encountered in clinical practice. However, hyperparathyroid crisis is a rare and potentially fatal presentation of primary hyperparathyroidism characterised by profoundly symptomatic hypercalcaemia, altered mental status, and cardiac and renal dysfunction. Recognising the need for rapidly controlling hypercalcaemia with aggressive medical therapy and definitive management with early parathyroidectomy are necessary to reduce morbidity and mortality. A 89-year-old man presenting with six weeks history of lethargy, polyuria, polydipsia, confusion and acute kidney injury was found to have raised serum calcium of 3.5 mmo/l (2.10-2.58), suppressed serum phosphate and highest parathyroid hormone (PTH) level of 178.2 pmol/l (1.6-6.9). An ultrasound neck revealed 3.5 cm hypoechoic likely parathyroid neoplasm in the right inferior thyroid pole. He was aggressively treated with intravenous fluids, cinacalcet and intravenous bisphosphonates. Due to refractory symptomatic hypercalcaemia, suspected parathyroid carcinoma and need for withholding anticoagulant, calcitonin was used as a bridging therapy allowing safe and early parathyroidectomy on 14th day of admission. An enlarged superior parathyroid located posterior to recurrent laryngeal nerve and adherent to surrounding structures was removed successfully under local anaesthesia. It resulted in complete resolution of hypercalcaemia and associated symptoms and electrolyte abnormalities. His PTH reduced to 1.2 pmol/l on 3rd and calcium to 1.94 mmol/l on 5th day post-surgery, the later treated with oral calcium and alfacalcidiol. On histopathologic examination, the parathyroid specimen showed multiple fragments with an encapsulated zone of proliferation, compressed normal parathyroid tissue focally in the peripheral regions and no evidence of complete capsular transgression or vascular invasion. These features are suggestive of parathyroid adenoma; immunohistochemical examination is pending. Our case demonstrates challenges of managing hyperparathyroid crisis. Aggressive control of hypercalcaemia, with multiple therapeutic agents, and definitive management with early parathyroidectomy after optimising patient's condition are crucial for a successful outcome.

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P33

Is Vitamin D Toxicity inevitable without tighter regulation of over the counter sales?

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Introduction
Vitamin D (Vit D) is required for maintaining optimal bone health and there is widespread campaign in the media for its use. There is however lack of awareness among the general public about therapeutic doses which if exceeded can result in harm. We present one such patient who was taking harmful quantities of vit D supplements procured over the internet which resulted in hypercalcaemia and renal failure.
Case Description
50year old lady, Nutritionist with Type 1 DM and multiple previous fractures secondary to osteoporosis, presented with persistent abdominal pain and vomiting, no DKA. Severe Hypercalcaemia, 4.38 mmol/l was noted with suppressed PTH and AKI 3. No causes of secondary hypoparathyroidism evident from history and clinical examination. She reported taking Vitamin D, 8000IU daily for 5yrs; increased to 40,000IU (8x5000IU) daily 6months prior to admission. Her Vit D concentration was $>$900 nmol/l. The hypercalcaemia and AKI responded well to IV Fluids and a course of steroid treatment. Vitamin D normalised over 6 months.
Discussion
Vitamin D toxicity (VDT), Vitamin D levels $>$375 nmol/l, causing severe hypercalcaemia/hypercalciuria is rare and may result from excessive Vitamin D intake, defective metabolism or endogenous production of active Vit D metabolites as in lymphomas and granulomatous diseases. Our patient's VDT was from the high Vit D intake.
Conclusion/Recommendations
Vitamin D deficiency is implicated in adverse outcomes for various health conditions; autoimmune disorders, COPD/cancer/pregnancy/ falls in elderly patients and lately COVID-19. These messages coupled with the easy availability of high dose vit D over the counter/internet is not always accompanied with clear information on the safe doses to use. VDT may become more common with increasing awareness of Vit D benefits but could be avoided if safe doses are clarified with improved regulation of over the counter sale of such suppliments.

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P34

Important learning lessons from a rare case of hypoparathyroidism

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Background
Genetic causes of hypocalcaemia can be overlooked in patients presenting without apparent syndromic features. One such example is DiGeorge syndrome, which is often diagnosed in childhood but rarely in adulthood.
Case presentation
A 21-year-old lady was referred to our endocrinology clinic regarding chronic hypocalcaemia (adjusted calcium 1.98 mmol/l). This was first diagnosed at the age of eight with no clear cause identified. Her past medical history included hypoparathyroidism treated with Adcal D3 and infertility. Besides a short stature, the rest of examination was normal. Initial workup showed low parathyroid hormone (0.6 pmol/l, reference range 1.6-6.9 pmol/l) with normal levels of magnesium, phosphate, alkaline phosphatase, renal and liver function tests. Urinary calcium: creatinine ratio was raised at 0.36 (reference <0.2) and 25-hydroxyvitamin D was 33 nmol/l suggesting insufficiency. Investigations for infertility (pituitary profile and androgens) were normal except suppressed gonadotrohins with raised oestradiol levels and pregnancy was later confirmed on a urinary pregnancy test and a 12-week gestational scan. Unfortunately, 20-23 weeks' scans demonstrated a congenital heart disease and the couple chose termination of pregnancy declining antenatal cytogenetics. The foetus was noted to have mild hypertelorism, micrognathia, arachnodactyly, hypoplastic thymus, large ventricular septal defect and type 1 truncus arteriosus. Karyotype was normal (46XX) but chromosomal microarray analysis revealed a 22q11.2 microdeletion. Similarly, the mother's karyotype was normal (46XX) but the same 22q11.2 microdeletion was found and DiGeorge syndrome was diagnosed. The father had normal genetic tests. Subsequent thorough examination of our patient revealed subtle hypertelorism and arachnodactyly with a normal echocardiogram. In following years, she birthed two healthy babies without the 22q11.2 microdeletion. Her calcium levels have been stable on 1-alfacalcidol and Adcal D3.
Conclusions
This rare case reminds clinicians to follow a systematic approach when evaluating hypocalcaemia and consider the possibility of a late diagnosis of congenital hypoparathyroidism even in adulthood.

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P35

The Accuracy of Imaging test (USS and Sesta MiBi scan) for pre-operative localization in a patient with Primary Hyperparathyroidism who underwent parathyroidectomy

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Background
The Ultrasonography (USS) and Tc-SestaMiBi (MiBi) scans are established tests to localize parathyroid adenoma. It is important to utilize these appropriately prior to surgery for a positive outcome.
Method
It was a retrospective study in patients diagnosed with primary hyperparathyroidism (PHPT) according to the NICE Guideline who underwent parathyroidectomy from 01/01/2015 to 31/12/2019. We aimed to assess the USS and Tc-Sestamibi scan's effectiveness in the preoperative localization of parathyroid lesions and concordance with the operative and histological results.
Results
There was a total of 159 patients, of whom, 31(19.5%) were male with a mean age of 63 years. Their mean biochemical markers were corrected calcium level (2.89 mg/dl), PTH level (26.5 ng/l), vitamin D level (60 ng/ml) and eGFR (70.1). The 78 patients underwent parathyroidectomy while 71 patients were managed conservatively. The 10 patients missed their clinic appointments. Of the 78 patients who underwent surgery, the 26 (33.5%) patients' USS and MiBi scan findings were concordant with pre-operative and histological findings. 84.6% had adenoma, 11.5% had normal parathyroid and 3.8% had hyperplasia. 93% of patient's hypercalcemia was resolved following the surgical intervention. The non-concordance of both scans with operative and histological results were 21 (26.9%) patients. The 20 patients had adenoma while 1 had normal parathyroid. The patient (9%) developed recurrence hypercalcemia. The 17 (21.7%) patients had adenoma which was consistent only with MiBi scan and no recurrence. The 14 (17.9%) patients had concordance between pre-operative findings and USS (10 had adenoma, 3 had normal parathyroid and 1 had hyperplasia). There was only one recurrence PHPT.
Conclusion
Both USS and MiBi scans should be used to localize adenoma pre-operatively and the non-concordant cases should be discussed in the MDT meetings to improve the surgical outcome for such patients.

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P36

Milk-alkali syndrome presenting as severe hypercalcemia in pregnancy

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Introduction
Milk-alkali syndrome is characterized by the triad of hypercalcaemia, metabolic alkalosis, and acute kidney injury and occurs due to excessive use of elemental calcium. Despite the widespread use of proton pump inhibitors, it is the third most common cause of hypercalcaemia after primary hyperparathyroidism and malignancy.
Case presentation
A previously normocalcaemic 33-year-old patient presented at 34 weeks gestation, feeling non-specifically unwell. She was delivered by emergency caesarean section due to an abnormal foetal cardiotocograph. Investigations showed severe hypercalcaemia (4.87 mmol/l), suppressed PTH (0.5 pmol/l), and acute kidney injury (peak creatinine 150 μmol/l). Despite severe hypercalcemia, the patient was asymptomatic except for constipation. The patient wasn't prescribed any regular calcium or vitamin D supplements. A detailed medication history elicited excessive use (frequently >10 tablets/day) of Rennie's Spearmint tablets for reflux symptoms during pregnancy. Each tablet contains 272 mg of elemental calcium. She was also taking Pregnacare tablets (200 mg of elemental calcium daily). This equated to a cumulative dose of 2.9 grams of elemental calcium per day. Investigations for other causes of non-PTH-dependent hypercalcaemia were negative and cross-sectional imaging excluded occult malignancy. Hypercalcaemia due to Milk-alkali syndrome was diagnosed. Hypercalcaemia and acute kidney injury resolved with aggressive rehydration with isotonic saline (4-6 L/24 hours) without the need for bisphosphonate therapy. The latter was avoided due to the risk of causing rebound hypocalcaemia. The patient was advised not to take any over the counter calcium supplements. She was normocalcaemic and well at outpatient review. This case highlights the importance of taking a detailed drug history which should include all over-the-counter medications, including antacids. Milk alkali syndrome can easily be overlooked, and a high index of suspicion remains the cornerstone of diagnosis in the absence of obvious causes of hypercalcaemia especially in the pregnant patient.

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P37

The management of autosomal dominant hypoparathyroidism with CaSR mutation in pregnancy and breastfeeding

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Autosomal dominant hypoparathyroidism (ADH) is caused by gain-of-function mutations in the calcium-sensing receptor (CaSR), increasing its sensitivity to extracellular calcium, suppressing PTH and resulting in hypocalcaemia. In contrast to idiopathic hypoparathyroidism, treatment to correct serum calcium results in high urine calcium excretion, causing nephrocalcinosis, stones and renal impairment. Unlike surgical hypoparathyroidism where calcium should be maintained, patients with ADH are treated symptomatically. Interactions of maternal and fetal physiology make pregnancy complex. As maternal gut calcium absorption increases markedly by 12 weeks, alongside increased serum concentrations of 1,25(OH)2D3 independent of PTH, maternal serum calcium should be maintained. Maternal hypocalcaemia can have severe adverse effects on pregnancy, including spontaneous abortion, premature labour and stillbirths. Fetal compensation to maintain its calcium level results in secondary hyperparathyroidism, causing skeletal undermineralization, fractures in utero or on delivery and neonatal rickets. Neonatal hypercalcaemia may result. Alfacalcidol and calcium supplementation are used in pregnant women with ADH to maintain calcium in the low-end normal range. We present a case of a 29-year old lady with ADH caused by a novel heterozygous CaSR missense mutation, p.(Asn855Asp). By time of genetic diagnosis she had had two successful pregnancies and was breastfeeding her second child whilst suffering from marked symptoms of hypocalcaemia, with serum calcium dropping to 1.84 mmol/l, necessitating alfacalcidol titration up to 3ug daily. Post-breast feeding, she became rapidly hypercalcaemic, serum calcium 2.66 mmol/l, and we reduced to 1ug alfacalcidol, her adjusted calcium remaining between 1.9 to 2.1 mmol/l at this dose. Currently, she is in her third pregnancy and alfacalcidol has again been titrated up. Due to nausea and vomiting she has limited dairy intake and does not tolerate calcium supplementation. Being unsure of the baby's

mutation status, we are trying to avoid hypocalcaemia and fetal secondary hyperparathyroidism, should the baby not have the mutation.

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P38

Humoral Hypercalcaemia in pregnancy

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We report a 32-year-old primigravida with type 2 diabetes and large uterine fibroid who was found to have incidental, asymptomatic, non-PTH driven hypercalcaemia of 2.67 mmol/l (NR 2.2-2.60 mmol/l) at 7 weeks gestation. Investigations revealed no evidence of malignancy. Interestingly, following initial blood test, her calcium normalised but with persistent complete suppression of PTH until 19 weeks gestation, when her calcium rose to 3.25 mmol/l. Her 1,25-dihydroxy Vitamin D was elevated at 278 pmol/l (NR 43-144 pmol/l) along with raised inflammatory markers. However, further biochemical tests and CT chest ruled out sarcoidosis, tuberculosis and lung malignancy. We considered the possibility of PTH-related peptide (PTHrP)-driven hypercalcaemia secondary to her large uterine fibroid. PTHrP levels were not available for testing nationally. Her hypercalcaemia could only be managed by intravenous fluid hydration. She had multiple admissions for this. Management proved to be a challenge due to development of pregnancy induced hypertension. Calcitonin was considered but dismissed at that stage in pregnancy due to limited duration of action and uncertain risk to foetus. Between 27-33 weeks gestation, she managed to keep her calcium levels around 2.7-2.8 mmol/l with 4ls/day oral hydration. Foetal growth was at 10th centile but stable and diabetes was well controlled. At 35+6 weeks, her calcium was at its highest level at 3.88mol/l. We were unable to give adequate IV hydration due to development of pre-eclampsia. She was treated with calcitonin, lowering calcium to 3.09 mmol/l. Decision was made for induction but due to foetal distress; she had an emergency caesarean section. She delivered a healthy baby boy. Her calcium normalised a week later. This case highlights the rare cause of hypercalcaemia likely mediated by PTHrP due to enlarging uterine fibroid in pregnancy. We would like to share our experience in the challenges of investigating and managing hypercalcaemia in pregnancy given the limited investigation/treatment modalities available.

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P39

An unusual case of severe hypercalcaemia due to treatment resistant Graves' disease

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A 32-years-old lady was admitted with raised calcium. She had palpitation, sweating, 3 stones weight loss and neck swelling. She was diagnosed with Graves' disease 5 months ago. Her mother had history of thyroid disease but no family history of hypercalcaemia. She had a small goitre and lid lag on examination. On admission, adjusted calcium was 3.04 mmol/l. PTH was < 0.5 pmol/l. Phosphate, vitamin-D, kidney functions, cortisol, myeloma screen and ACE levels were normal. Free T4 was 90.1 pmol/l (NR-11.5-22.7), free T3 >30.8 pmol/l (NR-3.5-6.5) and TSH <0.01 miU/l (NR-0.49-5.43). TRAb antibodies were positive. Ultrasound thyroid showed diffusely enlarged hypervascular thyroid gland. CT chest-abdomen-pelvis showed no malignancy. She was taking Carbimazole 40 mg with good compliance. Hypercalcaemia was treated with IV fluids. Carbimazole was increased to 60 mg and referred for thyroid surgery. Propylthiouracil was tried but not tolerated. She was readmitted a month later with back pain and adjusted calcium 3.17 mmol/l. Despite taking Carbimazole 60 mg, Free T4 was 96.1 pmol/l, free T3 >30.8 pmol/l and TSH <0.01 miU/l. MRI whole spine showed no sinister findings. She was treated with IV fluids and pamidronate. Carbimazole was increased to 100 mg/day in split doses. Surgery was brought forward. She was also given Prednisolone, Lugol iodine and cholestyramine prior to surgery. She underwent total thyroidectomy. She developed post-operative symptomatic hypocalcaemia. She remained stable on Levothyroxine and alfacalcidol.

Learning points

1. Hypercalcaemia occurs in 20% of hyperthyroid patients and usually mild. Severe hypercalcaemia is rarely reported. 2. Pathogenesis of hypercalcemia in thyrotoxicosis is due to increased osteoclast activity mediated by nuclear triiodothyronine receptors. 3. Our case highlights the importance of considering hyperthyroidism as a differential diagnosis for hypercalcaemia. 4. Mainstay of treatment for hyperthyroidism related hypercalcaemia is controlling thyroid status.

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P40

Yet another case of hypercalcaemia!

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We present an interesting case of immobilisation hypercalcaemia. Case: A 22-year-old female with no significant past medical history was admitted following a road traffic accident (RTA). She suffered severe abdominal injury, skull and multiple limb fractures and underwent left below-knee amputation, bowel resection and nephrostomy. The admission to ITU was prolonged, and seven weeks into the admission, she developed hypercalcaemia (adjusted calcium: 3.8, N: 2.2 – 2.6 mmol/l) with a suppressed PTH (1.1, N:1.6 – 6.9 pmol/l). She required prompt treatment with intravenous hydration, calcitonin and bisphosphonate as her ECG showed shortened QTc interval. After an initial improvement, calcium climbed again. She was then stepped down to the ward for rehabilitation. Further investigations: alkaline phosphatase 124 (38-126U/l), vitamin D 29(> 50 nmol/l), TSH <0.01miu/l, FT4 57 pmol/l, cortisol 487 nmol/l. Carbimazole and Colecalciferol were started with subsequent biochemical improvement. However, her calcium remained elevated (3.22 mmol/l). She had also developed depression and was reluctant to mobilise due to low mood and pain. Psychological support was sought, and antidepressants were started. Her bone markers were consistent with increased bone resorption with elevated C-terminal telopeptide of type 1 collagen (CTX) (2.25, N: 0.10 - 0.50ug/l). Furthermore, there was no evidence of metabolic bone disease on the isotope bone scan. Hence the diagnosis of immobilisation hypercalcemia (IH) was considered. She was treated with hydration and pamidronate infusions. Serum calcium stabilised once she started rehabilitation.

Conclusion

IH is an uncommon diagnosis and may go unrecognised in hospitals or rehabilitation settings. In the young patients with reduced mobility, it usually occurs after four to six weeks of immobilisation but may present months after. Increased bone resorption causes hypercalcaemia. The diagnosis requires intensive investigations and exclusion of other causes of PTH independent hypercalcaemia. Although treatment with hydration and bisphosphonate infusion help prevent acute manifestations of hypercalcaemia, early mobilisation remains the mainstay of management.

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P41

Advanced Software to Diagnose the Early onset of Osteoporosis

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There are currently no robust methods for screening patients at risk of developing osteoporosis. Women tend to be more susceptible to low bone mineral density (BMD), whether its genetic, disease related, or menopausal and osteoporosis can also affect men. Access to dual energy x-ray absorption units (DEXA), is scarce and waiting lists are long. This has been exacerbated by the pandemic and the growing referral lists for radiology services. The burden of the disease processes is found to create a reduction in patients' quality of life (QoL), and a permanent need for access to healthcare services. A recent Cushing syndrome QoL study showed that when patients are diagnosed with osteoporosis, they realise that if they had been diagnosed sooner and treated earlier, it would have reduced their life-long risk of fractures. The Solution An advanced software product has the proven potential to provide a solution to the osteoporosis crisis; [1] This software measures bone health from a standard X-ray, meaning that if a patient has a hip fracture, (which is often an early warning sign of poor bone health) the early onset of low BMD, could be identified, enabling patients to be referred for early treatment. In endocrine disorders, patients could be screened as part of their initial diagnostic assessment. Undoubtedly, advanced software and the use of artificial intelligence in radiology services is increasing, with the aim of supporting clinical decision making, thus speeding up diagnosis, increasing early intervention, whilst saving the financial burden of long-term healthcare.

Ref: Rangan A et al, 2021. Prospective comparative study of quantitative X-ray (QXR) vs dual energy x-ray absorptiometry to determine the performance of

QXR as a predictor of bone health for adult patients in secondary care. BMJ Open, Dec 2021. Volume 11, Issue 12.

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P178

Bone metabolism and bone mass density following successful treatment of catecholamine secreting tumors

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Introduction
Pheochromocytomas and paragangliomas(PPGLs) are catecholamine-secreting tumors. Catecholamine excess contributes to bone resorption and secondary osteoporosis. PPGLs are treated surgically but limited data exists on the subsequent effect on bone status.
Aim
To evaluate bone metabolism(BM) and bone mass density(BMD) before and after successful surgery of PPGLs.
Methods
A retrospective study on (BM) of (PPGLs) patients in comparison with non-functional adrenal tumors(NFAT) patients during the period(1991-2021) was conducted. Patients with malignancies, conditions and medications affecting (BM) and postmenopausal women were excluded. 63 (PPGLs) and 52 (NFAT) patients were included. They were evaluated at diagnosis and 1 year after (PPGLs) surgical resection or (NFAT) diagnosis.
Results
Both groups had comparable age(years)(50 ± 14vs48 ± 9,$P=0.26$), sex (females(%)) (47.6vs46.2,$P=0.44$) and BMI(kg/m ^{2})(26.3 ± 4vs24.8 ± 4, $P=0.05$). At diagnosis (PPGLs) patients had higher mean P1NP(μg/l)(46 ± 12vs39 ± 15, $P=0.01$) and b-crosslaps(pg/ml) (0.56 ± 0.21vs0.44 ± 0.2, $P=0.006$). BMD(g/cm ^{2}) and T-Score in Femoral Neck(FN)(0.75 ± 0.1vs0.81 ± 0.1, $P=0.02$ and -1.11 ± 0.7vs-0.79 ± 0.7,$P=0.039$) and BMD in Lumbar Spine(LS)(0.84 ± 0.1vs0.88 ± 0.1,$P=0.043$) were significantly lower compared to (NFAT) group. 1 year after surgery, P1NP had significantly decreased (38 ± 13vs46 ± 11.5,$P=0.0008$) and were comparable in the 2 groups (38 ± 13vs40 ± 13,$P=0.51$) while b-crosslaps were significantly lower in (PPGLs) patients (0.4 ± 0.2vs0.5 ± 0.2,$P=0.004$). Non-significant changes were noticed for BMD and T-Score in (FN)(0.77 ± 0.1vs0.75 ± 0.1,$P=0.29$), (-0.94 ± 0.8vs-1.11 ± 0.8, $P=0.26$) and (LS)(0.86 ± 0.1vs0.84 ± 0.1,$P=0.28$), (-0.83 ± 0.8vs-0.98 ± 0.8, $P=0.33$) of (PPGLs) patients. (PPGLs) patients did not differ any more for BMD and T-Score from (NFAT) patients in the (FN)(0.77 ± 0.1vs0.78 ± 0.2, $P=0.79$),(-0.94 ± 0.8vs-0.89 ± 0.8,$P=0.72$) and the (LS)(0.86 ± 0.1vs0.87 ± 0.1, $P=0.73$),(-0.83 ± 0.8 vs -0.77 ± 0.8,$P=0.68$).
Conclusions
(PPGLs) are associated with deterioration of (BM) and BMD. 1-year after surgical treatment (BM) markers improve while BMD remains unaltered in the cortical and trabecular bone.

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P179

Primary Hyperparathyroidism: Correlation between Image Findings and Histology Data

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Background
Parathyroid adenomas form a major proportion (80-85%) of the causative pathology in primary hyperparathyroidism (PHPT) followed by hyperplasia (10-15%) and cancers $<1\%$. The only definitive treatment option for PHPT is surgery.
Aim
To determine the pickup rate and correlation of the imaging modalities (ultrasound (US) and Sestamibi (MIBI)) with histological diagnosis of parathyroid adenomas in patients with PHPT
Methodology
Between 01/03/2019 - 01/03/2020, 64 patients were seen for PHPT; 32 undergoing surgical management were retrospectively identified. The imaging findings, surgery type and histology results were recorded. Histological findings were coded to either adenoma, other parathyroid tissue (parathyroid hyperplasia/abnormal parathyroid tissue or possible adenoma) or non-parathyroid tissue. Histology data was available for 29 patients.
Results
The majority of patients underwent a targeted parathyroidectomy (65%), neck exploration (28%) and 7% other (cardiothoracic / private surgery). On the histology, 19 patients had a confirmed adenoma, 9 had other parathyroid tissue and 1 no parathyroid tissue was identified. 48% of patients had concordant imaging (71% adenoma, 29% other-PTH on histology); 17% US only (60% adenoma, 40% other-parathyroid); 17% MIBI only (80% adenoma, 20% other-parathyroid) and 17% negative scan (40% adenoma, 40% other-parathyroid, 20% non-parathyroid).
Conclusion
All patients with positive imaging (concordant or single modality) were found to have a parathyroid adenoma or other parathyroid tissue on histology. Where the imaging was discordant, MIBI identified more adenomas than US alone. Those with negative imaging, the majority of patients were still found to have an adenoma or hyperplasia. This indicates that the majority of patients referred for surgery had the appropriate diagnosis of PHPT. However, changes in the histology reporting may be required to more clearly identify the underlying pathology (adenoma vs hyperplasia). The small number of patients preclude definitive conclusions on which imaging modality has greater correlation with the histology outcome.

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P180

Parathyromatosis

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Parathyromatosis is a persistent or recurrent hyperparathyroidism following parathyroidectomy. It usually presents as multiple nodules in the neck. Infrequently may present as a single palpable neck mass. It could be due to low grade malignancy, seeding of parathyroid tissue during parathyroidectomy and growth of persistent embryonic foci of parathyroid tissue. A 24-year-old patient presented with features of hypercalcaemia. She has undergone left inferior parathyroidectomy 1 year back which suggested a benign tumour. However, she has had persistent hyperparathyroidism and high calcium levels even after surgery. She also had multiple fractures in lumbar spine and right hip. She had been treated with IV hydration and zoledronic acid, cinacalcet, and calcitonine with no response. Her serum calcium level was 3.5 mmol/l inorganic phosphorus 1.68 mg/dl (2.5 – 4.5), intact PTH was 1900 pg/ml (10 – 65), her total bone density T score was -3.5. Her contrast enhances computer tomography neck revealed a mass of $4.2 \times 2.7 \times 3.7$ cm inferior to the left lobe of the thyroid. Tc99m Sestamibi scan suggested of a residual parathyroid tissue. Genetic condition causing hyperparathyroidism were excluded. She had pepper pot skull and multiple brown's tumours in the skull bones. The patient underwent excision of the parathyroid tumour with hemithyroidectomy. Her histology revealed extensive fibrotic and necrotic parathyroid tissue. Capsular and vascular invasion was not identified. Mitotic activities were increased. However, immunohistochemistry revealed Ki67 of 20% and positivity for chromogranin A and cyclinD1 weak to moderate positivity seen in 70 to 80 % and strongly positive in few cells. Post operatively her calcium and parathyroid hormone levels returned to normal. There is a spectrum of malignant parathyroid neoplasms according to the degree of invasiveness. It starts from parathyromatosis, atypical parathyroid adenoma and parathyroid carcinoma. This case therefore highlights a common presentation leading to rare diagnosis.

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P181

A novel mutation on GNA11 as a cause of familial hypocalciuric hypercalcaemia

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Introduction
Familial hypocalciuric hypercalcaemia (FHH) is commonly caused by mutations in the CASR gene, less commonly in AP2S1 and rarely in GNA11. Only four FHH-associated loss-of-function variants have been reported in GNA11 to date.

Clinical Case
A 30-year-old woman investigated for migraines and paraesthesia in hands and feet was noted to have ionised calcium of 1.38 mmol/l (ref 1.15-1.33 mmol/l), PTH of 5.6 pmol/l (ref 1.6-6.9 pmol/l), and 25-hydroxyvitamin D of 65 nmol/l. Levels of ionised calcium remained between 1.37-1.39 mmol/l, with varying PTH, between 1.9-6.4 pmol/l. Urine calcium/creatinine clearance ratio was 0.0055. Total urinary calcium excretion was 6.0 mmol/day. She had no nephrocalcinosis on ultrasound and normal bone mineral density on DXA. Ultrasound, Sestamibi scintigraphy and CT neck found no parathyroid adenoma or hyperplasia. Genetic sequence analysis was negative for MEN1, MEN4, CDKN1B and RET-mutations. However, she had a heterozygote loss-of-function mutation on GNA11 c.686T>C, p.(Leu229Pro), which was a variant of unknown significance. Investigation of her parents revealed that her father had ionised calcium of 1.42 mmol/l and PTH of 3.3 pmol/l. Later he had ionised calcium of 1.36 mmol/l with PTH of 8.0 pmol/l. Urine calcium/creatinine clearance ratio was 0.0216 and 0.0198. He had osteopenia but no nephrocalcinosis. Genetic testing of the father revealed the same heterozygote mutation. Evaluation of first-degree relatives is ongoing and will further elucidate the role of GNA11 in FHH.
Clinical Lesson
A heterozygote loss-of-function mutation on GNA11 is a novel pathogenic mutation causing FHH and the diagnosis can be difficult to elicit as patients may have normal urinary excretion of calcium. PTH can also vary within the normal range and may be elevated in response to lower levels of hypercalcaemia. Genetic sequence analysis is recommended in these patients.

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P182

A novel mutation on MEN1 as a cause of familial primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism is the commonest manifestation of multiple endocrine neoplasia type 1 (MEN1) syndrome, which is caused by germline mutations on MEN1. Loss of functional menin leads to tumour development through unregulated cell division. The MEN1 c.941G>C, p.(Arg314Pro) variant has previously been thought to co-segregate in one family with MEN1 with tumours of parathyroid glands and endocrine pancreas.
Clinical Case
A 37-year-old man had undergone surgery removing three of four parathyroid glands due to primary hyperparathyroidism. Histopathology demonstrated parathyroid hyperplasia. More than a decade later, he was found to have bilateral nephrolithiasis with ionised calcium of 1.35 mmol/l (ref 1.15-1.33 mmol/l) and PTH of 6.0 pmol/l (ref 1.6-6.9 pmol/l). Pituitary and pancreatic hormones were unremarkable. The patient's mother had previously twice undergone surgery to remove parathyroid glands due to primary hyperparathyroidism. The patient's brother had four parathyroid glands removed due to hypercalcaemia. The patient's son had hypercalcaemia with nephrolithiasis. Genetic sequence analysis identified that the patient had a heterozygote missense variant on MEN1 c.941G>C, p.(Arg314Pro) and the same mutation was found in his mother and brother. Screening of the pituitary and pancreas in all affected individuals have not shown any other manifestations of MEN1.
Clinical Lesson
A novel heterozygote mutation on MEN1 is now known to cause familial primary hyperparathyroidism, without the other manifestations of MEN1. Thus, one must consider that there may be other variants on MEN1 which lead to isolated tumour development in the pituitary gland or pancreas. Genetic sequence analysis should be considered in patients with a family history of hypercalcaemia or other isolated manifestations of MEN1.

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P183

Management of Cystic Fibrosis-related bone disease with bisphosphonates: An audit in a tertiary care hospital in the UK

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Background
Cystic Fibrosis-related bone disease (CFBD) increases morbidity and mortality. Treatment varies across UK CF centres. Dual-energy X-ray absorptiometry (DEXA) is used for bone mineral density (BMD) evaluation: CFBD is diagnosed when Z-score<-2. European Cystic Fibrosis Society (ECFS) criteria for prescribing bisphosphonates:
1. Presence of low-trauma fracture 2. Lumbar spine/ total hip/femoral neck Z-score <-2 and significant bone loss (>4% /year) on serial DEXA despite optimal therapy 3. Patient awaiting or has undergone solid organ transplantation and Z-score <−1.5 4. Patient: prolonged course of oral glucocorticoids (>3 months) and Z-score <−1.5. Challenges encountered with this approach.
Methods
Retrospective audit analyzing CF database, January 2017-December 2020. Data sets included: demographics; Zscore; bisphosphonate treatment; treatment response; contraindications to bisphosphonates (pregnancy, jaw osteonecrosis, active tooth disease, CrCl<30ml/min, oesophageal reflux, decline treatment).
Results
248 patients screened: 18 met ECFS criteria for bisphosphonate treatment. 3/18 eligible for bisphosphonates having contraindications excluded. Audit included 15/18. Average age: 33.8years. 45% (7/15) were prescribed bisphosphonates. Of the 7 prescribed bisphosphonates, 2(29%) had DEXA repeated for monitoring treatment response. Repeat DEXA not done in 5/7. Among untreated 8, 1 was being trialled off steroids, 4 were pending multidisciplinary review regarding treatment concerns. 1 had 13% increase in BMD though still meeting criteria for bisphosphonate therapy. 1 had not achieved peak bone mass due to age, 1 had missed clinic follow-up. All 15 patients were on steroids: 5 for solid organ transplant, 10 for allergic bronchopulmonary aspergillosis. Mean duration of steroids with no transplant: 3.5years.
Conclusions
Challenges noted in CFBD treatment with bisphosphonates as per ECFS guidance. E.g., management of patients who hadn't achieved peak bone mass; had improvement in BMD but Z score remained <-2. Long-term oral steroids impact on BMD was noted and hence importance of optimizing doses. A case-by-case approach is often indicated (+/-rheumatology input).

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P184

Post-Operative Bone Health Assessment and Optimisation Remains Suboptimal in Primary Hyperparathyroidism

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Background
One of the main indications for parathyroidectomy surgery in primary hyperparathyroidism (PHPT) is osteoporosis. NICE guideline recommends 2-3 yearly Dual-energy X-ray absorptiometry (DEXA) assessments to evaluate bone mineral density (BMD) in asymptomatic PHPT.
Objective
We undertook an audit to evaluate bone health practice in PHPT patients in line with NICE guidelines.
Methodology
Retrospective case notes and electronic records' review was undertaken to identify PHPT patients in University Hospitals of Leicester.
Results
$n=121$ (106F:15M) patients with PHPT & Osteoporosis (T-score < -2.5) or osteopenia (T-score <- 1.0 to -2.5) were identified between 1987 and 2022; 88% were females. Mean age: 61 years at diagnosis, Mean Adjusted calcium 2.76 mmol/l (2.12-2.51), Mean Parathormone 21.22 pmol/l (2-8.5). 104/121 (86%) had DEXA at diagnosis: 37% Osteopenia and 63% had Osteoporosis; 20/121 (16%) had fragility fractures. 57 (47%) were treated surgically achieving cure rate in 51 patients (90%); Adjusted calcium 2.78 mmol/l normalised to 2.39 mmol/l post-surgically. Of those, only 23 (40%), had at least one DEXA performed after parathyroidectomy. Mean T-scores improved from -2.74 to -2.17 from osteoporosis to osteopenia range post-surgically indicating BMD improvement. Of the 64/121 non-surgically-treated patients 7 (11%) had at least one DEXA repeated within 3 years. 30/64 (47%) of non-surgical patients received medical treatment for osteoporosis. Interestingly 24/57 (42%) of surgically excised parathyroid adenomas were localised the right inferior location.
Discussion
Although immediate improvement in T-scores were noted post-surgically, assessment of BMD and Osteoporosis treatment remained suboptimal. We intend to address this with a quality improvement project undertaken prospectively as a result of this audit.

Conclusion
1. Long term bone health assessment and treatment remains vital irrespective of PHPT surgery as it takes time to improve BMD even after surgery. 2. Patient education, prevention/treatment of osteoporosis, strict specialist monitoring such as DEXA evaluations is recommended.

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P185

Finding the Culprit: A Rare Case of Oncogenic Osteomalacia

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Oncogenic ostemalacia is a rare paraneoplastic syndrome characterised by renal phosphate wasting secondary to secretion of FGF-23 from mesenchymal tumours. Localisation of the tumour is wanted, as resection can lead to complete clinical and biochemical cure. We present a case of a 57 year old woman with a background of Vitamin D deficiency and secondary hyperparathyroidism, who presented with severe generalised aches and pain, worst in her ribs and thighs, such that she could no longer manage stairs. After Vitamin D repletion orally (100.3 nmol/l), the biochemistry still revealed a low phosphate (0.56 mmol/l), elevated alkaline phosphatase (195Units/l), and elevated parathyroid hormone (7.3 pmol/l). She remained symptomatic. Further investigation identified inappropriately high urinary phosphate excretion (10.89 mmol/l with fractional excretion 45.38%). FGF-23 levels were high at 213units/ml with an inappropriately normal 1,25(OH)2 Vitamin D of 29 pmol/l. Retinol binding protein level was normal. This picture was suggestive of oncogenic osteomalacia. Treatment with Sandoz phosphate and alfacalcidol was started. A diagnostic Dotatate PET scan was performed, identifying multiple tracer avid bone lesions at sites typical for insufficiency fractures, but failed to localise any specific lesions. Subsequent targeted history taking identified a small left sided lesion on the patient's oral mucosa developing over the past year, with the patient revealing daily betel nut usage. Excision biopsy was performed, which showed features consistent with a giant cell fibroma. On further review of the original Dotatate PET scan, subtle uptake corresponding to this location was noted. The patient improved biochemically, with fasting serum phosphate normalising off phosphate treatment post-operatively, but requires a repeat wide excision to ensure there is no recrudescence. Our case highlights the importance of proper work-up of hypophosphataemia. Localising FGF-23 producing mesenchymal tumours can be difficult, and a good history and examination are crucial.

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P186

Primary Hyperparathyroidism Audit: Does routine Ultrasound Kidneys add value?

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Introduction
Primary hyperparathyroidism (PHPT) is a commonly encountered endocrine pathology. Asymptomatic renal stones have been reported in 7-22% of patients. NICE guideline (NG132) published in May 2019 on PHPT recommends renal US in all patients. The value of renal ultrasound for all patients with PHPT has been debated. This audit aims to compare local practice to NICE guideline (NG132) and to see if a tailored approach for renal ultrasound would be safe, practical and economical; and to assess its positive impact on the NHS radiology service which is under immense pressure due to long waiting lists triggered by the Covid pandemic.
Method
The data was collected prospectively from electronic records of the patients with PHPT attending the endocrine service at Kingston Hospital between March 2021 and April 2022. The collected data were compiled and analysed on Excel.
Results
Demographics: Total number: 100 - males $n=26$ (26%), females $n=74$ (74%). Age of patients referred ranged from 33-88, mean = 60.6 years. Peak C. Ca: <2.85 $n=49$, >2.85 $n=51$ Mean PTH: 14 pmol/l (range 3-111) Urine CCCR: >0.01 $n=94$, <0.01 $n=1$, not done $n=4$ Vitamin D Levels: <50 $n=46$, >50 $n=53$, not done $n=1$ Renal US Results Stone $n=15$, no stone $n=70$ Did/would US help with decision making? Maybe $n=1$ (missed imaging appointment), No $n=99$
Conclusion
Routine renal US did not add value to clinical decision making in people with PHPT. We recommend that renal US should be limited to asymptomatic patients with no other clear indications for surgery. This will help reduce the demand for precious radiology resource while providing patient centric approach to management. There is annual saving of about £4000/100 patients in addition to reducing number of hospital visits for patients. We are planning to modify our practice considering these results

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P187

High Parathyroid hormone- Think out of the box!

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Parathyroid hormone is a polypeptide consisting of 84 amino acids. Quantification of circulating intact PTH assists in the differential diagnosis of hypercalcemia. It is important to interpret PTH results with caution and to keep in mind Immunoassays interference can also be a reason of falsely high PTH levels. We present an interesting case referred with high parathyroid hormone levels. A 74 years old female attended clinic with raised PTH levels of 11.7 pmol/l, a normal calcium of 2.29 mmol/l, Vitamin D levels of 60 nmol/l and normal kidney functions. She had a family history of Hyperparathyroidism. We repeated her blood tests including Pituitary functions to exclude MEN syndrome, 24 hour urine calcium creatinine ratio, Plasma metanephrines and normetanephrines. All of these results were normal. An US of parathyroid was arranged which showed no parathyroid adenoma. Her Parathyroid hormones were persistently high as shown below: As no obvious cause of high PTH was established, we decided to rule out immunoassay interference. Subsequently her serum sample was sent to another Laboratory using Roche intact PTH assay. Interestingly her PTH was found to be normal at 5.9 pmol/l. This lady had dogs and likely interference was due to Heterophilic antibodies in human serum which can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.
Conclusion
Our case report highlights the importance of thinking out of the box when High PTH is not fitting in the picture of hyperparathyroidism. Do think about immunoassay interference especially in patients routinely exposed to animals. This will also prevent unnecessary investigations.

11/11/2019	09/12/2019	09/10/2020	22/03/2021	Normal Range
PTH 11.7	PTH 11.1	PTH 11.4	PTH 5.9	PTH (1.1-6.9 pmol/l
Calcium-2.29	Calcium-2.35	Calcium-2.25	Calcium-2.25	Calcium (2.2-2.6 mmol/l)
vit D-60	vit D—	vit D-110	vit D-115	Vit D >50 nmol/L

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P188

Severe symptomatic and treatment resistant hypercalcaemia caused by a parathyroid adenoma

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A 74 year-old woman had 4 presentations to the hospital with severe symptomatic hypercalcemia despite intensive medical therapy. She had a background of right hemithyroidectomy, hypothyroidism and rheumatoid arthritis. She first presented with symptoms of muscle weakness, vomiting, confusion and muscle aches. Her initial test results showed an adjusted calcium level of 3.79 mmol/l and PTH of 28.1 pmol/l; she was treated with IV fluids, Pamidronate 60 mg and discharged home with an adjusted calcium of 3.04 mmol/l. The neck ultrasound showed a 1.9 cm spongiform intra-thyroid nodule in the anterior aspect of the left thyroid gland. Her initial tests showed a serum creatinine of 93umol/l, urine creatinine of 6.2 mmol/l, urine calcium of 5.90 mmol/l and calcium:creatinine ratio of 0.025. Her vitamin D level was 77 nmol/l. The SPECT/MIBI scan of her parathyroid reported an increased uptake in the lower pole of the left thyroid; suspicious for a parathyroid adenoma. A CT 4D parathyroid with contrast also showed an enlarging lesion in the inferior pole of the left thyroid. She was waitlisted for a

parathyroidectomy after discussion at the parathyroid MDT. 3 months after her first presentation, she presented to the hospital with an adjusted calcium of 3.69 mmol/l and was treated with Cinacalcet 60 mg BD and IV fluids. Her adjusted calcium improved to 2.9 mmol/l until she required a further 2 admissions within the subsequent 2 months. Despite Cinacalcet titration, she developed an adjusted calcium as high as 4.82 mmol/l, phosphate of 1.33 mmol/l, creatinine of 153umol/l and PTH of 38 pmol/l. She required urgent renal replacement therapy for her resistant hypercalcemia on both occasions. She remained in the hospital for over a month until she underwent a parathyroidectomy 6 months after her first presentation. Her biopsy results confirmed a parathyroid adenoma and her calcium improved to 2.41/mmol/l after the procedure.

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P189

Denosumab induced recurrent, prolonged and life threatening hypocalcaemia

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Introduction
Denosumab, a human monoclonal antibody used in osteoporosis and second line treatment option for hypercalcaemia, can cause profound hypocalcaemia especially in Vitamin-D depleted and cancer patients.
Case history
56 years female, with diabetes, hypertension on metformin, empagliflozin, amlodipine and ramipril, presented with 3 months history of backache, no red flag signs, clinically and hemodynamically stable except mild confusion and spinal tenderness but no other neurological deficit. Bloods showed hypercalcaemia with suppressed Parathyroid Hormone (PTH) and acute kidney injury (AKI) stage 3. X-ray spine showed possible wedge fracture and subsequent investigation confirmed spinal metastasis secondary to breast cancer. Hypercalcemia management with Denosumab led to severe hypocalcaemia within 14 days which was recurrent, requiring prolonged intravenous calcium infusions.
Investigations
Initial bloods: Urea: 32 (2.5-7.8 mmol/l), Creatinine: 382 (49-90umol/l), Corrected Calcium: 4.08 (2.20-2.60 mmol/l), PTH: 0.8 (1.3-7.3 pmol/l), Phosphate: 2.26 (0.8-1.5 mmol/l), Magnesium: 0.78 (0.7-1.0 mmol/l), Vitamin-D levels weren't checked pre-Denosumab but 2 weeks later were 31 (> 50 nmol/l). Bloods 1 month after Denosumab: Corrected Calcium: 1.58 (2.20-2.60 mmol/l), Phosphate: 1.45(0.8-1.5 mmol/l), Magnesium: 0.66 (0.7-1.0 mmol/l), 25OH-vitamin-D (post-replacement): 106 (>50 nmol/l). Full blood count, liver, thyroid, lipid, coagulation profile was normal. CT spine showed bone metastasis and pathological rib fractures. Biopsy of breast mass confirmed ductal carcinoma in situ.
Treatment
Given AKI, hypercalcaemia and bone metastasis she was treated with intravenous fluids (IVT) and Denosumab 120 mg subcutaneously which resulted in profound, recurrent, symptomatic hypocalcaemia with prolonged hospital stay (nearly 2 months) and frequent intravenous calcium infusions besides magnesium and Vitamin-D replacement. Calcium and Vitamin-D levels remained normal on high dose oral replacement on out-patient follow-up.
Conclusions
- IVT and bisphosphonates remains first line management for hypercalcemia unless contraindicated as per endocrine society guidelines.
- Vitamin-D must be replenished before giving Denosumab to prevent life threatening hypocalcaemia.
- Patient requires high dose vitamin-D and Calcium replacement post Denosumab to prevent hypocalcaemia and frequent monitoring.

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P190

Analysis of receipt of bone protection prescribed post hip fracture in patients presenting for DXA

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Background
Hip fractures are associated with high morbidity and mortality rates amongst older adults. The Irish Hip Fracture Database Standard 5 requires that all patients with a hip fracture have a bone health assessment completed. The majority are prescribed bone protection therapy to reduce further fractures. We sought to analyse the compliance and receipt of bone protection in patients presenting for DXA scan post hip fracture.
Methods
We retrospectively assessed receipt of bone protection therapy in 20 consecutive patients at presentation to DXA post hip fracture from April to July 2021. This was captured on the bone health questionnaire administered by the DXA technicians. Subsequently, we examined their medical notes to see the result of their bone health assessment and to investigate whether despite recommendations from their orthogeriatrician the patients had not received adequate bone protection therapy.
Results
14/20(70%) patients who had had a hip fracture were clearly taking prescribed bone protection therapy on presentation to DXA at St. Vincent's University Hospital (SVUH). In the remaining 6/20 (30%) it was unclear from discharge letters or prescriptions if they were in receipt of adequate protection. Analysis of medical notes revealed 2/20 (10%) had been discharged with the advice to start denosumab with their GP, 2 (10%) received IV Zoledronic acid prior to transfer to rehab. 1 (5%) was discharged for IV zoledronic acid as an OPD which has not been administered. 1 patient was discharged without adequate bone protection despite an orthogeriatrician recommendation. Zoledronic Acid was the most prescribed bone protection agent (45%), followed by denosumab (40%).
Conclusion
Despite clear recommendations from orthogeriatricians not all patients were in receipt of recommended bone protection therapy on presentation to DXA. Standardized templates for discharge letters to GPs and outpatient DXA clinics may help to improve compliance.

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P191

A case of Familial hypocalciuric hypercalcemia with markedly elevated serum calcium

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A 50-year-old lady presented with fatigue, tiredness and constipation, has more than twenty years history of hypercalcemia. She was clinically and biochemically diagnosed as familial hypocalciuric hypercalcemia with high calcium, normal parathormone, low urinary calcium, low fractional excretion of calcium, positive family history. Genetic confirmation was done by positive molecular genetic analysis of CASR gene. She has persistent high calcium level ranging between 2.8 and 3.10 mmol/l, which is rare finding in FHH. No intervention was needed as no evidence of end organ damage. FHH is an autosomal dominant condition with occurs as a result of mutation at calcium-sensing receptor gene (CaSR) causing decreased receptor activity. Patient have mild hypercalcemia, hypocalciuria, hypophosphatemia. Parathyroid hormone level is normal or mildly elevated. Mutations in the (CaSR) gene in the parathyroid gland increases the set point for calcium sensing. It makes the parathyroid glands less sensitive to calcium, and a higher than normal serum calcium level is required to reduce PTH release. In the kidney, this defect leads to an increase in tubular calcium and magnesium reabsorption resulting in hypercalcemia, hypocalciuria, and frequently high normal levels of serum magnesium.
29/06/18 01/11/16 22/09/15 15/10/14 05/04/05 10/12/04
Parathormone (63-82 pg/ml) 48 66 67
Serum Calcium 2.97 2.96 2.95 2.95 2.77 2.83
Corrected Calcium (2.2-2.6 mmol/l) 2.97 3.02 2.91 2.97 2.73 2.75
Inorganic Phosphate (0.8-1.5 mmol/l) 0.88 0.78 0.91 0.65 0.79
Serum 25-hydroxy vit D 77
Why this case of FHH is different
Familial hypocalciuric hypercalcemia 1 with heterozygous mutation is a benign condition with mild elevation of calcium with normal or mild increase of PTH. Patients with homozygous mutation may have severe hypercalcemia with marked elevated PTH. Despite heterozygous mutation this patient has persistently presented with marked hypercalcemia (2.8-3 .10 mmol/l) with mildly raised PTH.

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P192

An initial disturbing finding in the follow-up of medullary thyroid carcinoma after surgery- in the Vth laterocervical compartment may represent a positive course of the disease. Case Report

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A 60-year lady with a history of thyroidectomy for medullary thyroid presented for her regular follow-up - first presentation in our clinic in Nov 2020 (previous visits to another endocrinology clinic).

History

2005: uretheroplasty for left uretheral hypoplasia January 2017: thyroid ultrasound: a unique left lobe thyroid nodule (1 cm)- basal calcitonin x3 UNL (nr <11.5) and 94 pg/ml calcium stimulated CTN; RET gene - negative for mutations in exons 8/10/11/13/15/16 April 2017: total thyroidectomy with left inferior parathyroid autotransplantation on the posterior margin of the SCM; anatomopathological report: 1.1x0.8x0.6 cm unique tumour in the left lobe, no lymph nodes involvement and no parathyroid glands May 2017: TSH = 2,1 mUI/ml on Levothyroxine; undetectable calcitonin, PTH: 14.4 pg/ml (15-65), normal serum 25 OH vitamin D and Calcium (on cholecalciferol and calcium supplement); March 2019: left breast conservative surgery for DCIS (ER-, PRG-, HER 3+, Ki67-30%) with negative sentinel lymph node biopsy – followed by radiotherapy (42 Gy- June 2019) June 2020: PTH = 8.3 pg/ml (15-65), CaT = 9.6 mg/dl (8.8-10.4) (on cholecalciferol and calcium supplement); Nov 2020: PTH = 12.4 pg/ml (nr 15-65), CaT = 8.77 mg/dl (8.8-10.4), 25 OH vitamin D: 40 ng/ml ($n>30$) (on cholecalciferol and calcium supplement); TSH = 1.32 mUI/l (on Levothyroxine); converted to alphacalcidiol (active vitamin D) Clinical exam – 59 kilo/ 169 centimetres, Trousseau negative, euthyroid, postoperative scars following surgeries.

Discussion

Permanent hypoparathyroidism is a recognized complication of thyroidectomy. Parathyroid autotransplantation (PTHAT) has been performed to avoid permanent hypoparathyroidism. The incidence of transient hypocalcemia due to hypoparathyroidism is higher in patients who underwent PTHAT but, rarely permanent hypoparathyroidism occurs. In our patient, a recovery of the transient hypoparathyroidism was documented 6 months following neck surgery – with a rebound of the hypoparathyroidism and a nadir 12 months following radiotherapy in the ipsilateral breast area- with gradual recovery.

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P311

Comparison of newly derived and existing formulae for the estimation of biologically active calcium

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Introduction

Free ionised calcium is the biologically active component of total circulating calcium but is infrequently measured due to sampling requirements. Therefore, total calcium is 'adjusted' for albumin to provide a closer estimate of the biologically active ionised calcium level (e.g. James, Orell, Payne and Berry formulae). Here, we aim to derive a novel equation to estimate ionised calcium from readily available biochemical parameters and compare its performance to existing equations.

Material and Methods

Derivation cohort: 2806 serum samples (total calcium) taken with blood gas samples (ionised calcium) collected at Imperial College Healthcare NHS Trust were used to derive equations to estimate ionised calcium using multivariable linear regression. *Validation cohort*: The performance of newly derived and existing equations of calcium to predict PTH in a cohort of 5510 patients was compared using spearman correlation and multivariable linear regression, adjusted for vitamin D level.

Results

Derivation cohort: Adjusted calcium ($r2 = 0.269$) was less strongly associated with ionised calcium, than total calcium ($r2 = 0.314$). A newly derived equation incorporating total calcium, albumin, potassium and haematocrit levels had an r2 of 0.327, and 0.364 when all available laboratory variables were included, which were superior to the best performing existing formula (James: $r2 = 0.27$). *Validation cohort*: Adjustment of total calcium by the Berry resulted in a higher calcium level, whereas adjustment by Orell resulted in a lower level. The relationship between calcium and PTH was strongest in the setting of hypercalcemia, with the James formula having the highest correlation coefficient ($+0.495$).

Discussion

Accurate determination of calcium status has important implications for interpretation of PTH levels and reaching the correct diagnosis especially in borderline cases. Adjustment of total calcium levels for albumin using current equations does not always outperform unadjusted total calcium levels in reflecting ionised calcium, especially in scenarios of extreme perturbations of physiology.

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P312

Hypercalcaemia in Renal Transplant Patients

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Background

Hypercalcaemia is common in renal transplant recipients, the majority of whom have PTH-dependent hypercalcaemia due to tertiary hyperparathyroidism. PTH-independent hypercalcaemia is less common and is associated with significant, treatable underlying pathologies. In this study, we aimed to evaluate the prevalence and aetiology of PTH-independent hypercalcaemia in post-renal transplant patients.

Method

This was a retrospective, single-centre biochemical and electronic records audit of renal transplant recipients treated at the renal unit of the Royal London Hospital. Inclusion criteria included patients with renal transplants performed between January 1972 and January 2022. Patients with inadequate records were excluded. A corrected serum calcium of ≥ 2.6 mmol/l, occurring any time after 3-months post-transplant, was used to determine prevalence of hypercalcaemia. A PTH value of <1.6 pmol/l was used to define PTH-independent aetiology.

Results

1876 renal transplant recipients were studied, including 484 patients who had a functioning graft within 12 months of their death. The prevalence of post-renal transplant hypercalcaemia was 41.2%. 5.2% of patients with hypercalcaemia had a suppressed PTH. Of these, 23.7% had transient hypercalcaemia in the context of calcium and activated vitamin D replacement following pre-transplant parathyroidectomy. In all cases, the calcium normalised on adjustment of their oral calcium/vitamin D replacement. Opportunistic infection accounted for 21.1% of PTH-independent hypercalcaemia cases, which included PJP and Aspergillus infections. 18.4% had an underlying malignancy, the commonest of which were Renal Cell carcinoma of the native kidney and PTLD. 2.6% of patients had Sarcoidosis. 15.8% had concurrent, unrelated infections. The aetiology of hypercalcaemia remained unknown in 18.4% of patients. Hypercalcaemia improved in all cases after hydration and treatment of the underlying aetiology. A statistically significant increase in kidney function occurred 6-months after correction of hypercalcemia ($r = 0.7722$; $P < 0.0001$).

Conclusion

PTH-independent hypercalcaemia in renal transplant patients is rare, but is associated with significant underlying pathology, including malignancy and infection.

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P313

Bone Turnover Markers for Assessment of Anti-Resorptive Effect in Clinical Practice: A Good Idea Meets the Problem of Measurement Uncertainty

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Background

Bone turnover markers (BTM) are potential measures for understanding the effect of antiresorptive medications upon osteoclast activity. As a dynamic marker of therapy effect, they could complement or replace DXA-BMD. The translation of population data on BTM changes with therapy to the individual patient is less established. Post-hoc trial data suggests a reduction in BTM of 40% may represent a target for defining appropriate response to therapy.

Aim
We modeled the clinical application of this target threshold in an individual patient setting where assay measurement uncertainty and biological variation are included.
Methods
Using C-telo-peptide (CTX), we constructed hypothetical scenarios of CTX measurement pre and post bisphosphonate therapy. Using typical CTX assay characteristics (analytical CV 5.0%) and published intra-individual CTX data for post-menopausal women (CVi 18.0%), we calculated the level of post-therapy CTX that must be seen on single repeat measure in order to be 95% confident that the observed result was $\geq$40% lower from baseline. Sensitivity analyses considered greater and lesser variations in the combined sources of variation.
Results
The one-tailed 95% reference change value for any detectable therapeutic decrease in CTX was 22% at the mid-point reference interval. However, to have 95% confidence of having achieved a reduction $\geq$ 40%, an observed CTX decrease of 56% is required. Even larger decreases are needed for scenarios of greater analytical or intra-individual variation.
Conclusions
Although population data may suggest a CTX decrease of 40% is commensurate with adequate therapeutic response to anti-resorptives, the application to an individual patient where measurement and natural variation are present is problematic. CTX decreases much greater than 40% are required in order to be certain of having achieved a 40% decrease. It is uncertain whether this is a legitimate change to be expected in most individual patients and therefore clinical application of this threshold is uncertain.

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P314

Appropriateness of parathyroid imaging in patients with primary hyperparathyroidism

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Aim
To assess the appropriateness of parathyroid imaging performed in patients with primary hyperparathyroidism at the United Lincolnshire Hospital NHS Trust from 2018 to 2019.
Background
Primary hyperparathyroidism (PHPT) is a clinical and biochemical diagnosis. Reported sensitivity for imaging localisation of parathyroid adenomas for ultrasound and sestamibi scans are not high at 65 to 85% and 71 to 92%, respectively. Surgeons use combined ultrasound and sestamibi scan (sensitivity $>$90%) for preoperative localisation to facilitate minimally invasive surgeries. Bilateral neck exploration is considered if parathyroid imaging is negative. Thus, imaging in PHPT should be used as a localising tool preoperatively to determine surgical approaches.
Methods and Results
Imaging appropriateness was evaluated for patients (n=126) who had sestamibi scans from 2018 to 2019 from their clinic letters. An independent endocrinologist assessed the accuracy of the evaluation. If the patient had established PHPT, familial hypocalcaemia hypercalciuria ruled out and met the criteria for surgery based on NIH and NICE guidelines, the scans were deemed appropriate. The initial audit showed: Overall, 22% of the imaging was requested inappropriately. Amongst patients who had appropriate and inappropriate imaging, the proportion of patients who had or are awaiting surgery is 68% and 34%, respectively. 32% of appropriately imaged patients were managed conservatively or deemed unfit for surgery after the multidisciplinary team meeting (MDT) discussion. 74% of patients had clear surgery discussions, but the same was unclear for the remaining 26%.
Conclusion
PHPT patients should be offered imaging as localising tools only after they meet the criteria and are deemed fit for surgery. This audit showed that one-fourth of the patients had avoidable parathyroid imaging. When the diagnosis is ambiguous, imaging should be requested after MDT discussion to ensure the appropriate use of NHS resources and limit unnecessary radiation exposure.

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P315

Comparison of Preoperative Imaging Modalities in Primary Hyperparathyroidism

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Introduction
Accurate preoperative localisation in primary hyperparathyroidism enables a localised approach to a parathyroidectomy operation. Ultrasonography is the most commonly used first-line imaging modality due to its widespread availability and safety. Parathyroid scintigraphy using MIBI is commonly used as the second-line imaging modality, as recommended by NICE. 4D-CT may have a role as a third-line imaging modality, when ultrasound and scintigraphy do not clearly localise a parathyroid adenoma. We audited our use of these preoperative imaging modalities in routine clinical care for parathyroid localisation in primary hyperparathyroidism.
Materials and Methods
We did a retrospective review of 36 patients who had parathyroid surgery in 2020-2021. We looked at the imaging results of these patients including parathyroid ultrasound, MIBI scan and 4D-CT and correlated the results with the operative and histopathological findings.
Results
Of 36 patients, 7 (19.4%) were males and 29 (80.6%) were females. Mean age was 63.6 years (Range: 41-84). Parathyroid ultrasound was done in all 36 patients and was successful in accurately localising a parathyroid adenoma in 19 patients (Sensitivity: 52.8%). MIBI scan was done in 25 patients and was successful in accurate localisation of a parathyroid adenoma in 17 patients (Sensitivity: 68%). 4D-CT was done in 11 patients with equivocal or unsuccessful imaging, after review and discussion at our parathyroid MDT. It was successful in correctly localising a parathyroid adenoma in 8 patients (Sensitivity: 72.7%).
Conclusion
If a parathyroid adenoma cannot be localised by ultrasonography and MIBI scan, 4D-CT could be considered. Accurate preoperative localisation makes it possible to perform a localised parathyroidectomy operation rather than full neck exploration, which is associated with advantages in terms of operating time. This helps reduce waiting times and could be factored into a cost-benefit analysis of pre-operative imaging protocols for primary hyperparathyroidism.

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P316

Severe hypercalcaemia with short QT interval due to vitamin D intoxication secondary to unsupervised exogenous vitamin D administration

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Case
A 34-years-old male, construction worker, referred by GP with the history of vomiting, fatigue and near-collapse. Apart from alcohol excess, his past medical history was unremarkable. He did not have any personal or family history of any endocrinopathy, and was not taking any medication. Initial blood result were as below. ECG showed short QTc interval of 354 ms. His presentation was initially thought to be vomiting due to alcohol excess leading to dehydration and hypercalcaemia with AKI. He was commenced on IV fluids and Pabrinex. Further tests showed suppressed PTH 0.5 pmol/l, TSH 1.4mU/l, and negative myeloma screen. CT thorax was normal which excluded sarcoidosis, TB, and malignancy, therefore, a possible explanation of PTH independent severe hypercalcaemia was made. His vitamin D level returned after a few days which was grossly elevated at 1821 nmol/l. On direct questioning, he reported taking 50,000IU vitamin D injection every 1-2 days for last several months, which he bought online without any medical advice or supervision. He was given IV zoledronic acid due to inadequate response from IV fluids alone. He was counselled against the use of vitamin D preparation without medical advice or supervision as this could have been fatal in his case. His calcium level normalised and AKI resolved with the resolution of ECG changes after the treatment. Discussion: Among all causes of hypercalcemia, primary hyperparathyroidism and malignancy are the most common, accounting for $>$90% of cases. Although hypercalcemia due to exogenous use of vitamin D is unusual, it is important to consider it in the differential diagnosis as part of initial work up. This case highlights that this could result in symptomatic life-threatening hypercalcaemia and patient should be effectively counselled regarding perils of over-the-counter vitamin D use.

Ca	3.78 mmol/L
Urea	12.3 mmol/L
Creatinine	209μmol/L
Na	137 mmol/L
K	4.1 mmol/L
HCO3	28 mmol/L
Albumin	41g/L

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P317

A rare case of asymptomatic hyperplastic ectopic parathyroid tissue within the thymus: what are the clinical implications?

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61-year-old-male with a background of treated hypertension and dyslipidaemia presented to accident and emergency with progressive shortness of breath. His most recent bloods were within normal limits. He has a positive family history of cardiac disease, and underwent investigation by CT scanning. This revealed a 10.2 mm anterior mediastinal nodule, which was not avid on PET CT scan. His case was reviewed by the respiratory team and he underwent a left VATs thymectomy. Thymic tissue was sent for histology revealing thymic hyperplasia with ectopic hyperplastic parathyroid tissue within the specimen. Post-surgery his biochemistry was normal. At endocrine follow up 4-months later he demonstrated a low/normal calcium of 2.20 mmol/l, phosphate 0.77 mmol/l, total vitamin D 77 nmol/l and PTH 6.7 pmol/l. There was no family history of parathyroid dysfunction or multiple endocrine neoplasia. His breathlessness improved and interestingly he remains asymptomatic of any endocrine imbalances. He remains under blood surveillance. Ectopic parathyroid glands have a prevalence of approximately 16%. The inferior parathyroid glands and thymus derive from the third embryological pouch. Their anatomical variability owes to abnormal migration during embryogenesis. The thymus is the most common site of ectopy. Most reported cases present with symptoms of hypercalcaemia, and are localised by PET scan. In this case, FDG-PET was used; assumedly due to its wider availability. Notably this modality has a reduced sensitivity and positive predictive value in detecting pathological parathyroid glands compared to 18F-FCH PET. At present, the function of the hyperplastic parathyroid gland is unknown. It also remains unclear as to whether resection of the asymptomatic parathyroid tissue will lead to abnormalities in bone biochemistry over time. This poses an important clinical consideration: despite normal biochemistry, should we be refining the way we evaluate the thymus pre-operatively? Long term follow up will provide more clarity.

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P318

Hypocalcaemia Driven by Proton Pump Inhibitors: An Increasing but Poorly Recognised Problem

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Hypocalcaemia can present with paraesthesia, twitching, mood and memory changes and should be considered a medical emergency given potential to cause seizures, tetany, arrhythmia and cardiac arrest. It may be caused by hormonal dysregulation including hypoparathyroidism or pseudohypoparathyroidism or other factors such as vitamin D deficiency, chronic kidney disease or hypomagnesaemia. In this case series, we highlight the use of various protein pump inhibitors (PPIs) in driving hypomagnesaemia which resulted in severe hypocalcaemia: the first case involved a 72 year old woman who presented with shortness of breath and agitation and was taking regular esomeprazole. Confusion screen was completed whilst awaiting psychiatry input and found adjusted calcium of 1.66 mmol/l and serum magnesium of 0.34 mmol/l. Intravenous electrolyte replacement and stopping the PPI eventually normalised serum calcium and magnesium levels. The second case was of a 66 year old woman who presented with fall alongside reduced oral intake, slurred speech and paraesthesia and they were taking furosemide and lansoprazole chronically. Blood tests revealed severe hypocalcaemia of 1.58 mmol/l and hypomagnesaemia of 0.31 mmol/l and despite intravenous replacement of electrolytes, improving oral intake and holding of diuretics calcium and magnesium failed to normalise and only did so after stopping lansoprazole. The third case involved a 75 year old woman who presented with muscle cramps and paraesthesia. Serology revealed severely low magnesium of 0.26 mmol/l and adjusted calcium of 1.56 mmol/l. Intravenous electrolyte replacement was given and regular omeprazole was switched to an alternate class of gastro-protection which led to normalisation of both magnesium and calcium. Therefore, multiple PPIs can be implicated in driving hypomagnesaemia and consequently hypocalcaemia; given their increasingly common use more must be done to raise clinician awareness of this association and ensure correct management i.e. stopping of PPIs to treat the hypocalcaemia.

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P319

Denosumab for refractory hypercalcemia due to primary hyperparathyroidism in patient with COVID-19

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Background
There is limited data on the use of Denosumab for hypercalcaemia in patients with primary hyperparathyroidism (PHPT). We describe a case of severe hypercalcaemia in a critically ill patient with COVID, on a background of mild PHPT prior to hospital admission.
Case report
Seventy-seven-year-old gentleman with mild hypercalcaemia dating back to 2019, was referred to endocrinology with hypercalcaemia (adjusted calcium 4.02 mmol/l) and associated acute kidney injury (AKI). His PTH level at the time 31.8 pmol/l while his vitamin D level was 60 nmol/l. He remained hypercalcaemic despite intravenous fluids, Calcitonin, 2 doses of Pamidronate 60 mg, and Zoledronic acid 4 mg. Cinacalcet titrated to 360 mg daily was ineffective and poorly tolerated with a nadir adjusted calcium of 3.17 mmol/l. He then received 60 mg of Denosumab which brought his calcium level down to 2.80 mmol/l and subsequently within normal range, with resolution of the AKI and reversal of symptoms. A Sestamibi Parathyroid SPECT CT scan identified a solitary parathyroid adenoma and a renal ultrasound did not show any evidence of end organ damage. He remained hospitalised for 5 months due to COVID-related deconditioning and has required additional doses of Denosumab 4-6 monthly since discharge to maintain normocalcaemia, until optimised for a parathyroidectomy. Unlike prior cases in literature, we did not see hypocalcaemia in our patient, who has continued to require Denosumab.
Conclusion
This case illustrates that Denosumab is useful in the management of refractory hypercalcaemia associated with PHPT, particularly in those who are resistant to other therapies prior to surgery, or in patients in whom surgery is contraindicated or requires to be deferred. Denosumab could be considered when other modalities, like dialysis and emergency parathyroidectomy, cannot be easily undertaken due to comorbid conditions.

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P320

Primary Hyperparathyroidism in a patient with Alport syndrome

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A 50 years old man was seen in the Endocrine clinic with elevated calcium (2.80 mmol/l, normal 2.20-2.60) and Parathyroid hormone (10.7 pmol/l, normal 1.6-6.9) levels. His medical background includes Alport Syndrome, Renal Allografts (1st 1990, 2nd 2000 and 3rd 03/11/2005), and Osteopenia on DEXA scan in February 2020. He did not have any renal stones in the past. There was no family history of hypercalcemia. He was on Vitamin D 1000 Units daily (Vitamin D 55 nmol/l, normal 50-120), Lamotrigine, Aspirin, Azathioprine, Lansoprazole, Prednisolone, Tacrolimus, Losartan, Clonazepam and Paracetamol. He was noted to have raised calcium over 20 years and raised parathyroid hormone levels for few years. Even with the creatinine of 180 umol/l (59 – 104 umol/l) his calcium level was 2.7 mmol/. His 24 hours calcium/creatinine ratio was 0.0160 mmol/mmol when eGFR was 74 ml/min/1.73 m^2. Ultrasound of neck showed 7.2 x 6.6 x 3.1 mm lesion on posterior left lower lobe and avascular 4.7 mm hypo-echoic cystic lesion medial to right carotid and inferior right lobe of thyroid. Nuclear scan showed 3 parathyroid adenomas – left superior and inferior and right inferior. In view of the possibility of worsening renal function in patients undergoing parathyroidectomy post renal transplant, it was decided to manage his primary hyperparathyroidism with Cinacalcet. We acknowledge that some of the raised parathyroid hormone level in the past could be related to renal impairment. However he continued to have elevated levels even when the eGFR was between

62 and 74 mL/min/1.73m^2. His calcium and parathyroid hormone levels have normalised whilst on Cinacalcet.

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P321

Unusual Association of Hypercalcemia in a Patient with Coeliac Disease

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A female born in 1950, with history of Coeliac Disease since 1985, hypolactasia, pernicious anaemia, osteoporosis, asthma, lymphocytic colitis and non-alcoholic fatty liver disease with portal hypertension was referred to the Endocrinology team in June 2021 as the calcium was noted to be high. She had strongly positive anti endomyseal antibody, high Tissue Transglutaminase tire and duodenal biopsy proved villous atrophy with no evidence of Enteropathy associated T cell Lymphoma. She was on a strict gluten free diet but despite that she had weight loss, multiple nutritional deficiencies which includes iron, B12, folate, vitamin D deficiency. She was on replacement for all the above. She was noted to have hypocalcaemia in 1999 and 2000 but hypercalcemia since 2006. There was no family history of increased calcium. She had hypercalcemia of 2.65 mmol/l (2.20-2.60), raised PTH of > 46.5 pmol/l (1.6-6.9), low Vitamin D <9 nmol/l (50-120) and low phosphate 0.36 mmol/l (0.8 -1.50) The patient was thought to have either primary hyperparathyroidism (in which case familial hypocalciuric hypercalcemia (FHH) had to be ruled out) or secondary hyperparathyroidism due to Vitamin D deficiency. She was started on Vitamin D supplements and her calcium supplements were discontinued. She has persistently raised Calcium of 2.79 mmol/l (2.20-2.60) and PTH of 14.5 from 46.5 pmol/l(1.6-6.9) in spite of improving Vitamin D levels. Her urinary Calcium and creatinine clearance ratio was 0.007 which is more in keeping with hypocalciuric hypercalcemia. She is awaiting genetic testing to confirm Familial Hypocalciuric hypercalcemia. Coeliac disease is usually associated with hypocalcemia and the elevated parathyroid levels if any would be considered as secondary hyperparathyroidism. There are only few case reports of hypercalcemia due to primary hyperparathyroidism in patients with coeliac disease.

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Endocrine Cancer and Late Effects

P42

Hydroxymethylation is dysregulated in pancreatic neuroendocrine tumours and associated with aberrant DNA methylation

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Pancreatic neuroendocrine tumours (PNETs) have a lower mutational burden than other tumours, indicating that other mechanisms contribute to tumourigenesis. One such reported mechanism is DNA methylome dysregulation, however, inconsistencies have been observed between gene methylation and protein expression, potentially stemming from the use of standard methylation assessment methods which do not distinguish methylation (5'methylcytosine (5'mC), repressive mark) from hydroxymethylation (5'hydroxymethylcytosine (5'hmC)), at CpG (Cytosine cis-Guanine) sites, the latter protecting against promoter methylation. The aim of our study was therefore to investigate the hydroxymethylome in PNETs. Nine PNETs (5 non-functioning and 4 insulinomas), 5 with adjacent normal tissue, and 2 additional normal pancreata were investigated for 5'hmC by immunohistochemistry. Using paired DNA samples in which one had undergone oxidation prior to bisulfite conversion, specific 5'hmc sites and enrichment of pathways were also interrogated using the Illumina MethylationEPIC array (consisting of >850,000 CpG sites, annotated to 28,637 genes). Normal islets were significantly enriched in 5'hmC, compared to exocrine tissue and PNETs, $P<0.0001$. Moreover, MethylationEPIC array analysis revealed that PNETs had significantly ($P<0.001$) lower 5'hmC (0.01% (57/723,389)) compared to normal tissue (8.9% (64,478/727,322), and that 4.1% (29,761/724,156) of CpGs were differentially methylated, of which 50.8% (15,104/29,761) were hypermethylated and 24.9% (3616/15,104) of these were hydroxymethylated in normal tissue ($P<0.0001$, vs 5'hmC in normal tissue (8.9%)). In normal tissue, 5'hmC were enriched in 36 Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways ($P<0.01$, false discovery rate (FDR) <0.05), that included insulin and glucagon signalling. In PNETs, 5'hmC loss and 5'mC gain at the same CpG site were present in >300 genes including DAXX, ($P<0.01$). Overall, our results indicate that 5'hmC is lost in PNETs, compared to normal islets, and thus important cell specific CpG sites are no longer protected from methylation, and this may therefore lead to the downregulation of anti-tumourigenic pathways.

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P43

Gene-specific application of computational prediction tools aids the classification of rare missense variants in the diagnosis of hereditary endocrine tumour syndromes

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Introduction
The successful implementation of clinical genetic testing relies on accurate variant interpretation, as misclassification can result in significant harm to the patient and wider family. Missense single nucleotide variants (SNVs) pose a particular challenge, with current interpretation methods often unable to differentiate pathogenic variants from rare neutral variants, resulting in high numbers of variants of uncertain significance (VUS), and diagnostic uncertainty. *In silico* tools are frequently used during interpretation, but established methods lack specificity and are inconsistently applied. Here, we assess the utility of state-of-the-art computational tools in the classification of missense SNVs in five hereditary endocrine tumour genes (*MEN1*, *NF1*, *RET*, *SDHB*, *VHL*).
Methods
Fourteen recently reported computational variant prediction tools based on DNA sequence ($n=8$) or protein structure ($n=6$) were used to assess four groups of missense SNVs ('benign', 'pathogenic, 'VUS' and 'GnomAD rare') identified from publicly available repositories (ClinVar, LOVD, GnomAD), totalling > 7,400 unique variants. Relevant protein structures were obtained from Protein Data Bank and AlphaFold2. The performance of tools was assessed using multiple statistical metrics.
Results
The majority of sequence-based tools (e.g. ClinPred, VARITY, MutPred2) demonstrated good performance at standardised 'pathogenicity' cut-offs for differentiating known benign and pathogenic variants (e.g. sensitivity ~70-100%, specificity ~60-90%) and generally outperformed structure-based tools (Rhapsody and SNPMuSiC performing well for specific genes). However, all tools lacked discriminatory ability when classifying 'VUS' and 'GnomAD rare' SNVs with high proportions of deleterious variants predicted. The development of gene-specific 'pathogenicity' cut-offs for each tool improved specificity and the stratification of variant groups, which was further enhanced when concordance between combinations of the highest-performing tools was assessed.
Conclusions
Here, we demonstrate the utility of recently described computational variant prediction tools when applied to several hereditary endocrine tumour genes and advocate a gene-specific approach that incorporates combinations of tools to optimise specificity and clinical utility.

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P44

Abstract Withdrawn

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P45

Emergency Ambulatory Outpatient Management of Immune Checkpoint Inhibitor-mediated Hypocortisolaeamia

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Background

Immunotherapy mediated adrenocorticotrpic hormone (ACTH) deficiency is an important toxicity related to immune-checkpoint inhibitors (ICPi) potentially resulting in significant morbidity. Early diagnosis and optimal management are essential and frequently necessitate inpatient hospital treatment. We have previously reported an ambulatory management pathway for ICPi-induced ACTH deficiency in 4 patients. We sought to report the outcomes of this pathway in a larger cohort to validate its utility.

Methods

Patients presenting with clinical features and findings consistent with ICPi-induced hypocortisolaemia in the absence of severe features (sodium $\leq$125 mmol/l, hypotension, reduced consciousness, hypoglycaemia, visual field defects) have been managed using our ambulatory management pathway; briefly, suitable patients are administered a single intravenous dose of hydrocortisone (100 mg) and then observed for at least 4 hours and then discharged on oral hydrocortisone (20 mg, 10 mg, 10 mg) and an hydrocortisone emergency pack. Patients are then seen urgently in the endocrinology clinic for further assessment and management. We excluded patients with suspected adrenalitis, asymptomatic incidentally discovered hypocortisolaemia and with a history of exogenous glucocorticoid use.

Results

Thirteen patients (aged 40-79; 11 male) were managed using our pathway. All the patients had biochemically proven ACTH deficiency. The mean time from discharge to endocrinology outpatient follow-up was 8 days. There were no 30-day readmissions nor was there any associated hypocortisolaemia-related mortality. Every patient continued the ICPi therapy without interruption.

Conclusion

Our ambulatory care pathway has been utilised successfully to treat patients with ICPi-induced hypocortisolaemia. There was no observable adverse outcome related to its use and the adoption of this pathway for appropriate patients can potentially lead to reductions in hospital admissions, minimise interruptions to cancer care and enhance the patient experience.

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P46

Neuroendocrine Tumour (NET) patient satisfaction in the COVID-19 recovery period: A patient survey from a European Neuroendocrine Tumour Centre of Excellence

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Introduction

The COVID-19 pandemic has affected patient care and experience. We assessed the evolution of NET patient perceptions during and peri-pandemic via a bespoke patient satisfaction survey.

Methods

In February 2022, questionnaires with a pre-paid return envelope were posted out to 87 randomly selected NET patients, treated between January and December 2021. This consisted of 29 questions covering: initial contact, physician care and support, illness with COVID-19, experiences with telemedicine, and delays to care and treatment. Response types included free text and multiple-choice. The anonymised data was tabulated in an Excel spreadsheet, analysed numerically and thematically and then compared with 2017 and 2020 data.

Results

51 out of 87 responses were received. 90% of patients surveyed felt very well cared for by their NET physicians, up from 71% in 2020. In 2017, 77% reported receiving very or fairly good psychological support. This was 56% in 2020 but has since increased to 82% in 2021. 90% felt that the wait period before examinations or treatments was very or fairly acceptable, in comparison to 79% in 2020. None felt their chemo/radiotherapy was delayed. 8% reported their follow-up was delayed, down from 34% in 2020. 63% felt follow-up care was very well organised, 6% reported it was not. The free text highlighted patients' preferences for telemedicine as it removed travel time. Equally, it highlighted advantages of face-to-face appointments with patients feeling more reassured, allowing for examination, and preferable for the hard of hearing or those with a poor Wi-Fi connection.

Conclusion

The COVID-19 pandemic saw a reduction in patient satisfaction in 2020 in areas such as physician care and psychological support. The recovery period has demonstrated an improvement in patient satisfaction. The results have highlighted the importance of patient preference in choosing telemedicine and the value of organised follow-up care.

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P47

A Rare Occurrence of Phaeochromocytoma in an Adult with Previously Diagnosed Wilms Tumour - Case Report

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Introduction

Phaeochromocytoma affects $<$1:100000 people per year. Wilms tumour (WT) affects almost 1:10000 children each year. Both tumours are associated with somatic genetic alterations: Phaeochromocytoma (RET, VHL, NF1, SDHA, SDHAF2, SDHB, SDHC, SDCD, TMEM127 and MAX); WT (WT1, 11p13, 11p15, tp53, NSD1, KDM3B, BRCA2). Both tumours affecting the same person have only been reported twice in the literature.

Case Report

We report a lady who, at the age of 5 years, was diagnosed with left-sided WT and underwent left nephrectomy. At the age of 50, she complained of anxiety, palpitations and raised blood pressure despite taking anti-hypertensives. Plasma and urine metanephrines were raised and MRI scan showed 4.5x4.6x2.4 cm nodule in the left adrenal gland, ipsilateral to the previously diagnosed WT. Whole body MIBG scan showed increased uptake in the left adrenal mass consistent with phaeochromocytoma with no other uptake elsewhere. She responded well to alpha and beta blockade and has been listed for left adrenalectomy. The patient's grandmother had a renal cancer removed at the age of 30. There is no other family history of malignancies. Due to the occurrence of 2 primary malignancies, including phaeochromocytoma, and family history of a renal tumour, this patient has been referred for genetic screening.

Discussion

The diagnosis of phaeochromocytoma and WT in the same patient has only been described twice before, in one adult and one child, however neither had genetic analysis. Mutations predisposing to both WT and phaeochromocytoma are unknown and our case may help find a common mutation. All patients with phaeochromocytoma in our practice are referred for genetic screening but in addition, the presence of multiple primary malignancies should also trigger referral for genetic analysis. Detection of somatic genetic alterations associated with malignant diseases can play a vital role in the screening and early management of those life-changing conditions.

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P193

Clomiphene Citrate induced changes in the Estrogen and Estrogen receptors in the ovary of female Sprague-Dawley rats

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Endocrine therapy in hormone sensitive cancers is on the increase and substances that reduce estrogen level and upregulate estrogen receptor can reduce activities of ovarian cancer. Clomiphene citrate (CC) is a selective estrogen receptor modulator. This study is aimed at investigating how different doses of CC affect estrogen level and level of alpha and beta estrogen receptors in the ovary of adult female rats. Fifty female Sprague-Dawley (SD) rats were divided into 5 groups of 10 rats each. Group A (control) received sterile water. Groups B, C, D received 0.2 mg/kg, 2 mg/kg, 4 mg/kg of CC dissolved in distilled water at diestrus respectively. Group E was given 6 mg/kg of CC dissolved in distilled water daily via oral administration. Estrous cycle was monitored daily and the phases recorded. Serum analysis of estrogen level was done alongside the estrogen alpha (ERa) and estrogen receptor beta (ERb) levels after ovarian homogenization at different phases of the estrus cycle. In all the phases, CC caused a significant decrease ($P<0.05$) in estrogen level for groups D and E compared with control. Groups B and C showed significant ($P<0.05$) increase at metestrus. ERa did not change significantly ($P>0.05$) for groups B and C at proestrus and estrus phases but there is a dose-dependence changes at metestrus and diestrus in the treated groups (B, C, D, and E). Group B showed a significant decrease ($P<0.05$) in ERb across the phases compared with control. Meanwhile, ERb it significantly increased ($P<0.05$) in all the phases for Group E compared with control. Clomiphene citrate reduced the estrogen level and increase ERb at high dose. This shows that high doses of clomiphene could be useful as an adjunct in the management of ovarian cancer.

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P194

The incidence and clinical significance of metabolically active brown adipose tissue in patients with pheochromocytomas and paragangliomas: A retrospective cohort study, systematic review and meta-analysis

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There is limited research into the impact of active brown adipose tissue (aBAT) in patients with phaeochromocytomas and paragangliomas (PPGLs). A small body of evidence has shown that patients with PPGL patients can exhibit a high prevalence for aBAT recognized as ranging between 8 - 28% without specific correlation to germline mutations. Furthermore, it has been suggested that aBAT may be linked to increased mortality. Systematic searches of the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), EudraCT, ClinicalTrials.gov, medRvix CINAHL and Scopus databases were conducted. Our study was registered with PROSPERO international registry for systematic reviews with ID: CRD42021276073. Furthermore, we conducted a retrospective cohort study evaluating our records for patients between 2013-2021 with PPGLs who had an 18F-FDG PET/CT and metabolically aBAT. Meta-analytical calculations were performed using R software and SPSS was used for analyses of variables from our retrospective cohort study. Our systematic search produced 4 studies, the data of which were pooled into a meta-analysis including the data from our study. Our meta-analysis demonstrated a significant correlation between 18F-FDG PET/CT avidity and concentration of plasma metanephrines and normetanephrines using a random effect model ($P<0.05$). A total of 61 patients with PPGLs and 18F-FDG PET/CT were identified of which 8 (13%) had metabolically aBAT. A statistically significant correlation between SUVmax levels and number of locations with active BAT ($r=0.822$, $P=0.012$) was observed. A statistically significant difference in metadrenaline levels between mutational status clusters (Kruskal-Wallis statistic = 11.435, df = 2, $P=0.003$) with post-hoc analysis suggesting significant difference between clusters 1 (SDH/VHL) and 2 (MEN/RET), as well as between cluster 1 and control group. Patients with PPGLs exhibit a high prevalence of BAT activation on 18F-FDG PET/CT.

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P195

Repurposing Nandrolone, an Anabolic Steroid drug for Cancer Therapeutics: An In silico approach

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Finding novel drugs and repurposing existing ones have gained increasing attention in addressing various setbacks faced by researchers in cancer research and treatment owing to the increased cancer rate, low efficacy, availability, and affordability of cancer drugs. Thus, the goal of this research is to repurpose nandrolone (ND), an inexpensive and widely available anabolic steroid, to a potential anticancer therapeutic candidate. A computer-aided drug design approach (CADD) involving virtual screening was used to obtain the binding scores (kcal/mol) and inhibiting efficiencies (IC50 μ/mol) of ND against DNA Topoisomerase II Alpha (TOP2A), Cyclin D1, Cyclin-dependent kinases IV & VI (CDK4/6) and cancer cell lines (HEPG2, MHHNB11, SW1573, and SNU245) by employing PyRx, Pymol, Discovery studio, and PaccMann web tool. Data warrior tool and SwissADME online tool were used to conduct in silico pharmacokinetic studies involving drug-likeness and ADMET profiling of ND. The findings of these analyses were compared with the conventional (standard) cancer medicines (doxorubicin, palbociclib). Results of this study showed ND had a higher binding affinity for TOP2A, CDK4, and CDK6 with binding scores of -74kcal/mol; -5.9kcal/mol; and -9.4kcal/mol when docked into the binding pockets of three of the four proteins in comparison with that of the standards. Furthermore, it exhibited a high level of inhibitory activity against cancer cell lines with an average $IC_{50}=0.55$ and demonstrated good pharmacokinetics as it possesses the required ADMET (absorption, distribution, metabolism, excretion, and toxicity) criteria. In keeping with the findings from this study, nandrolone shows promising potential as an anticancer drug candidate. However, further studies using *in vitro* and animal models should be conducted to elucidate the underlying mechanisms of nandrolone in combating cancer.

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P196

Prevalence of vitamin B12 deficiency in neuroendocrine tumour-Single Centre Experience

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Background
Neuroendocrine tumours (NET) are heterogenous group of tumours commonly arising from Gastro-pancreatic (GI) and pulmonary origins. Combination of bowel resection, disease related diarrhoea and somatostatin analogue therapy (SSA) can contribute to vitamin B12 deficiency (B12D). International guidelines do not suggest routine screening. Total serum cobalamin (B12) level can be falsely normal in patients with B12D. Cells take up B12 in the form of Holotranscobalamin (HoloTC) and measuring HoloTC has greater diagnostic accuracy for B12D. NICE recommended its use in indeterminate cases (B12 level 135-300 ng/l).
Aim
We aim to investigate our practice of B12 deficiency in our NET service. Method: Data of all NET patients from May 2007-May 2022 were reviewed retrospectively.
Results
Total number of NET were113 (13 deceased, 55 females, mean age 70.33 year ± SD 10.7, 86 GI origin, 17 pulmonary and 10 other source. 61 (54%) had a serum B12 level measured since NET diagnosis and 12 (19%) had B12D ($P<0.0001$). Interestingly, only 7 were GI NET, 10 on SSA, 5 had bowel resection and on SSA. Additional 14 (23%) patients' cobalamin level were borderline. No HoloTC were carried out in those cases. Risk factors for B12D were present among those where cobalamin were not measured (36 GI NET, 21 bowel resection, 25 on SSA, and 6 had bowel resection and on SSA).
Conclusion
B12D is common in NET patients when assessment was carried out. Symptoms of B12 can be nonspecific and not all will have typical macrocytic anaemia pattern. We recommended implementation of measuring serum cobalamin and subsequent HoloTC for indeterminate cases as a routine interval investigation in patients with NET. This is especially important if they have one or more risk factors. Further evaluation such as national audit of practice of B12 and other micronutrient deficiency such as iron, zinc, vitamin D is also recommended.

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P197

Immunotherapy and its impact on the endocrine system: Guidelines a need of the hour

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Introduction
Endocrine dysfunctions are a well known side effect of Immunotherapy with check point inhibitors. Endocrine dysfunction can begin as early as 6 days post initiation of therapy. There is a growing consensus that prompt recognition and early management of these endocrinopathies is essential; however there is a lack of specific guidelines regarding the monitoring of endocrine function. We present a case report of an asymptomatic patient known to have renal cell cancer who presented with multiple endocrine abnormalities which were incidentally diagnosed.
Case Prsentation
A 43 year old gentleman was admitted with seizures. He was on ipilimumab and nivolumab for metastatic renal cell cancer, the first dose of which had been initiated 43 days ago and the second dose 14 days ago. He had no symptom of any endocrine dysfunction. His BP was 90/40 mm Hg. Routine evaluation showed ACTH deficiency (ACTH 6 pmol/l), low cortisol levels (41 nmol/l) along with low testosterone (7.7 nmol/l) low normal IGF-1 levels (7 nmol/l). Patient also had hyperthyroidism (TSH:0.09mIu/l, T3:6.6 pmol/l T4: 30 pmol/l) which on thyroid uptake scan was found to be secondary to thyroiditis. Seizures were found to be secondary to multiple brain metastasis. His blood pressure responded to cortisol replacement therapy. Unfortunately, due to rapid progression of the disease, he was put on palliative pathway and discharged with comfort care.
Discussion
The society for endocrinology clinical committee has recently endorsed a comprehensive management plan for the acute presentations of endocrinopathies post immunotherapy. However, to the best of our knowledge, no guidelines are there to help come to a diagnosis before the endocrine dysfunction have begun to manifest clinically. As the endocrinopathies can progress silently, suddenly manifesting with a catastrophic event, there is an urgent need to establish guidelines regarding the initiation and frequency of endocrine testing.

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P198

Acute life-threatening hyponatremia post first chemotherapy cycle with epirubicin and cyclophosphamide: Need for changing protocols?

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64 years old lady with history of breast cancer (post lumpectomy followed by radical mastectomy) received chemotherapy with Epirvlacin 140 mg and cyclophosphamide 600 mg 1 day prior. Past medical history included hypertension on ramipril and type 2 diabetes on diet control. Bloods on day of chemotherapy normal particularly sodium 135 mmols/l. Presented in 18 hours after 20 seconds tonic clonic seizure noted by family followed by abnormal flexion. Presented with GCS 7 which then dropped to 5/15 following which patient needed intubation and ventilation. Bloods on admission revealed severe metabolic acidosis with pH 6.90 HCO3 12.4 and lactate 10.2. Sodium 110 mmols/l (normal 135-145 mmols/l) with glucose 12 mmols/l. Given 150mls hypertonic saline which made sodium rise to 119 mmols/l and rapidly normalized in 24 hours. As felt to be acute hyponatremia, advised by endocrinology to avoid further rapid rise with 5% dextrose. Hyponatremia screen included low serum osmolarity 247 (Normal 260-290), random urine sodium was 60, urine osmolarity was 606. This was felt to be similar to an SIADH picture. Lipid profile, TSH were normal. 9AM cortisol and short synacthen test revealed a basal cortisol of 506, 30 minutes cortisol of 881 and 60 minutes cortisol of 1050. Renal function and liver function were normal. MRI Brain/Pituitary was normal. CSF analysis was negative. Therefore, it was opined that seizures were related to medications rather than an intracranial pathology. Patient was gradually stepped down to ward and remained well without fluid restriction. This case highlights the importance of recognising complications associated with medications in chemotherapy day units particularly acute hyponatremia and calls into question whether we need a change in practice and monitoring/admission of these patients post chemotherapy for monitoring.

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P322

Investigating the role of cell fate regulator *ASCL1* in driving and maintaining lethal neuroendocrine castrate resistant prostate cancer

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Neuroendocrine castrate resistant prostate cancer (NE-CRPC) is a lethal CRPC subtype that arises as prostate cancer cells transdifferentiate to neuroendocrine cells, evading the potent selective pressure of androgen deprivation therapies (ADT). Currently, clinicians lack biomarkers to detect NE-CRPC evolution and specific therapies to target it. With ~50% of prostate cancer (PC) patients receiving ADT and NE-CRPC accounting for ~25% of CRPC deaths, CRPC and NE-CRPC are a significant clinical challenge. Whilst neuroendocrine transdifferentiation (NEtD) of PC is not fully understood, there are several parallels between NE-CRPC and small cell lung cancer (SCLC); an aggressive neuroendocrine lung tumour. Driver of neurogenesis, *ASCL1*, is essential for SCLC survival and SCLC switching to a neuroendocrine-like lineage to escape chemotherapy. We have shown *ASCL1* induction accompanies NEtD of PCa. Whether *ASCL1* actively initiates NEtD of CRPC and/or maintains the NE-CRPC phenotype is unknown. We investigated *ASCL1*'s role in driving NEtD by culturing androgen-sensitive LNCaP cells in androgen-deprived conditions with the potent anti-androgen, Enzalutamide, to model NEtD. *ASCL1* target genes (*DLL1*, *DLL3*, *HES6*), cell fate (*NOTCH1-3*), androgen signalling (*AR*, *KLK3*) and neuroendocrine (*ENO2*, *TUBB3*) gene expression was analysed by qRT-PCR. Morphological and molecular changes associated with NEtD of LNCaP cells (loss *KLK3*, induction of *ASCL1*, *ENO2* & *TUBB3*) were accompanied by marked induction of *DLL1* and *NOTCH3*. Temporal analysis showed initial induction of *ASCL1* that was sustained and accompanied by an initial increase, and subsequent decrease in *DLL1* expression, suggesting these may be involved in driving NEtD. CRISPR knockout will ascertain if *ASCL1* is essential to initiate and maintain NEtD of LNCaP cells. This data indicates *ASCL1* is active during early NEtD of CRPC by inducing direct and indirect target genes that may initiate NE-CRPC formation, akin to SCLC evolution. In future, this knowledge may facilitate development of precision therapies to target lethal NE-CRPC.

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P323

Managing PPGL surveillance in the COVID-19 recovery period: experience of a newly-established Endocrine Genetics MDT

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Background
Lifelong surveillance should be offered to people with hereditary phaeochromocytoma and paraganglioma (PPGL), including asymptomatic carriers of pathogenic gene variants. Regular biochemical and radiological surveillance aims to improve disease detection and prognosis. During the COVID-19 pandemic, outpatient appointments were cancelled or postponed. Departments continue to face large backlogs of work. Clinicians in the USA reported 15% PPGL patients missing at least one element of their care. Anecdotally, in our centre, PPGL surveillance has been markedly disrupted.
Methods
We set up a twice-yearly multidisciplinary team (MDT) meeting, comprising consultants in Endocrinology and Clinical Genetics, specialist nurses, and trainees. At each meeting, the electronic records of PPGL patients are reviewed. We agree surveillance plans, based on consensus statements and assessment of individual risk. We assign 'red' surveillance status to those overdue investigations or follow-up, 'amber' to those awaiting results, and 'green' to those whose surveillance is up-to-date.
Results
Between meetings in November 2021 and June 2022, the PPGL cohort under our care increased from 30 to 34 patients. Of these, SDHB mutation carriers comprise the largest proportion. People with MEN are discussed in a separate MDT. The number of people up-to-date with surveillance increased from 60% to 65% between meetings. In November 2021, 23% were overdue surveillance; by June 2022, all of these bar one were up-to-date. 18% patients had 'red' status in June 2022, however, with the majority not offered appointments within the timeframe specified in their surveillance plan.
Conclusions
Coincident with service disruption, surveillance has been delayed for people with PPGL conditions. In our experience, MDT meetings have produced a small improvement in rates of patients up-to-date with care. A joint approach to surveillance planning is welcomed by the clinical team. Plans to run cohorted clinics and assess patient satisfaction will help to improve and refine service provision further.

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Metabolism, Obesity and Diabetes

P48

Spatial proteomics of skeletal muscle isolates high-fat diet produced inflammatory events

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Metabolic dysfunction in skeletal muscle disturbs both the critical vascular network and fundamental muscle fibre architecture. However, the molecular drivers during metabolic stress responsible for transmitting these events remain poorly defined. To reveal these we mapped changes in the spatial proteome occurring as a result of impaired metabolic health. We exposed male and female mice (C57/BL6J) to high fat diets and conducted digital spatial profiling (NanoString GEOMX) on skeletal muscle comparing it to standard chow controls($n=12$). Male ($n=6$) and female mice ($n=6$) were fed $\pm$high fat diet (60% kcals from fat) for 8 weeks. Skeletal muscle tissue (tibialis anterior) was collected and sectioned for spatial profiling. Samples were also cryosectioned for immunofluorescence with the muscle marker Desmin and endothelial cell marker CD31, to highlight the vascular networks within the tissues. Digital spatial profiling within HFD muscle defined regions demonstrated reduced Desmin immunoreactivity (control diet 55,0000 $\pm$ 5430.0 vs high fat 15,1533 $\pm$ 0.15 $P<0.01$) and elevated CD31 expression (control diet 7.99 $\pm$ 0.15 vs high fat 10.04 $\pm$ 0.15 $P<0.05$), markers of tissue stress and cellular maladaptation. We find that increased expression of proinflammatory markers (CD68 $P<0.001$, CD39 $P<0.05$, and CD40 $P<0.01$) was identified in areas of depleted Desmin in high fat diet samples compared to control. Our data suggest a dietary driven relationship between the spatial abundance of the sarcomere protein Desmin and the influx of inflammatory mediators. This supports the notion that pro-inflammatory events underpin the muscle metabolic dysfunction associated with chronic non-communicative diseases such as type 2 diabetes, metabolic ill health, and chronic obstructive pulmonary disorder.

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P49

Investigating NtsR1-expressing neurons extending from the duodenum to pancreas

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Neurotensin is widely expressed in the brain and gastrointestinal tract. Centrally, neurotensin acts as a neuropeptide to suppress appetite, induce hypothermia and modulate analgesia. Peripherally, neurotensin inhibits gastric emptying and is reported to aid lipid absorption. There is also evidence that neurotensin can influence glucose homeostasis, though this role is contentious. We have found that neurotensin acutely improves insulin release and glucose tolerance in mice, and that this effect is mediated via the neurotensin receptor 1 (NtsR1) but does not require central or vagal NtsR1 signalling. We therefore investigated peripheral NtsR1 neurons in the enteric nervous system and their connections to the pancreas. Using a NtsR1-Cre::Ai9 reporter mouse model, we have visualised NtsR1-expressing entero-pancreatic neurons. NtsR1-Cre::Ai9 mice express Tdtomato red fluorescent protein, which is flanked by a loxP STOP cassette within the Ai9 construct, exclusively in NtsR1-expressing cells as a result of cre-mediated recombination. From these mice, the first centimetre of the proximal duodenum and adjacent pancreatic section was harvested and cleared for whole-mount imaging using RTF tissue clearing, a simple immersion type technique to homogenise the overall refractive index of the tissue. Confocal imaging revealed that a population of NtsR1-expressing neurons extend from the myenteric plexus of the duodenum into the pancreas. Whole-mount immunostaining, using the iDISCO technique for labelling large volumes, revealed that NtsR1-expressing neurons within the pancreas approach and surround islets and appear to innervate them directly. Further work is now required to determine whether neurotensin mediates its effect on glucose homeostasis via these neurons and whether this system can be exploited pharmacologically to treat metabolic disease.

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P50

Single-nucleus RNA sequencing identifies wide-ranging changes in gene expression in mouse nodose ganglia cell populations in response to fasting

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Obesity is a leading global health concern. The gut-brain axis is critical to appetite regulation. The vagus nerve represents the major neural pathway between the gastrointestinal tract and the central nervous system, capable of rapidly communicating information about the nutrient content from different regions of the gastrointestinal tract, directly via nutrient receptors expressed on vagal afferents and indirectly by responding to gut hormones and enteric nervous system signalling. The cell bodies of vagal neurons reside in the nodose ganglia, and these cells are known to express various mechano- and chemoreceptors, allowing the body to appropriately regulate processes including gastric motility and appetite. Recent studies have characterised the cell populations comprising the nodose ganglia, but there has been little investigation into how changes in physiological state can alter the gene expression profiles of these cells. Given the importance of vagal signalling in appetite and metabolism, we investigated the response of nodose ganglia cells to fasting. 10X single-nucleus RNA sequencing was performed on left and right murine nodose ganglia extracted from fed and 12-hour fasted mice (n = 10, pooled). 1832 nuclei were analysed and identified as belonging to 19 different nodose ganglia cell clusters. There was no difference in cell types between left and right ganglia or fasted and ad libitum status. However, there were wide ranging changes in gene expression across cell types in response to fasting, with neuronal cells showing significant changes in 5008 genes. These included changes in the expression of receptors involved in energy and glucose homeostasis, including the leptin and insulin receptors in specific cell types. These data demonstrate the profound changes in gene expression that occur in nodose ganglia cells in response to altered nutritional status and provide insight into putative targets for the treatment of metabolic disease.

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P51

Regulation of 5-HT secretion from human duodenal enterochromaffin cells

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The majority of the body's 5-HT (serotonin) is produced from enterochromaffin cells (ECs) of the intestinal epithelium. 5-HT has important roles within the gastrointestinal tract in the modulation of motility, secretion and inflammation, while also signalling satiety and discomfort to the central nervous system. The factors regulating release of 5-HT from human small intestinal ECs have not been clearly elucidated: although circulating 5-HT levels typically increase after a meal and EC-derived 5-HT is a critical postprandial satiety signal, the importance of direct nutrient stimulation of ECs vs paracrine regulation by other gut hormones – including GLP-1 – remains debated. To investigate the mechanisms of 5-HT release from ECs, organoids established from human duodenum, ileum and rectum were CRISPR-Cas9-modified to fluorescently label tryptophan hydroxylase 1 (TPH1) expressing ECs. Bulk RNA sequencing was performed on human duodenal ECs purified by fluorescence-activated cell sorting and this dataset was considered in parallel with single cell RNA sequencing of human small intestinal enteroendocrine cells, isolated based on chromogranin A expression. The long-chain fatty acid receptor FFAR1 was notably absent in duodenal ECs but most other nutrient-sensing receptors were significantly enriched, including the amino acid responsive GPR142, the short-chain fatty acid receptor FFAR2, the monoacylglycerol receptor GPR119 and the bile acid receptor GPBAR1. Receptors for several gut hormones (including GIP, insulin-like 5 and somatostatin) were also significantly enriched in duodenal ECs, with GLP1R detectable at lower levels. Consistent with transcriptomic data, single cell calcium and cyclic AMP imaging suggests a stimulatory role for several short-chain fatty acids, the aromatic amino acid tryptophan and adrenergic agonists in duodenal EC subpopulations. Ongoing work aims to measure 5-HT secretion from human duodenal organoids in response to these potential regulators of EC function. Collectively this data will provide novel insights into the physiological control of 5-HT release from human small intestine.

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P52

Nrf2 activator Sulforaphane attenuates maternal adiposity and hepatic steatosis

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Intro/Aims
Maternal obesity is a major risk factor for the development of first onset of diabetes in pregnancy, also known as gestational diabetes mellitus (GDM). Recent studies also indicate that non-alcoholic fatty liver disease (NAFLD) is an independent predictor of GDM. Sulforaphane (SFN) is a well-known dietary activator of the redox-sensitive transcription factor Nrf2, with reported anti-adipogenic and NAFLD ameliorating effects in non-pregnant obese rodent models. In this study we sought to determine whether sulforaphane could exert metabolic protection in GDM murine dams.
Methods
Wildtype (WT) and Nrf2 deficient C57BL/6 dams were fed a highly palatable obesogenic diet 6 weeks prior to pregnancy, then received either vehicle (corn oil) or SFN throughout pregnancy and the postpartum period. Bodyweight was measured throughout the developmental period, with visceral and subcutaneous adiposity (parametrial and inguinal fat pads, respectively measured relative to bodyweight and tibia length) determined upon post-partum termination. H&E staining of liver tissue was used to quantify maternal steatosis.
Results
SFN significantly reduced postnatal weight retention, with a reduction in subcutaneous inguinal adipose tissue depots noted in WT not Nrf2 deficient dams. Preliminary results also indicate that hepatic lipid deposition quantified as % lipid area and mean lipid area were also attenuated by SFN intervention in WT not Nrf2 deficient dams.
Conclusion
SFN exerts maternal metabolic protection against obesogenic dietary feeding, reducing subcutaneous adipose deposition as well as liver lipid accumulation. Protection is ameliorated in Nrf2 deficient dams suggesting that SFNs protective effects are mediated via Nrf2 activation.

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P53

Pharmacological potential of annona squamosa ameliorates insulin secretion from clonal pancreatic β-cells and regulates blood glucose in type 2 diabetic rats

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Annona squamosa has been shown to have anti-diabetic properties, although the underlying mechanisms are not fully known. In the present study, ethanol extract A. squamosa (EEAS) leaf were investigated *in vitro* and *in vivo* , to elucidate the mechanism underlying anti-diabetic actions. EEAS significantly ($P<0.05$–0•001) increased insulin release 2.2-5.5-folds at 5.6 mM/16.7 mM glucose at concentrations between 8-5000μg/ml from BRIN-BD11 cells. Similar insulin secretory responses to 25-200μg/ml EEAS were seen using isolated mouse islets with stimulatory effects comparable to 1μM GLP-1. Insulinotropic effects of EEAS (200μg/ml) on BRIN-BD11 cells were significantly inhibited by verapamil (30%), diazoxide (38%) and calcium free conditions (62%) showing importance of ion channels and Ca2+ in mechanism of action. Insulin secretion was further potentiated by activation of multiple pathways using IBMX (200μM, 1.5-fold, $P<0.001$), tolbutamide (200μM, 1.5-fold, $P<0.05$) and KCl (30 mM, 1.4-fold, $P<0.001$). At 200μg/ml, EEAS induced membrane depolarization and increased intracellular Ca2+ by 7 and 7.5-folds, respectively. EEAS significantly inhibited starch digestion, protein glycation, DPP-IV enzyme activity and glucose diffusion *in vitro*. In addition, EEAS increased transport of glucose and insulin action in 3T3-L1 adipocytes. Following the ingestion of sucrose, EEAS substantially reduced postprandial hyperglycaemia and increased unabsorbed sucrose content throughout the GIT. EEAS reduced glucose absorption during *in situ* gut perfusion with glucose. EEAS inhibited intestinal disaccharidase enzyme activity and increased gastrointestinal motility. Thus, EEAS improves glycaemic control through a variety of mechanisms. Further studies are needed to identify the molecular compounds of EEAS that play a vital role in the treatment of type 2 diabetes mellitus.

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P54

Metabolic Endotoxemia impacts mitochondrial function and adipocyte browning in a depot specific manner in Human abdominal adipose tissue

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Introduction
Central obesity is a significant risk factor for type 2 diabetes mellitus (T2DM), with omental adipose tissue (AT) particularly involved in such risk. Additionally, obesity can cause low-level gut-derived endotoxemia, which may drive metabolic dysfunction in AT through mitochondrial damage and reduced BRITE (brown-in-white) adipocytes. Bariatric surgery reduces obesity and may prevent such dysfunction. This study investigated whether endotoxin: 1) impairs mitochondrial function and reduces browning in human AT, 2) has a depot specific effect on pathogenic risk, 3) has reduced impact following bariatric surgery.
Methods
Ex-vivo AT was collected from human abdominal subcutaneous (AbdSc) and omental (AbdOm) depots ($n=134$) from Caucasian women (lean:BMI = 22.3 ± 1.9 kg/m2, age = 32.0 ± 5.2, $n=38$; overweight (OW):BMI = 27.3 ± 1.4 kg/m2, age = 31.5 ± 7.5, $n=40$; obese (OB):BMI = 38.1 ± 6.1 kg/m2, age = 40.8 ± 12.9, $n=63$). Sub-cohort analysis of participants with severe obesity (BMI > 35 kg/m2) examined AbdScAT pre- and post-bariatric surgery (BMI = 42.2 ± 5.6 kg/m2, age = 54.5 ± 5.9, $n=26$). Mitochondrial function and adipocyte browning genes, and serum endotoxin were assessed.
Results
With increased weight, rising endotoxin levels correlated with reduced mitochondrial fission and fusion in AbdOmAT, noted by FIS1 ($P<0.05$, r = -0.37, OW), DRP1 ($P<0.05$, r = -0.43, OB), and OPA1 ($P<0.05$, r = -0.39, OB); no such associations were observed in AbdScAT depot. Rising endotoxin levels also correlated with reduced BRITE gene expression in AbdOm from participants classed as overweight, indicated by Cidea ($P<0.05$, r = -0.3962), ELOVL3 ($P<0.05$, r = -0.42), PLIN5 ($P<0.01$, r = -0.46) and SLC27A2 ($P<0.01$, r = -0.48); this was not observed in AbdScAT. Endotoxin change with bariatric surgery negatively correlated with brown gene change ($P<0.05$).
Conclusion
These data suggest that gut-derived endotoxemia may impair mitochondrial function and reduce adipocyte browning in abdominal AT. This appears to preferentially impact AbdOmAT over AbdScAT, and may therefore have more profound metabolic consequences. Overall, these data highlight that reduced gut-derived endotoxin may improve AbdAT mitochondrial health and BRITE adipocyte development, and therefore lower metabolic risk.

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P55

Effect of sulforaphane, an activator of the Nrf2 antioxidant defence pathway, on maternal adiposity in a model of diet-induced insulin resistant pregnancy

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The incidence of maternal obese and/or gestational diabetic (GDM) pregnancy are increasing globally, with ~10-20% of mothers classified as obese and/or GDM within the U.K. Both obese and GDM pregnancy are associated with increased risk of cardiometabolic disease, with mothers and their children at greater risk of developing later-life Type 2 diabetes, obesity and/or cardiovascular disease. Higher adiposity in pregnancy leads to increased inflammation, which may be countered by antioxidant defence genes regulated by the transcription factor Nrf2. Dietary activators of Nrf2 such as sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetables such as broccoli, may therefore be used as anti-obesogenic cardiovascular protectants. In this study we examined the effect of SFN on maternal adiposity. C57BL/6 WT and Nrf2 deficient dams were fed a highly palatable obesogenic diet 6 weeks prior to pregnancy, then received with vehicle (corn oil) or SFN throughout pregnancy and the postpartum period. Inguinal and parametrial fat pads were weighed at termination, tissued fixed with 5μm sections stained with H&E to measure adipocyte area. SFN treatment reduced maternal inguinal and to a lesser extent parametrial adipose depots in WT dams. Nrf2 deficient dams treated with SFN showed no change in adipose fat pad mass. Preliminary data showed parametrial adipocyte area was reduced by SFN treatment in WT not Nrf2 deficient dams, however Nrf2 deficiency by itself resulted in a reduced adipocyte size. In summary, SFN has anti-adipogenic properties and appears to mediate its effects through Nrf2, however Nrf2 deficiency by itself alters adipose morphology.

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P56

Macrophage-specific SHIP2 knockdown mice display sex-dependent liver steatosis

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Background
Non-alcoholic fatty liver disease (NAFLD) is a spectrum of progressive liver diseases driven in part by macrophages, occurring in the absence of excessive alcohol consumption that ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), ultimately progressing to fibrosis/cirrhosis and hepatocellular carcinoma. NAFLD is associated with insulin resistance and confers an increased risk of cardiovascular disease. Pre-menopausal women are protected against NAFLD, which has been provisionally attributed to oestrogen levels and/or differences in sex hormone receptor expression levels in immune cells, but definitive mechanisms are unclear. SHIP2 is a 5' lipid phosphatase which acts as a negative regulator of the PI3K arm of insulin signalling. SHIP2 is expressed in insulin sensitive mouse and human cells including macrophages. Mouse studies overexpressing SHIP2 or knocking out SHIP2 show dramatic effects impacting insulin sensitivity and protection from obesity.
Methods
To explore the impact of macrophage specific-insulin resistance on NAFLD progression we generated a novel mouse model of macrophage-specific SHIP2 catalytic activity knockdown (M-SHIP2 ^{KD}).
Results
The M-SHIP2 ^{KD} model is viable, fertile, and exhibits normal development. Bone marrow derived macrophages (BMDM) from M-SHIP2 ^{KD} display expression of the catalytically inactive SHIP2 mRNA and altered response to insulin. Despite no high-fat high-cholesterol diet challenge, 12 month old male mice reveal increase in abundance and size of lipid droplets in their livers compared to controls. Female M-SHIP2KD mice at 12 months of age do not exhibit fatty livers compared to controls. Ongoing transcriptomics analyses from liver samples are revealing multiple significant differentially regulated genes in male vs female livers.
Conclusion
Macrophage-specific insulin resistance through SHIP2 knockdown in aged mice without diet challenge results in lipid droplet accumulation in the livers of male mice only, females are protected, which may be reflective of the protective effects that premenopausal females exhibit in the clinical situation.

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P57

Parameters associated with neutrophil to lymphocyte ratio in patients with severe obesity

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Obesity has been associated with a status of subclinical inflammation. Neutrophil to lymphocyte ratio (NRL) is a widely available and inexpensive inflammatory marker which can be reliable in evaluating the inflammatory status occurring in patients with severe obesity The aim of our study was to investigate the association between NLR and anthropometric and body-composition parameters, in a group of patients with obesity
Patients and Methods
737 patients with obesity, consecutively evaluated in our tertiary endocrinology center were included. They were all clinically evaluated (medical history, basic clinical examination, blood pressure and anthropometric measurements). Blood tests were performed for all patients (including complete blood count with NLR measurement, lipids and glucose profile). For a subgroup of 334 patients, whole body DXA scans were performed to analyse body composition (total fat mas, total lean mass)
Results
Our group included 264 men and 473 women with obesity, mean age 41.31 ± 11.2 years, mean BMI 44.7 ± 7.9 kg/m2. NLR was higher in women (2.24 ± 0.9 vs 2.03 ± 0.8, $P < 0.05$) and, in univariate analysis, positively correlated with BMI ($r = 0.174$, $P < 0.01$), waist circumference ($r = 0.09$, $P = 0.02$), and waist/height ratio ($r = 0.134$, $P < 0.01$). There was no impact of diabetes status on NLR values, but hypertensive patients had higher NLR values ($P < 0.05$). In the subgroup of patients with body composition analysis, NLR positively correlated with total fat mass ($r = 0.136$, $P = 0.019$) and gynoid fat mass ($r = 0.179$, $P = 0.002$), but not with lean mass (total or regional). In a linear regression analysis, with NLR as dependent variable and factors previously shown to significantly correlate to its level as independent variables, gender and BMI remained independently associated with NLR
Conclusions
Gender and adiposity level, but not lean mass, are factors associated with NLR in patients with severe obesity

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P58

Weight reduction in diabetic adult male wistar rats model using aqueous and ethanolic extract of Zingeber officinale and Allium sativum

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Introduction
When an individual predisposed to diabetes has excess weight, the cells in the body become less sensitive to the insulin which regulate blood sugar level. Ginger (Zingiber officinale) and Garlic (Allium sativum) are plants that have been acknowledged over years for their medicinal and therapeutic effects on mammals.
Aim of The Study
Was to determine the effect of ethanolic and aqueous extract of Zingiber officinale and Allium sativum on weight reduction of streptozotocin induced diabetes mellitus in adult male wistar rat model.
Materials and Methods
Thirty six (36) adult male wistar rats weighing 100g-210g were used and divided into 9 groups (Normal control, diabetes control, metformin treated control, ethanolic extract of ginger, ethanolic extract of garlic, aqueous extract of ginger, aqueous extract of garlic, aqueous extract of ginger + garlic and ethanolic extract of ginger+ garlic). Diabetes was induced intraperitoneally with streptozotocin (35 mg/kg) and was confirmed using Accu-check glucometer. Treatment followed for two weeks with the administration of aqueous and ethanol extract of ginger and garlic as grouped respectively. The weight and blood glucose level of the rats were assayed and were subjected to analysis
Results
Showed that there was a significant ($P < 0.05$) reduction in the body weight of the rats treated with aqueous and ethanolic extract of Zingiber officinale & Allium sativum when compared with the diabetic group. However, the normal control group showed a significant increase in the body weight compared to other groups. There was associated significant decrease in the concentration of blood glucose ($P < 0.05$) in groups treated with aqueous and ethanol extract of Zingiber officinale and Allium sativum compared with metformin treated group only
Conclusion
Aqueous and ethanolic extract of Zingiber officinale and Allium sativum produced a significant weight reduction and anti-diabetic effect in diabetic rats than metformin (standard drug).
Keywords
Zingiber officinale, Allium sativum, Weight reduction, streptozotocin
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P59

The role of glucocorticoid activation by 11bHSD1 for muscle wasting in a mouse model of renal impairment

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Background
Chronic kidney disease aggravates loss of skeletal muscles mass and function, which is an independent risk factor for hospitalisation, morbidity and mortality. Glucocorticoid signalling has been implicated as a critical factor in the pathogenesis of muscle atrophy in kidney disease. This study tests whether genetic deletion of the glucocorticoid-activating enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11bHSD1) protects against muscle atrophy in the adenine-diet mouse model of renal impairment.

Methods
The experiment used 9-week-old male mice with wild-type (WT) or global 11bHSD1 knock-out (11bKO) genetic background. Persistent renal impairment was induced through dietary exposure to adenine. Animals received either normal chow or chow supplemented with 0.15% adenine for 7 weeks ($n=8$-11 animals per experimental group). Grip strength was measured as a readout of muscle function *in vivo* . Quadriceps, soleus and tibialis anterior muscles were dissected post-mortem for measurement of muscle weights.
Results
Adenine-induced renal impairment led to a significant reduction in quadriceps muscle weight in WT mice (-19.4%, $P<0.001$) and in 11bKO mice (-16.0%, $P<0.001$). The reduction in quadriceps muscle weight was not significantly different between WT and 11bKO groups. Adenine treatment also led to a comparable muscle weight reduction in WT and 11bKO mice for soleus muscle (WT: -20.2%, $P<0.01$; 11bKO: -19.0%, $P<0.01$), but not for tibialis anterior muscle (WT: -3.3%, $p>0.05$; 11bKO: -5.7%, $p>0.05$). Mean grip strength was not significantly different between adenine-treated WT and 11bKO mice (148.7g vs 133.1g, $p>0.05$). There was no discernible phenotype divergence with genetic deletion of 11bHSD1 in the control condition of normal chow in terms of body weight, muscle weights or grip strength.
Summary
Genetic deletion of 11bHSD1 did not reduce skeletal muscle atrophy in the adenine-diet mouse model of renal impairment. Quadriceps and soleus muscles were more susceptible to atrophy than tibialis anterior muscle in the adenine-diet mouse model of renal impairment.

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P60

Asprosin exerts pro-inflammatory effects via the TLR4 pathway in THP-1 macrophages

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Background
Adipose tissue exhibits an altered adipokine secretion profile in obesity which is pro-inflammatory and relates to higher risk of cardio-metabolic diseases. Asprosin is a novel pleiotropic adipokine with orexigenic and glucogenic effects which is secreted in response to fasting. Elevated circulating asprosin levels have been shown in obesity and type 2 diabetes, as well as in other cardio-metabolic diseases. Furthermore, *in vitro* studies have reported pro-inflammatory effects of asprosin in various tissues. Previously, we have shown that asprosin acts partly via the NFkB pathway to induce an acute pro-inflammatory response in THP-1 macrophages. The present study aimed to investigate the *in vitro* effects of a Toll-like receptor 4 (TLR4)-specific signalling inhibitor (TAK-242) on THP-1 macrophages.
Methods
THP-1 monocytes were differentiated to macrophages by 48-hour treatment with 100 nM Dihydroxyvitamin D3. Macrophages were treated with 100 nM recombinant human asprosin, 100 ng/mL LPS and 1μM TAK-242. The expression and secretion of pro-inflammatory mediators were measured by qPCR, western blot, ELISA and Bioplex.
Results
Asprosin stimulation significantly upregulates the expression and secretion of pro-inflammatory cytokines; TNFα, IL1β, IL8, and IL12. Furthermore, a 15-minute asprosin stimulation increased the phosphorylation of AMPK, JNK and NFkB. Pre-treatment with TAK-242 significantly inhibited gene expression and release of key pro-inflammatory cytokines, including TNFα ($P=0.0028$ and $P=0.023$, respectively), IL1β ($P=0.0004$ and $P=0.021$, respectively) and IL8 ($P=0.0012$ and $P=0.0126$, respectively). Furthermore, TAK-242 treatment significantly inhibited MCP1 secretion ($P=0.0001$) in THP1 macrophages.
Conclusion
Asprosin induces a pro-inflammatory response in macrophages which is significantly inhibited by a TLR4-specific signalling inhibitor. Although further studies are still required to identify the complete signalling pathways involved, the present findings suggest that the asprosin-induced pro-inflammatory effects are partly mediated through the TLR4 signalling pathway.

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P61

Growth hormone increases at the onset of lactation and promotes mammary metabolism: Insights from clinical and cellular studies

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Increased mammary metabolism after child-birth supports the synthesis of milk components and is critical for initiating lactation during postpartum days 1-4. We utilised clinical and cellular approaches to investigate whether growth hormone (GH), which is reported to increase milk yield in breastfeeding women, may play a role in initiating lactation and promoting mammary metabolism. We recruited $n=30$ pregnant women (age range 24-41 years) following informed consent and measured serum GH at 36 weeks' gestation and on postpartum day-4. All women had term births and initiated lactation by postpartum day-4. Serum GH significantly increased at the onset of lactation (0.5 ± 0.1 mIU/l on postpartum day-4 *vs.* 0.2 ± 0.02 mIU/l at 36 weeks' gestation, $P<0.05$). We next assessed the effects of GH in cultured primary human mammary cells (HMECs). Recombinant human GH (rhGH) caused a dose-dependent increase in the phosphorylation of Akt, which is a key signalling protein required for initiating lactation. Thus, 50 ng/mL and 500 ng/ml rhGH caused ~1.5-fold and ~2-fold increases in Akt phosphorylation, respectively ($P<0.05$, $n=4$ experiments). Phosphorylated Akt also influences oxidative phosphorylation and glycolysis, and we assessed these processes by measuring extracellular O_2 and pH, respectively, in HMECs treated with rhGH. Administration of 50 ng/mL rhGH did not affect pH, but after 30min caused a significant increase in the rate of O_2 consumed by these cells (579 ± 28 vs. 456 ± 14 pmol O_2/min/10^6 cells for control HMECs, $P<0.01$, $n=4$ experiments), consistent with an upregulation of oxidative phosphorylation. Reverse transcription-quantitative PCR (RT-qPCR) of HMECs treated with 50 ng/mL rhGH for 24hrs demonstrated a significant increase in the expression of the *ATP5A1*, *ATP5C1* and *ATP5F1* genes ($P<0.05$, $n=4$ experiments), which all encode subunits of the mitochondrial ATP synthase. In summary, these clinical and cellular studies highlight a pivotal role for GH in promoting mammary cellular metabolism at the onset of lactation.

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P62

Effects of ethanolic extract of Allium Sativum L on the hippocampus of male Wistar rats with Streptozotocin (STZ)- induced brain insulin resistance

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Alzheimer's disease (AD) development has a direct relationship with Brain-insulin resistance. Central in the pathology of AD are beta-amyloid and tau proteins associated with cognitive decline in the hippocampus. *Allium sativum L.* has been shown to have a neuroprotective effect. Thirty-two male Wistar rats (80-150 g) were assigned into A-D ($n=8$ each), and housed in standard plastic cages at 23 ± 1°C. Group A received saline , groups B and C were administered 3 mg/kg of streptozotocin while C was then treated with 300 mg/kg of *Allium sativim L.*, group D received only 300 mg/kg of *Allium sativum L.* Intracerebroventricular method was utilized for STZ administration; *Allium sativum L.* ethanolic extract administration was orogastrically; administration in all groups lasted for 21 days. Elevated plus maze and Y-maze was used to assess behaviours, after which rats were sacrificed by cervical dislocation. Following brain removal, the hippocampus was excised and processed for Cytoarchitecture (H&E, Cresyl Fast violet), Neurotransmitters (Gamma Amino Butyric Acid and Glutamate), immunohistochemical (amyloid beta protein) and RNA (Insulin receptor substrate, glycogen synthase kinase and Beta-region amyloid precursor protein cleaving enzyme 1) assays. The data obtained were analysed by ANOVA and identification of mean differences by Turkey's *posthoc* test. The intervention group C showed good explorative activities, *Allium sativum L*, reduced significantly the expression of amyloid beta proteins as well as improved overall cytoarchitecture in the hippocampus. The increased expression of insulin, insulin

receptor substrate, GSK-β3 and BACE-1 proteins in the STZ groups suggests its role in the onset of amyloidogenesis. This study reported an overall inhibition of hippocampal functions as a result of STZ as well as the neuroprotective intervention of *Allium sativum L* in the brain metabolic pathways whose modulatory effects should also be studied at graded doses.

Keywords
Alzheimer's disease, brain insulin sensitivity, Allium sativum L, hippocampus
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P63

Is SIMBA impactful in improving participants' confidence in managing cases of obesity via simulation-based learning, irrespective of the mode of attendance or country of residence?

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Introduction
Simulation via Instant Messaging - Birmingham Advance (SIMBA) is a simulation learning modality designed to recreate real-life clinical scenarios, in a safe environment to help improve participants' confidence in solving such cases.
Objective
To study SIMBA's effectiveness in improving confidence in managing obesity-related cases and whether the country of residence and modality of attendance influence change in confidence.
Methods
Participants solved four obesity-related cases via Whatsapp in real-time. Moderators used standardised transcripts, developed using anonymised patient notes and presented to participants in an interactive live-simulation which involved clerking, diagnosing and managing a patient. Following simulation, a specialist chaired an interactive session to answer participants' queries about simulated cases, both in-person and via Zoom. The change in participants' confidence levels before and after simulation was measured using the Wilcoxon signed-rank test. We compared the difference between participants based on their country of residence and mode of attendance using Kruskal-Wallis test.
Results
27 participants completed both surveys and were divided into three groups (A = UK in-person ($n=12$); B = UK virtual ($n=6$); C = non-UK virtual ($n=9$). There was a significant improvement in confidence for simulated (37.0%, $P<0.001$) and non-simulated (13.0%, $P<0.001$) cases, with higher improvement in simulated cases. Improvements were seen in clinical competencies (55.5%), patient management (85.1%), practice-based learning (70.3%), system-based practice (51.8%), professionalism (33.3%), and communication (25.9%). Majority of participants rated the session as excellent/good (96.3%), engaging (92.6%), personally (92.6%) and professionally (85.2%) impactful, and accommodated their personal learning style (85.2%). While all groups showed significant improvement in confidence (*P*-values-A-<0.001; B = 0.002; C = 0.002), there was no difference between the groups for both pre- ($P=0.273$) and post- ($P=0.840$) session.
Conclusion
SIMBA has the potential to be the future of post-graduate medical education and continued professional development in both in-person and virtual settings without compromising quality.

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P64

Novel contrast enhanced ultrasound imaging approaches to understand and treat gastrointestinal disease

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About one in six hospital admissions are for a primary diagnosis of gastrointestinal (GI) disease in the UK, according to the British Society of Gastroenterology, and there is a similar incidence of disease in other developed countries. Inflammatory disease of the gut, in particular, alters the release of cytokines and gut hormones. Medication is used to manage GI diseases and endoscopies help visually monitor its progression. However, this procedure is invasive and causes distress to patients. Contrast enhanced ultrasound (CEUS) imaging is a non-invasive technique using microbubbles filled with gas as a contrast agent. In this work, CEUS imaging was used to study the effect of GI inflammation in mice. Developing such a protocol is a critical step towards using CEUS as a tool in GI disease research. Imaging them non-invasively would allow the field's understanding of gut function in health and disease to significantly progress. For this work, mice were anaesthetised and imaged with a Verasonics high frequency L22-14Vx probe. A volume of 50μl of microbubbles was injected intravenously at a concentration of 1 billion microbubbles/ml. After the data was acquired, the tissue signal was removed using singular value decomposition; ultrasound localisation microscopy was then applied to the remaining blood and bubble signal. This processing chain allowed individual bubbles to be localised and tracked allowing blood flow through individual villi to be visualised. These images allow structural metrics such as villi length and density to be collected; while dynamic information regarding the direction and rate of blood flow can also be calculated, providing detailed information on gut physiology and pathophysiology. This data demonstrates the potential of CEUS to investigate gut disease. Future work will longitudinally monitor gut pathology using CEUS and link this to cytokine and gut hormone profiles to better understand gut disease and treatment response.

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P65

Assessment of the Acute Effects of Rice and Potato Protein Isolate Intake on Markers of Glycaemic Regulation in Healthy Males Using a Randomised Study Design

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Background
Animal-derived protein consumption has been rising globally, driven by socioeconomic factors and shifts in dietary patterns to improve performance and support weight loss. In recent years an increasing trend has been observed for plant-based proteins due to sustainability concerns. Previous studies indicate that the metabolic effects of proteins may vary according to their origin. Thus, the aim of this single-blind, crossover study was to assess the acute effects of two high-purity, plant-based protein isolates (potato – PP and rice - RP) on the peptide hormones GLP-1 and insulin in nine male participants aged 30.8 ± 9.3 years.
Methods
Participants consumed equal volumes of protein shakes with matched energy and protein content following a 12h overnight fast, with at least a week washout between visits. Peptide hormones were assessed at baseline and 30-, 60-, 120- and 180-min following shake consumption.
Results
Insulin levels at 30 min were significantly higher with RP vs PP (64.4 ± 20.9 pmol/l; $P=0.046$). Additionally, GLP-1 levels remained significantly lower with PP at 60, 120 and 180 min ($P=0.003$, $P=0.001$ and $P=0.001$, respectively). However, Pearson's correlation coefficient revealed significant positive correlations with PP between GLP-1 (30 min) vs insulin (120min) ($r=0.786$, $P=0.036$) and GLP-1 (120 min) vs insulin (120min) ($r=0.809$, $P=0.028$), whereas there was no significant correlation between GLP-1 and insulin at any time point with RP.
Conclusion
These data show that in the case of RP, the increase in GLP-1 did not induce insulin release, suggesting a potential incretin effect independent of insulin release. Although targeted population studies with increased sample size are required alongside assessing further non-animal protein sources, our results suggest that RP may be better suited for groups at risk of beta-cell dysfunction.

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P66

Assessing the effect of different fatty acid compositions on *in vitro* cellular models of human hepatocytes

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Background
Pathological accumulation of intrahepatocellular triglyceride (IHTG) is the first stage non-alcoholic fatty liver disease (NAFLD), which encompasses a spectrum of disease from simple steatosis through to cirrhosis. Dietary interventions have demonstrated alterations in dietary fat quantity and quality affect IHTG content; diets rich in saturated compared to unsaturated fat increase IHTG accumulation to a greater extent. Studying the underlying mechanisms *in vivo* in humans remains challenging therefore, *in vitro* cellular models which recapitulate the effects of dietary alterations are needed for mechanistic insight.
Objective
To develop an *in vitro* cellular model to investigate dietary fatty acid (FA) composition influence on the development of IHTG accumulation as well as hepatocellular function and metabolism.
Methods
Human primary and Huh7 hepatocytes (maintained in human serum) were exposed to media enriched in unsaturated or saturated FAs at 200μM or 800μM for 7 days; both mediums contained 5.5 mM glucose. Cells and media were collected and cellular viability, FA storage, synthesis and secretion assessed.
Results
Although the IHTG composition of the Huh7 cells reflected the FA treatment, there were no notable differences in IHTG content between treatments, between respective FA concentrations. The FA treatment did not alter Huh7 cell viability but reduced *de novo* lipogenesis (DNL) was observed with increasing FA concentration for both FA compositions, with larger reductions for mediums with more unsaturated FAs at both concentrations. Primary human hepatocyte IHTG also reflected the media composition with similar changes in DNL to Huh7 cells when exposed to the respective FA compositions and concentrations. However, primary hepatocytes had poorer viability, greater variation (likely due to phenotype) and reduced TG secretion under all conditions, compared to Huh7 cells.
Conclusions
Observations suggest that compared to primary human hepatocytes, Huh7 cells are a useful model for investigating the effects of FA quality on the development of IHTG accumulation.

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P67

Intrahepatocellular insulin resistance and lipid droplet morphology: Influence of fatty acid composition

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Background
Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of diseases starting with pathological accumulation of intrahepatocellular triglyceride (TG) (i.e. steatosis), which can progress to steatohepatitis (NASH) and cirrhosis. Insulin resistance is often associated with the development of steatosis and disease progression however, the underlying mechanisms for this are poorly defined. A major challenge in modelling human NAFLD disease progression is the lack of physiologically-relevant preclinical models to investigate mechanisms.
Objective
The aim of the study was to use a physiologically-relevant and human-centric cellular model to determine the impact of fatty acid (FA) composition on the development of hepatic steatosis and insulin resistance.
Methods
Human Huh7 hepatocytes were maintained in human serum and exposed to repeated doses of a mixture of sugars (glucose, fructose), two compositions of FAs, one enriched in unsaturated FAs (OPLA) and the other saturated FAs (POLA), and insulin for 7 days. Cell and media were collected and TG synthesis and secretion, along with glycogen and glucose production were measured.
Results
Both OPLA and POLA-treated cells had similar intracellular TG content and were considered steatotic. Despite this, POLA-treated cells expressed greater markers of ER stress and had attenuated secretion of TG compared to OPLA-treated cells. In contrast to OPLA treatment, POLA-treated cells were unable to suppress glucose production, synthesize glycogen, or activate key proteins in insulin signaling with acute insulin treatment, suggesting insulin resistance. Further, POLA-treated cells, compared to OPLA, displayed more microvesicular (small droplet) steatosis.
Conclusions
POLA treated cells were steatotic, insulin resistant, and displayed lipid droplet morphology suggestive of disease progression toward NASH. This cellular model can be used to dissect the key proteins and pathways that differentiate NAFLD prognosis.

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P68

The perils of steroids and salt in Covid-19 associated Diabetes

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Background
Following the RECOVERY study, dexamethasone is prescribed for patients requiring inpatient treatment of Covid. Cases of new and atypical diabetes have been reported during this pandemic. The risk of steroid induced hyperglycaemia is well recognised but other metabolic sequelae less so. We present a patient who developed severe hypernatraemia following commencement of dexamethasone.
Case Report
A 44-year-old man (unvaccinated) was diagnosed with Covid-19 infection a week prior to hospital admission. Shortly after his Covid-19 diagnosis, he developed weakness, breathlessness and polyuria which deteriorated until he presented on day 7 to the ED. He was diagnosed with new T1DM and severe DKA (pH 6.9). Dexamethasone 6 mg was commenced despite no evidence of pneumonitis. He received 5 litres of intravenous 0.9% saline on day 1 of admission and about 3 litres on subsequent days. His serum Na rose to 156 mmol/l by day 3 so fluids were changed to Hartmann's and subsequently to 5% Dextrose yet the Na level rose to 162 mmol/l by day 5. Hypokalaemia (2.6 mmol/l) was also noted. The Endocrine team advised that Dexamethasone stopped as the patient was not requiring supplementary oxygen. Afterwards, the Na level progressively improved and normalised on the 4th day.
Conclusion
Steroids can cause hypernatraemia by enhancing water excretion and exhibiting mineralocorticoid effects. Resistant hypernatraemia should be recognised as a side effect of high dose steroids, and when identified a risk-benefit analysis regarding continuation of steroids conducted. Caution is advised in prescribing dexamethasone in patients with Covid and diabetes.

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P69

The effect of novel adipokine asprosin on mitochondrial function in human airway epithelial cells

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Background
Asprosin is a novel adipokine involved in appetite and glucose regulation. During obesity, circulating asprosin is increased, which leads to increased inflammation and can disrupt cellular functions such as mitochondrial respiration. Asthma is a comorbidity of obesity, with both diseases sharing an inflammatory profile and mitochondrial dysfunction. This study investigated the molecular links between asthma and obesity, by exploring whether asprosin causes mitochondrial dysfunction in airway epithelial cells, as experienced in asthma.
Methods
Human airway epithelial cells (BEAS2B-R1) were treated with 10 ng/mL asprosin for 6 and 24hrs. Mitochondrial function analysis was undertaken using the mitochondrial stress test assay on the Seahorse XFe Analyzer to measure oxygen consumption rate (OCR). Mitochondrial copy number was assessed using RT-qPCR, using taqman gene expression assays for BECN1 and mtND1. Cells were stained for total and active mitochondria using MitoTracker dye.
Results
Asprosin treatment initially reduced the mitochondrial copy number by 57% at 6hr compared to control ($P<0.05$), however at 24hr asprosin treated cells had 10% more mitochondria than control ($P<0.05$). The ratio of active to inactive mitochondria was unchanged with asprosin treatment at 6hr, but was decreased by 51% at 24hr ($P<0.0001$), suggesting that the increase in mitochondrial copy number is compensating for this inactivity. This is highlighted by the

mitochondrial stress test which showed no difference in OCR between control and asprosin treated cells at 6 or 24hrs.
Conclusion
Asprosin impacts the total number of mitochondria, and the number of active mitochondria in airway epithelial cells, forcing mitochondria to work harder to achieve the same OCR. This could be an early indicator of mitochondrial dysfunction which is present in asthma. As such, it is possible that asprosin may drive the link between obesity and asthma, making it a possible target to reduce such disease.

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P70

Liver specific microparticles to improve islet transplantation outcomes in Type 1 diabetes

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Background
Islet transplant into the liver is a therapy for type 1 diabetes patients experiencing severe hypoglycaemia or impaired hypoglycaemic awareness. Widespread use is not currently considered due to the requirement for immunosuppression for the lifetime of the graft, and the attrition in graft function over the following 1-5 years. Following transplant into the liver, inflammation results in >60% islet loss, with few patients achieving insulin independence. The liver contains a high density of asialoglycoprotein receptors (ASGPR) with high affinity for galactose. Poly(lactic-co-glycolic acid) (PLGA) is an FDA approved, biodegradable polymer which can be manufactured into microparticles. We hypothesised that particles expressing galactose may target the liver and in the future may be loaded with anti-inflammatory and/or pro-vascularisation agents to help reduce islet inflammation and improve islet vasculature.
Aim
To test if galactosylated PLGA ((PLGA-Gal)) microparticles target the liver and to determine the optimal microparticle size and dose.
Methods
Fluorescent PLGA-Gal microparticles were injected into the liver in mice. A range of diameters (13 um and 20 um), doses (0.1 mg and 1 mg) and controls (PLGA-Gal and non-galactosylated microparticles) were tested. Biodistribution was assessed to find optimum microparticle size and dose that specifically located to the liver without necrosis.
Results
13 um PLGA-Gal microparticles located specifically to the liver with least necrotic effects when at 0.1 mg dose. 20 um microparticles and 1 mg dose of all microparticles were associated with liver necrosis at day 1 and 3 post-transplant, which resolved by day 7 post-transplant.
Conclusion
PLGA-Gal microparticles target the liver specifically; 0.1 mg of 13 um microparticles are associated with minor liver necrosis (compared to the more severe necrosis seen with all other formulations and doses) and may be developed to encapsulate factors that promote islet engraftment and vascularisation to improve islet survival.

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P71

From pathological insulin resistance to pathological insulin sensitivity - a rare case of insulinoma unmasked by bariatric surgery

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Introduction
Hypoglycaemia following bariatric surgery is a recognised complication, secondary to increased incretin secretion to nutrient intake due to altered gut anatomy. It is predominantly postprandial, and usually occurs >6 months postoperatively. We report a case of insulinoma unmasked during the early postoperative period after sleeve gastrectomy (SG).
Case presentation
A 49-year old female with severe obesity without diabetes underwent SG. Within 4-weeks, recurrent severe hypoglycaemic episodes were observed, with fasting glucose levels ranging from 1.1-2.9 mmol/l together with symptoms of sweating, palpitations, confusion & collapse. Hypoglycaemia appeared predominantly in fasting state and relieved with food intake. For a corresponding plasma glucose of 2.0 mmol/l, insulin was 26.9 mIU/l (4.4-26) & C-peptide 1119 pmol/l (298-2350) (inappropriately unsuppressed), indicating insulinoma biochemically. Sulphonylurea screen: negative, 3-hydroxy-butyrate: 0.1 mmol/l, IGF-1: 81 ng/l (53-215) and 9am cortisol: 322 nmol/l. IGF-2 not processed yet. Computed Tomography scan revealed an arterially hyper-enhancing 1.6 cm pancreatic body lesion avid on FDG-PET confirming an insulinoma. FDG-non avid incidental 6.5 cm possible right renal cell carcinoma was also noted.
Progress
Monthly lanreotide injection was initiated to prevent hypoglycaemias; currently awaiting surgery for removal of both tumours.
Discussion
Obesity induced severe insulin resistance appeared to have negated the insulin action at tissue receptors despite hyperinsulinaemia from insulinoma. The rapid improvement in insulin resistance due to calorie restriction and weight loss post-SG triggered hypoglycaemias, unmasking an underlying insulinoma during the early postoperative period. IGF2:IGF-1 ratio is typically >3 and insulin and C-peptide are suppressed in Non-Islet Cell Tumour Hypoglycaemia- hence renal carcinoma even if diagnosed in this case, is not the cause of hypoglycaemia.
Learning points
1) Post-bariatric surgery fasting hypoglycaemias, especially within the first 6 months, should raise the suspicion for insulinoma. 2) Insulinoma differential should be considered if fasting hypoglycaemias occur after definitive treatments for other insulin resistant states (for example Cushing's syndrome).

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P72

A novel compound heterozygous variant of Gitelman's syndrome in a patient with Sjorgren's syndrome: latent rather than acquired?

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Gitelman's syndrome (GS) is an autosomal recessive renal tubular disorder caused by mutations of the SLC12A3 gene coding for the thiazide-sensitive sodium chloride co-transporter (NCCT). Hypokalaemia, hypomagnesaemia, hypocalciuria and metabolic alkalosis are consequent. Sjorgren's syndrome (SS) is a connective tissue disorder primarily affecting lacrimal and salivary glands resulting in sicca complex. The coincidental presence of both syndromes is rare. A 28 year old female presented with hypokalaemia (2.8 mmol/l) and hypomagnesaemia (0.52 mmol/l). Potassium levels 3 and 17 years earlier were 3.5 and 3.4 mmol/l respectively. Six months earlier a diagnosis of SS was made when she presented with a painful, swollen right parotid gland. Anti-ENA, ANA, anti-Ro and rheumatoid factor were all positive. At 7 and 12 years of age painful, swollen left and right submandibular glands respectively were removed without diagnosis. Review of the histology however suggested a diagnosis of paediatric Sjorgren's syndrome. Investigations confirmed normal renal function, venous pH 7.46, bicarbonate 28 mmol/l, hypocalciuria (0.97 mmol/24 hours), PRA 13.9 nmol/l/hr and aldosterone 300 pmol/l. SLC12A3 gene analysis confirmed compound heterozygosity with:
1. The known mutation c.460A>T, p.(Ile54Phe) maternal heterozygous carrier, non-affected. 2. A novel c.1258-1262 del, p.ALA (420GLNFS*103) paternal heterozygous carrier, non-affected. There are 10 previous reports of GS coincidental with SS. Two reported heterozygous mutations, 4 reported absence of mutations and in 4 mutations were not sought. The acquired cases of GS were attributed to antibodies to the NCCT.
The apparent late onset of the GS in our case could be due to:
1. Latent hypofunction of NCCTs induced by the compound heterozygous mutations with compensation mechanisms.

2. The development of auto-antibodies to the NCCTs overriding the compensatory mechanisms.
3. A combination of a. and b.

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P73

The Unusual Suspects: Steroid receptors & hormones found in the mitochondria

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Appreciation of hormonal control over mitochondrial function has increased over recent decades. Mitochondria adapt to the cellular environment through a variety of mechanisms; mitochondrial dynamics (fusion, fission, transfer) or through the signalling of a variety of proteins to induce mitophagy, depending on the cell stressor. In parallel, nuclear receptors and the production of their steroid hormone ligands within mitochondria have been a reoccurring incidental measurement. This is of interest as glucocorticoids such as dexamethasone and sex hormones such as progesterone have been linked to mitochondrial fusion and mitophagy, but the mechanisms remain largely unknown. Our study highlights a nuclear-mitochondrial phenomenon whereby nuclear receptors are located inside mitochondria along with steroidogenic enzymes. Our study examines over 20 mitochondrial proteomics datasets and identifies a cohort of proteins including glucocorticoid, androgen, and estrogen receptors, and steroidogenic enzymes, an important observation as the mitochondria are responsible for the biosynthesis of many steroid hormones including aldosterone and pregnenolone through P450scc (cholesterol side-chain cleavage). We have investigated the localisation of these proteins to the mitochondria with Western Blotting and high-resolution imaging techniques (NanoLive, confocal, epifluorescence) using live and fixed cells and a variety of cell lines including adipocytes, skeletal muscle, neuronal and cardiovascular cells. We postulate the existence of a novel signalling axis that recruits conventionally nuclear-located endocrine responses to mitochondria.

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P74

Ferric-induced hypophosphatemia ironed out with electrolyte replacement: a case report

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Parenteral iron is commonly used in management of iron deficiency especially due to gastrointestinal, obstetrics and gynaecological bleeding. There is a variety of intravenous iron formulations available nowadays and they are generally preferred over oral iron preparations in raising haemoglobin and ferritin, especially in cases of noncompliance and patients with gastrointestinal problems. However, one of the frequently missed complications of iron transfusions is hypophosphatemia. The precise incidence of iron-induced hypophosphatemia is unclear as it is uncommon to measure phosphate levels after iron infusion. Interestingly, abnormal uterine bleeding is considered an independent risk factor of developing post-iron transfusion hypophosphatemia. We report a case of a 57-year-old lady known for iron deficiency anaemia secondary to heavy uterine bleeding who developed hypophosphatemia following parenteral iron transfusion (Ferinject-Ferric Carboxymaltose). The patient presented to the medical assessment unit with worsening frontal headache associated with vomiting, blurred vision, and a metallic taste over a 10-day period after having an iron infusion. She was active, independent and had received 2-3 iron transfusions in the past. Additionally, she was on hormone replacement therapy (Evorel Sequi patches), and had two doses of COVID vaccine, otherwise, her past medical and social history was unremarkable. On admission, her serum phosphate was 0.41 mmol/l and calcium was 2.25 mmol/l. Routine blood tests, inflammatory markers, bone profile, and CT-head were all normal. She was treated with 3 doses of phosphate infusion (Phosphate Polyfusor), each dose administered as 50 mmol/500mL over 24 hours, and subsequently her symptoms dramatically improved. Hypophosphatemia is commonly asymptomatic and often incidental. However, in severe cases serious complications including but not limited to osteomalacia, bone fractures, heart failure, seizures, and coma were reported. Awareness of this potential complication is paramount to guide clinical practice and to ensure that patients requiring iron transfusions are well-informed of the risks of hypophosphatemia.

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P75

Health Inequality and its link to HbA1c Test Recovery in a Developed Health Economy: In a 'Nearly Post COVID-19' World

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Background
We previously showed that in first 6 months of the UK Covid-19(C19) pandemic >6.6million HbA1c tests were missed, including 1.4million in people with diabetes(DM). Furthermore, C19 more significantly impacts people with DM / socioeconomically disadvantaged individuals.
Aim
To examine variability in recovery rate of HbA1c testing, and links to demographics, including deprivation status.
Methods
We examined HbA1c tests across 7 UK sites (570 general practices; 4.57m population) between Oct-2017 and Dec-2021. We compared monthly tests during 4 periods: Apr-Jun2020 (C19 Impact Period; CIP1), Jul-Dec2020 (Inter-Lockdown Recovery; ILR), Jan-Feb2021 (CIP2) and Mar-Dec2021 (Post-Lockdown Recovery; PLR), with the equivalent period in 2019. We then examined effect of practice size/diabetes prevalence/proportion aged >65 years and deprivation score.
Results
For all 7 centres, monthly requests dropped by 85.2-89.4% of the mean monthly 2019 request numbers in Apr-2020. During the following 3 periods, degree of recovery showed greater variability between centres (ILR: 74.0-93.2%, CIP2: 78.6-94.2%, PLR: 89.0-105.7%). No link between age/practice size/diabetes prevalence and post-pandemic recovery was seen. Return to pre-pandemic levels during the two recovery periods was associated with deprivation status. Compared with equivalent pre-pandemic periods, HbA1c testing during the PLR period was lower in higher deprivation areas (deciles 6-10: 91.3-93.5% of 2019 levels) than those with lower deprivation (deciles 1-5:96.2-99.7% of 2019 levels; $P<0.001$). Similar findings were noted for the ILR period: deprivation deciles 6-10 were 79.2-82.6% of 2019 levels compared with 83.8-88.9% for deciles 1-5 ($P<0.001$). This trend was not evident during CIP1/CIP2. UK-wide, these account for ~582,000 and ~358,000 additional missed tests during the ILR and PLR periods in areas at greatest social disadvantage.
Conclusions
C19 continues to have a major impact on diabetes management/HbA1c testing with some centres yet to return to pre-pandemic testing levels. This appears most significant in areas of greatest socio-economic deprivation.

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P76

Plasma Erythroferrone is negatively correlated with total body fat

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Background
Abdominal fat accumulation is a risk factor for type 2 diabetes and cardiovascular disease, whereas lower body fat is protective. Erythroferrone (ERFE) is a recently discovered protein that increases intestinal iron absorption by inhibiting hepcidin. ERFE has been shown to inhibit BMP2 signalling and work from our group has shown that BMP2 is a differentiation factor for subcutaneous abdominal, but not gluteal, adipocytes. Because of this, we hypothesised that ERFE would regulate regional fat mass.
Methods
We measured plasma ERFE by ELISA in the Oxford Biobank (OBB), a cohort of healthy men and women aged 30-50 years old based in Oxfordshire. Body composition was determined by anthropometric measurements and Dual-Energy X-ray Absorptiometry (DEXA) scanning.
Results
Plasma ERFE showed a weak negative correlation with BMI in women ($n=1,119$, r=-0.062, $P=0.04$) but not in men ($n=1,130$, r=-0.021, $P=0.50$). However, ERFE was negatively associated with android-to-total fat ratio (r=-0.093, $P=0.002$) and was positively correlated with leg-to-total fat ratio ($r=0.094$, $P=0.004$) after adjustment for BMI in women. Furthermore, plasma

ERFE was negatively correlated with plasma triglycerides in both sexes after accounting for BMI.
Conclusions
In women, plasma ERFE displays negative correlations with BMI and is associated with a shift to lower rather than upper fat accumulation. This is directionally consistent with the suppression of the adipogenic signalling by ERFE in abdominal preadipocytes when stimulated by BMP2 and could describe a link between the regulation of iron homeostasis and fat deposition.

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P77

Investigating the effects of experimentally induced insulin dysregulation on adiponectin concentrations in metabolically healthy ponies

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Background
Endocrinopathic laminitis is a painful equine condition that may cause persistent lameness warranting euthanasia. Hypoadiponectinemia and insulin dysregulation (ID, manifesting as hyperinsulinemia, tissue insulin resistance (IR), and/or excessive insulin responses to non-structural carbohydrates) are independently associated with increased laminitis risk, although underlying mechanisms remain unclear.
Methods
This study aimed to investigate the relationship between adiponectin and ID. Two forms of short-term ID were induced in healthy insulin-sensitive ponies ($n=6$; four mares, two geldings; 6-18 years; 210-420 kg). Tissue IR was induced via intravenous administration of dexamethasone (0.08 mg/kg) with blood samples collected every 15 min over 3 h. Fourteen days later, hyperinsulinemia was induced for 9 h via euglycemic-hyperinsulinemic clamp, with blood samples collected every 30 min. Insulin and adiponectin concentrations were measured using validated assays and gene expression (adiponectin receptors [AdipoR] 1 and 2, insulin receptor, insulin-like growth factor 1 receptor [IGF-1R]) was assessed via qPCR. Finally, whole-blood was incubated with 10, 100, and 1000 ng/mL dexamethasone for 3 h at 37°C to investigate its direct effect on AdipoR1 and IGF-1R gene expression.
Results
Induced tissue IR did not alter circulating insulin or adiponectin concentrations at any time-point, but significantly upregulated AdipoR1 (two-fold, $P<0.01$) and IGF-1R (four-fold, $P<0.05$) expression at 150 and 180 min. Ex vivo incubation with dexamethasone did not cause similar upregulation, confirming the observed changes were not a direct effect of dexamethasone on leucocytes. There was no change in adiponectin concentrations or gene expression associated with induced hyperinsulinemia (serum insulin: 689.08 $\pm$ 172.36 mIU/mL).
Conclusion
Short-term induced hyperinsulinemia and tissue IR did not affect circulating adiponectin concentrations in metabolically healthy ponies. However, tissue IR caused upregulation of two receptors linked to adiponectin signalling. The effect of longer-term ID (including excessive insulin responses to carbohydrates) on adiponectin signalling requires further research.

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P78

Reversal of Diabetes after 25 years - Not a chronic disease anymore?

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Traditional literature has dictated diabetes to be a chronic irreversible disease with progression of micro and macrovascular complications. Modern medicine has now started to include bariatric surgery, starch restriction as potential interventions which could control diabetes at initial stages. Our case report is unique as it illustrates patient directed reversal of diabetes with lifestyle intervention. 77 years old gentleman was diagnosed with Type 2 diabetes at the age of 52 years. C-peptide, anti-islet cell and anti- GAD antibodies. HbA1c 76 on admission. Patient started on oral therapy maximally on metformin 1gm BD, Linagliptin 5 mg OD and gliclazide 80 mg BD. Patient's BMI 30 kg/m2 on diagnosis. Patient referred to dietician initially and offered lifestyle advice. Patient started dropping weight related to walking 30-60 minutes per day and dropping carbohydrates and fats in meal. As patient was southasian this included interventions like reducing 'rotis', rice and 'chapattis' (main carbohydrate source) in diet and oils. With a drop in patient's BMI a corresponding drop in HbA1c was noted from 70 to 45 in 10 years. Patient's medications were gradually stopped and he is now off oral medications. Lifestyle advice has been re-iterated however this case report demonstrates the importance of 'simplistic' measures of diet and lifestyle adapted to a patient's lifestyle in the so called cure of diabetes.

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P79

Severe rhabdomyolysis secondary to rapid correction of hyponatremia in a patient with psychogenic polydipsia

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Patients with chronic schizophrenia and psychosis are prone to develop hyponatremia secondary to psychogenic polydipsia. Hyponatremia secondary to water intoxication and its rapid correction are linked with rhabdomyolysis, an under-recognized yet serious condition. We report a case of 31 year old male with schizophrenia on Risperidone, who was brought to the emergency due to an unwitnessed fall and confusion. Serum sodium was 111 mmol/l, urine osmolality 55 mosm/kg and urine sodium <20 mmol/l, serum osmolality 229 mosm/kg giving a picture of hypotonic hyponatremia. He was diagnosed with psychogenic polydipsia induced hyponatremia, having drinking 20 liters water per day. Due to rapid correction of sodium in next 24hrs, he was started on 5% dextrose (Table-1),which led to an improvement in his sodium levels, however creatine kinase(CK) levels started rising from baseline. Intravenous fluid were started with fluid restriction relaxed to 3 liters/ day. Risperidone held due to suspicion of rhabdomyolysis, that resulted in significant improvement of CK levels in next 3 days with stable sodium levels (Table-1). eGFR remained >90 throughout inpatient stay. The management of this case was complicated by development of rhabdomyolysis due to rapid sodium correction, highlighting the challenges associated with managing rhabdomyolysis with intravenous fluids that can result in worsening of hyponatremia, hence emphasizing the importance of close monitoring of sodium and measurement of CK in any patient who presents with severe hyponatremia, particularly in the presence of other risk factors for rhabdomyolysis and consideration of careful fluid administration strategies in relation to the relative onset and risk of over-correcting hyponatremia

Table-1

Date & Time of Blood Collection	Serum Sodium (mmol/l)	Serum creatine Kinase (iu/l)
09/10/2021, 12:32	111	3356
10/10/2021, 13:09	130	-
12/10/2021, 15:33	133	131072
13/10/2021, 09:58	137	103334
14/10/2021, 10:34	136	55339
15/10/2021, 11:13	137	19617
18/10/2021, 12:14	138	1669

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P80

Predictors of Diabetic Peripheral Neuropathy: A Multi-Center Cross-Sectional Study

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Background
Diabetic peripheral neuropathy (DPN) is one of the microvascular complications of diabetes mellitus (DM) that causes substantial morbidities including pain, foot ulcers, lower limb amputation, and depression. It is said to affect about 50% of adults with diabetes. Understanding the predictors of DPN will help to re-focus on early preventive strategies to reduce its enormous untold morbidities.
Methods
This is a multi-center cross-sectional study aimed at determining the predictors of DPN in North Central Nigeria. One thousand and forty (1040) persons with DM were consecutively enrolled from hospitals across North Central Nigeria

following institutional ethical approval and participants' consents. Relevant medical history, clinical examinations, and laboratory investigations were done. IBM SPSS version 23 was used for statistical analysis. Multiple logistic regression was used to determine the predictors of DPN. Significance level used was $P<0.05$.

Results

Significant predictors of DPN include age (OR 1.99, $P=0.003$); female gender (OR 1.94, $P=0.023$); duration of DM (OR 2.01, $P=0.032$); history of systemic hypertension (OR 1.68, $P=0.037$); height (OR 2.02, $P=0.001$); generalized obesity (OR 2.02, $P=0.002$); central obesity (OR 1.12, $P=0.047$); poor systolic blood pressure (SBP) control (OR 1.78, $P=0.001$); poor diastolic blood pressure (DBP) control (OR 1.45, $P=0.006$); pulse pressure (OR 2.03, $P=0.028$); poor control of FPG (OR 2.43, $P=0.004$); poor control of 2HrPP (OR 2.83, $P=0.001$); and peripheral artery disease [PAD] (OR 1.89, $P=0.002$). The negative predictors of DPN include statins (OR 2.21, $P=0.004$); and antiplatelets (OR 2.46, $P=0.030$)

Conclusions

Significant predictors of DPN include age, duration of DM, female gender, height, history of systemic hypertension, PAD, and obesity. Others include poor control of SBP, DBP, FPG, 2HrPP, and HbA1c. Negative predictors include the use of statins, and antiplatelets which suggest possible protection, however, a prospective cohort study is needed to confirm this.

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P81

Altered Androgen Metabolism in Rheumatoid Arthritis Influences Synoviocyte Function

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive joint destruction and inflammatory activation and hyperproliferation of synoviocytes. We have previously reported a marked shift towards reduced local androgen metabolism in active RA, driven by changing expression of SRD5A1 and AKR1C3 within macrophages. In this study we examined the role of altered androgen metabolism and availability in the inflammatory function of both macrophages and fibroblast-like synoviocytes (FLS).

Methods

Primary cultures of rheumatoid FLS and peripheral blood monocyte derived macrophages, were stimulated with the pro-inflammatory factor TNFα (10 ng/ml) in combination to incubation with either androstenedione (A4) (100 nmol/l), testosterone (T) (100 nmol/l) or dihydrotestosterone (DHT) (10 nmol/l) for up to 48 hours. Inflammatory gene expression was determined by qRT-PCR and ELISA. Viability and phagocytosis were assessed by MTT and colorimetric assays respectively. FLS proliferation, viability and migration were assessed in a Countess 3 cell counter and via scratch assay.

Results

Macrophages were unresponsive to the actions of androgens and androgen precursors on viability, phagocytosis and inflammatory cytokine output following stimulation with TNFα. In contrast, following stimulation with TNFα treatment with both testosterone and DHT markedly reduced proliferation (15%, $P<0.05$) in FLS, increased migration (12%, $P<0.05$), without impacting on cell viability or live dead cell counts. Whilst the mRNA expression of inflammatory mediators did not change using this setup, a significant reduction in secreted IL-6 were apparent secondary to reduced cell numbers.

Conclusions

This study reveals a previously unreported effect of active androgens in suppressing the inflammatory hyper-proliferation of rheumatoid FLS. These data suggest that the reduced activation of androgens within the synovium in patients with RA may contribute to synovitis and progressive joint destruction.

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P82

The prevalence and management of vitamin D deficiency in people with type two diabetes: Systematic review

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Diabetes type two and Vitamin D deficiency has stirred a great interest recently due to rising prevalence globally. Currently, diabetes is one of the largest and fast growing non- communicable disease of the 21st Century with a close to a half a billion people living with diabetes globally. Vitamin D is a fat- soluble vitamin that is also referred to as the "sunshine vitamin" is an essential vitamin for humans. It is found in two forms: ergocalciferol (vitamin D2) which is derived from plant sterol ergosterol and cholecalciferol (vitamin D3) is synthesised in the skin from 7-dehydrocholesterol under the influence of Ultra-Violet (UV) light. Recent studies have found Vitamin D receptors (VDR) in almost all tissues. This has led to interesting studies that have associated Vitamin D as an immune modulator. The spiked interest in this vitamin has led to some researchers referring to this vitamin as a prohormone due to its extensive benefits, both skeletal and non-skeletal. Hypovitaminosis D has been associated with impaired glycaemic control in patients with type two diabetes. This was the first systematic analysis that assessed the prevalence of vitamin D deficiency in persons with type two diabetes. Several studies have looked at different supplementation of vitamin D focusing on improvement of glycaemic control. This systematic analysis evaluated the different dose regimes of vitamin D supplementation including the different outcomes. Out of 107 studies identified through data search, 11 studies with 2,637 participants with diabetic type two were selected for analysis of the prevalence of Vitamin D deficiency. The prevalence of hypovitaminosis D was between 23% to 98.11%, with majority of the studies demonstrating a high prevalence of hypovitaminosis. Regimens using treatment dose of Vitamin D for treating deficiency either as a single or daily dose demonstrated positive outcomes.

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P83

Examining Smartphone Use During Mealtime and Its Association With Eating Disorders Among Adolescents

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Background

38% of teens use social media more than once an hour and 16% use it almost constantly (Rideout, 2018). Even so, the connection between smartphone use and nutrition and eating disorders is understudied and merits further study. Therefore, this study aims to examine the associations between smartphone use and eating disorders among adolescents.

Methods

The study enrolled 325 participants aged 14-19 years in Florida, US, with 46% ($n=150$ participants) with diagnosis of binge eating disorder (BED). Participants were assessed on demographics, household structure, eating disorders, nutrition, and smartphone use during meals.

Results

The mean participant age was 16.3 ± 1.2 years. The statistical significance of study factors was assessed by using two-tailed t-tests with a 95% confidence level. Participants with BED were found more likely to browse their smartphones during meals (64.1% vs. 45.8%, $P< 0.01$). Similarly, participants affected by obesity (66.6% vs. 49.4%, $P< 0.05$), with high ultra-processed foods intake (64.2% vs. 40.2%, $P< 0.01$), who eat dinner alone (74.2% vs. 30.2%, $P< 0.01$), and with divorced parents (58.4% vs. 48.0%, $P< 0.05$) were more likely to use smartphone during meals. We analyzed activities that smartphones were used for during meals – social-media (59% of participants), watching movies (45%), games (17%), sports (13%), shopping (12%), sports (12%), email (9%), news (5%).

Conclusions

Smartphone usage is significantly associated to BED, obesity, and high intake of ultra-processed foods. The study findings support the inclusion of smartphone usage when eating meals in future research and development of effective interventions.

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P84

Chronic heart failure in hospitalized elderly subjects with diabetes type 2

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Introduction

Chronic heart failure (cHF) is an often and unrecognized cause of mortality among people with type 2 diabetes (T2D), more often in elderly. Assessment of

cHF comprises of a combination of clinical symptoms, echocardiography and a biomarker N-terminal pro b-type natriuretic peptide. It is underestimated and not treated timely. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are treatment of choice for subjects with T2D and cHF, frequently not initiated in elderly. The AIM of our study was to assess presence of cHF, diabetes control, estimated glomerular filtration rate (eGFR) and SGLT2-inhibitor use in elderly with T2D hospitalized at the "Zvezdara" University Medical Center, during 2019.

Methods

This was a retrospective, observational study done with search of electronic data of hospitalised subjects 65 years of age, with the primary diagnosis of T2D, in whom echocardiography was performed. Duration of diabetes, presence of cHF, SGLT2-inhibitor use, HbA1c, eGFR and ejection fraction (EF) were assessed

Results

Search identified 123 hospitalized elderly subjects with T2D in whom echocardiography was performed. Of those, 70 were female, 53 male, on oral or insulin therapy, but only 3 subjects were on SGLT2-inhibitors. Chronic heart failure was identified in 72 subjects: 31 with preserved EF, while 41 had reduced EF. Subjects with cHF were significantly older (78.08±7.80 vs 74.82±6.78 years, $P<0.02$), with longer duration of diabetes (16.74±7.15 vs 12.45±7.51 years, $P<0.001$), higher HbA1c (8.73±2.66% vs 7.68±1.76%, $P<0.01$), lower EF (41.62±8.79% vs 55.41±6.40%, $P<0.001$) and a lower eGFR (46.20± 23.51 vs 62.68±27.90 ml/min/1.73m2, $P<0.001$).

Conclusion

Chronic heart failure is a frequent cause of hospitalization of elderly subjects with T2D. It is associated with increasing age, longer duration of diabetes, poor diabetes control and lower eGFR. SGLT2-inhibitors were hardly present in therapy, even upon discharge from hospital, necessitating education of doctors.

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P85

Fluoxetine Contributing to Non-diabetic Hypoglycaemia

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Introduction

Non-diabetic hypoglycaemia (NDH) has many causes including insulinoma, non-insulin producing cancers and gastric bypass surgery but medications like fluoxetine are rarely reported.

Case history

55 years female, university lecturer, history of Roux-en-Y gastric bypass in 2015 and depression, referred for recurrent symptomatic hypoglycaemia 1 to 2 hours post-meal (reactive hypoglycaemia) with recorded capillary blood glucose up to 1.6 mmol/l and symptoms resolution with carbohydrate (fulfilling Whipple's triad). No history of diabetes and medications included Lansoprazole, Fluoxetine and Multi-vitamins. After excluding other causes of NDH she was diagnosed as post gastric bypass hypoglycaemia (PGBH), treated initially with Acarbose 50 mg TDS along-with small frequent, low glycaemic index meals and later Diazoxide 100 mg BiD with no benefits. She was started on Flash glucose monitoring (FGM) , which confirmed post-prandial hypoglycaemia with time below range (TBR) (<3.9 mmol/l) of 25%, of which 1 % was below 3 mmol/l. Liraglutide 1.2 mg subcutaneously OD reduced hypoglycaemic episodes but did not eliminate completely. Surprisingly, she remained euglycaemic when she accidentally missed fluoxetine and then complete discontinuation along-with other ongoing measures resulted in significant hypoglycaemia improvement with FGM showing 97% time in range and only 3% TBR.

Investigations

Full blood count, thyroid, liver, and renal function tests, pancreatic imaging and esophagogastroduodenoscopy were normal. Mixed meal test confirmed post-prandial hypoglycaemia with insulin levels 36.2 pmol/l (Normal: <18 pmol/l) and C-peptide levels 0.96 nmol/l (Normal: <0.2 nmol/l) with venous blood glucose of 2.9 mmol/l.

Results and treatment

Stopping fluoxetine besides other measures like dietary modification, Acarbose and Liraglutide resulted in reduction of hypoglycaemia frequency from 25% of the time to only 3% on FGM along-with symptom improvement and QoL.

Conclusions and points for discussion

1. Medications like Fluoxetine/SSRI should be considered as potential contributory agents in non-diabetic hypoglycaemia.
2. Consideration of FGM can help detecting hypoglycaemic episodes, improving patient's confidence in managing hypoglycaemia and thus QoL.

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P86

Real-world effectiveness and safety of semaglutide for weight loss

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Introduction

Obesity is a global public health challenge. Semaglutide, a weekly GLP-1 agonist, was recently approved in Europe for weight loss. There is paucity of real-life data about the effectiveness and safety of semaglutide for weight management.

Methods

Real-world data of semaglutide use in a weight management clinic in Athens, Greece, for individuals with BMI (body mass index) > 30 kg/square meter without diabetes, including all patients with at least 3-month follow-up.

Results

Analysis included 18 individuals (12 females, 6 males) with a mean age of 49.5 years and weight of 105 kg. Average BMI was 38.8, with eight having BMI >40, four BMI 35-40, and six BMI 30-35. The most common weight-related complications were prediabetes (12/18), dyslipidaemia (12/18), non-alcoholic fatty liver disease (10/18), obstructive sleep apnoea (5/18), and hypertension (3/18). Baseline mean fasting glucose and HbA1c were 6.3 mmol/l and HbA1c 39 mmol/l/mol, respectively. One patient discontinued semaglutide after 8 weeks due to protracted vomiting, but pancreatitis was excluded. Among the remaining 17 patients, mean percentage 3-month weight change was -6.4%, with three achieving weight loss <5%, eleven 5-10%, and three >10%. Six-month data were available for 8 individuals, with average weight loss of 11.6%, including four patients with 14-20%, two with 5-10%, and two with <5% (4.4% and 4.6%) weight reduction. In total, 14 out of 18 participants (77.7%) responded well, with 8 attaining weight loss of 5% or more in 3 months and 6 weight loss of >7% in 6 months. Two patients achieved 6-month weight reduction of 4.4-4.6%, while one did not lose weight.

Discussion

Real-world data confirm the effectiveness and safety of semaglutide for weight management. Ensuring access to semaglutide, in line with recent NICE recommendations, could change the current paradigm of care, reducing the burden of obesity and its comorbidities.

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P87

Proliferative diabetic retinopathy as a presenting feature of Type 1 Diabetes mellitus- A case report

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Background

Type 1 diabetes mellitus is an autoimmune disorder caused by the destruction of the pancreatic beta cells which produce insulin. People with type 1 diabetes usually require at least 3-5 years to develop microvascular complications in comparison to those with type 2 diabetes, who may develop such complications even before the diagnosis of diabetes due to its insidious onset and the delay in diagnosis. We discuss a patient who initially presented with proliferative diabetic retinopathy and later diagnosed with type 1 diabetes. Microvascular complications including diabetic retinopathy as the presenting feature of Type 1 diabetes in rarely known or reported in the literature.

Case presentation

A 33-year-old male was seen by the opticians due to one week history of blurred vision. The ophthalmology assessment confirmed proliferative retinopathy of right eye and severe non proliferative retinopathy of left eye with bilateral clinically significant macular oedema. He denied any osmotic symptoms or weight loss. His BMI was 24.9 kg/m2 and random glucose of 24.9 mmol/l. The plasma ketones was 0.7 mmol/l and HBA1c was 177 mmol/mol. The nervous system examination revealed bilateral stocking type of peripheral neuropathy. His Anti Glutamic acid decarboxylase (GAD) antibody was positive confirming the diagnosis of type 1 diabetes mellitus. He was started on basal bolus regimen for blood glucose control and was started on Aflibercept injection to both eyes followed by pan-retinal photocoagulation. Later Nerve conduction studies confirmed the presence of large fiber sensory more than motor, axonal, length dependent peripheral neuropathy suggestive of diabetic symmetric polyneuropathy

Conclusions

The pathogenesis of the development of microvascular complications of type 1 diabetes mellitus is multifactorial. Usually, the development of complications is seen at least few years after the diagnosis. Occurrence of microvascular

complication at presentation is rare and makes the management challenging and extremely important to prevent the progression of the disease.

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P199

Temporal periods of mild hyperglycaemia in pregnancies complicated by gestational diabetes and LGA alter placental transcriptomic networks associated with vascularisation and M2 hofbauer cell polarisation

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Background
Gestational diabetes (GDM) leads to an increased risk of delivering large-for-gestational-age infants (LGA), which has been linked to altered placental vascular development. Women with GDM who deliver LGA infants have temporal periods of mild hyperglycaemia, detectable by continuous glucose monitoring (CGM), compared to women who deliver appropriate-for-gestational-age infants (AGA). This study aimed to assess the impact of physiological periods and levels of hyperglycaemia on placental gene expression and function.
Methods
To mimic in-vivo glucose levels in GDM-AGA and GDM-LGA pregnancies, healthy term placental explants were cultured for 48-hours in fluctuating 5/5.5 mM (normoglycaemia) or constant 7 mM (mild hyperglycaemia) glucose, respectively. RNAseq ($n=5$) and functional enrichment (over representation, Ingenuity pathway (IPA) and Cytoscape analyses) were performed. TMT-proteomics was conducted on placental macrophages (Hofbauer cells; HBCs) isolated from healthy term placentae ($n=6$). Immunohistochemistry of CD206 and CD163 was performed assess localisation of M2 HBCs ($n=4$).
Results
Mild hyperglycaemia altered 584 genes ($P<0.05$, log2foldchange >0.5 <-0.5). Differentially expressed genes (DEGs) were enriched in immune/inflammatory and vascular development pathways ($P<0.001$). In IPA, several biological functions were predicted to be decreased by mild hyperglycaemia, including angiogenesis ($P=1.44E-10$, Z-score=-3.386), vasculogenesis ($P=5.88E-10$, Z-Score=-3.465), and activation of macrophages ($P=1.94E-07$, Z-score=-2.017). A comparison of DEGs to the HBC proteome revealed that 87 DEGs are produced by HBCs, including regulators of placental vascularisation (e.g., PECAM1, IL1B, PTGS2). DEGs were associated with an M2 phenotype when compared to M1/M2 macrophage transcriptomics (GSE5099). In immunohistochemistry, M2 markers, CD206 and CD163, were localised to the villous stroma, and in close proximity to fetal blood vessels.
Conclusions
Mild hyperglycaemia altered the placental transcriptome. Given that M2 HBCs are known to play roles in placental vascularisation, mild hyperglycaemia may activate M2 HBCs which in turn contribute to altered placental angiogenesis and may ultimately lead to LGA.

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P200

The American lifestyle-induced obesity syndrome diet (ALIOS) in mice alters the diversity and composition of the gut microbiome

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Dysbiosis of the gut microbiome contributes to the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Reduced diversity and composition of the microbiome are associated with increased intestinal barrier permeability, increased bacterial translocation and NAFLD progression. The ALIOS diet in rodents replicates many of the metabolic and histological features of NAFLD in humans and here we report the effect of the ALIOS diet on the gut microbiome. Male and female C57BL/6 mice were fed normal chow (NC) or an ALIOS diet (45% fat [30% trans-fat], 55% fructose: 45% glucose in H2O) for 52 weeks and caecal samples sent for 16S amplicon sequencing. The composition of the microbiome was altered in the ALIOS mice. Principal coordinate analysis showed a difference in diversity between ALIOS vs NC fed mice ($P<0.01$) although this was reduced ($P<0.1$) when weighted for relative abundance. The ALIOS diet decreased bacterial diversity within samples. Shannon entropy was reduced in ALIOS-fed mice ($n=17$: 9 female, 8 male) compared to NC ($n=13$: 8 female, 5 male) (ALIOS: 5.53 ± 0.19 vs NC: 6.19 ± 0.33, $P<0.05$, data are mean $\pm$ SEM). Pielou evenness was reduced in ALIOS-fed mice compared to NC (ALIOS: 0.62 ± 0.15 vs NC: 0.69 ± 0.19, $P<0.01$, data are mean $\pm$ SEM). The ALIOS diet altered the relative abundance of microbes at different taxonomic levels. Phyla analysis revealed no difference in Firmicutes/Bacteroidetes ratio, however, compared to NC, ALIOS-fed mice had increased Acidobacteria ($P<0.01$), Chloroflexi ($P<0.01$), Gemmatimonadetes ($P<0.01$), Nitrospirae ($P<0.01$), Verrucomicrobia ($P<0.01$) and Latescibacteria ($P<0.05$). ANCOM analysis revealed ALIOS-fed mice had enrichment of the genus Lactococcus (W=4310), and species Lactobacillus salivarius (W=4237). Whereas the families Muribaculaceae (W=4247) and Lachnospiraceae (W=4229), and genera Prevotella (W=4180) and Ruminococcus (W=3927) were reduced. In conclusion, ALIOS-fed mice had reduced microbiome diversity and altered composition that may contribute to the NAFLD phenotype observed in these mice.

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P201

Angiotensin II dependent pericyte activation causes neuropathic pain in a type-2 rodent model of diabetes

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Neuropathic pain (NP) is a microvascular complication affecting between 30-50% of people living with diabetes. Current painkillers including non-steroidal pain killers and anti-convulsant are ineffective. At the level of the spinal cord (SC), capillary regression is associated with the onset of NP in diabetic rodent models. Our aim was to investigate angiotensin II mediated pericyte activation in relation to vascular degeneration and the onset of NP. Adult male C57Bl/6J mice were fed either a standard diet (18% kcal from fat) or high fat diet (HFD; 60% kcal from fat) for 8 weeks. HFD fed mice led to an increased blood glucose compared to standard diet (17.3%¬¬↑¬ blood glucose mmol/l, $*P<0.015$, $n=8$ per group). This was accompanied by a reduction in nociceptive withdrawal latency to thermal stimuli (41.95%↓,$***P<0.0003$, HFD vs. standard diet). There was increased capillary (CD31 positive) breakdown depicted by reduced vessel branching count in the lumbar SC (37.9%↓$*P<0.024$, $n=6$) and reduced angiotensin converting enzyme 2 (ACE2) expression ($*P<0.05$) in the HFD fed rodents. Following this the angiotensin II type 1 receptor antagonist, Losartan, was investigated as a potential analgesic agent in HFD fed rodents. At week 8, Losartan (intraperitoneal delivered, 20 mg/kg) induced increased withdrawal latency to thermal stimuli in HFD rodents compared to vehicle treated HFD fed rodents (intraperitoneal delivered, PBS) (78.4%↑¬$****P<0.0001$ HFD+losartan vs. HFD+vehicle). Furthermore, primary mouse SC pericytes were cultured to investigate renin-angiotensin system activity within high glucose environments. ACE2 showed reduced expression in high glucose (47 mmol/l, 29.27%↓ $*P<0.035$, $n=5$) compared to normal glucose (17 mmol/l, $n=3$) environments. These data demonstrate that hyperglycaemia induces an angiotensin II dependent pericyte vasoconstriction that causes microvessel degeneration in the spinal cord of high fat rodents. This initiates the breakdown of the blood-spinal cord-barrier breakdown, a mediator of diabetic neuropathic pain.

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P202

Identifying the amino acids which mediates the effect of protein on glucagon release

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Background
The beneficial effects of high protein diets on glucose homeostasis are thought to be in part mediated by the modulation of gastroenteropancreatic hormones by protein-derived metabolites such as amino acids. However, the precise mechanisms by which amino acids drive these beneficial effects are not well understood. Protein intake stimulates both insulin and glucagon release; glucagon is now recognized to have other metabolic roles besides increasing blood glucose levels during hyperglycaemia. Glucagon can promote weight loss and may play a

role in stimulating insulin secretion via intra-islet signalling. Preliminary data from our group found that circulating levels of 15 amino acids were positively associated with circulating glucagon levels after a high protein meal in humans.
Aim
To identify the amino acids which mediate the effects of protein on glucagon release using isolated pancreatic islets from mice.
Method
The effects of amino acids on glucagon release were investigated using islets isolated from PPG-Cre; GCaMP6 mice, which express tamoxifen-inducible CreERT2 recombinase under the control of preproglucagon (PPG) promoter and have a floxed-STOP cassette upstream of the cytosolic calcium indicator GCaMP6f. Following tamoxifen induction, the islets specifically expressed GCaMP6f in α-cells. Islets were maintained in 6 mM glucose HKRB solution for an hour before being treated with amino acids; 30 mM KCl was used to confirm α-cells viability.
Results
Specific amino acids increased intracellular calcium signalling in α-cells, with the signal peaking 10-20 seconds after the addition of treatment at t60 and gradually returning to baseline at 260-300 seconds after t0. In particularly, compared to vehicle, 10 mM alanine increased the maximum calcium by signal sixfold, 10 mM asparagine and 10 mM ornithine resulted in a fourfold increase, and 10 mM phenylalanine a threefold increase. Understanding how amino acids, regulate glucose homeostasis may help identify new therapeutic targets for type 2 diabetes.

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P203

Monitoring obesity-induced hyperglycaemia and insulin sensitivity in obese murine pregnancy

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During pregnancy progressive maternal insulin resistance occurs which is normal, 'sparing' glucose that can be transported across the placenta to be used by the fetus. In gestational diabetes mellitus (GDM) maternal glucose dysregulation is exacerbated, characterised by hyperglycaemia and associated with long-term adverse outcomes in mother and child, such as increased risk of diabetes and/or cardiovascular disease in later-life. Continuous glucose monitoring (CGM) is an emerging technology aimed at improving glucose homeostasis in pregnant and non-pregnant diabetic patients. This study sought to use CGM in a well-known mouse model of GDM to ascertain if a similar gestational glucose dysregulation could be observed, and to assess the effect of a potential therapy for GDM, the dietary isothiocyanate sulforaphane, on maternal glucose homeostasis. Glucose telemetry probes (HD-XG probes, DSI) were implanted in WT C57BL/6J dams fed a normal chow diet (lean) or high-fat high-sugar diet (Ob). A subset of obese dams received sulforaphane (ObSFN) from mating or gestational day (GD) 0. Blood glucose is continuously monitored throughout gestation and the postpartum period, with glucose and insulin tolerance testing performed. Data represent mean ± SD or SEM n=4-7. In early pregnancy (GD2.5) obese mice demonstrate raised blood glucose levels (8.58 ± 0.45 mM) vs. lean (7.94 ± 0.44 mM) and show increased glucose excursions. Later in gestation (GD17.5) all groups demonstrate reduced blood glucose levels compared with early pregnancy although obese groups maintained elevated 24h blood glucose (Lean 6.25 ± 0.73 mM, Ob 7.59 ± 0.78 mM vs. ObSFN 7.48 ± 0.70 mM). By the postpartum period, SFN improved maternal glucose tolerance (AUC 2806 ± 117 Ob vs. 2270 ± 249 ObSFN) and insulin (AUC 298 ± 16 Ob vs. 242 ± 23 ObSFN). To conclude, CGM in obese dams reveals gestational glucose dysregulation with SFN treatment in pregnancy reducing maternal hyperglycaemia, at least partially by increasing sensitivity to insulin.

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P204

Clinical and cellular studies highlight a role for insulin at the onset of lactation in promoting mammary glycolysis and oxidative phosphorylation

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The onset of lactation during post-partum days 1-4 is hormonally-regulated and critical for successful breastfeeding. Insulin represents a key lactogenic hormone as evidenced by women with type 1 diabetes who have delayed lactation onset. However, the role of insulin in lactation and its influence on mammary cells are unclear. We utilised clinical and cellular approaches to investigate this, and recruited n=12 women following informed consent and measured serum insulin in pregnancy (36 weeks' gestation) and during post-partum days 1-4. Serum insulin progressively decreased from 36 weeks' gestation to day 4 post-partum (260.6 ± 59.1 pmol/l vs 109.8 ± 48.8 pmol/l, P<0.05), reflecting increased maternal insulin sensitivity at lactation onset. We hypothesised that insulin promotes lactation by influencing mammary metabolism and used human mammary epithelial cells (HMECs) to evaluate this. Reverse transcription-quantitative PCR (RT-qPCR) demonstrated that HMECs express the insulin receptor. Moreover, stimulation of HMECs with 10nM insulin caused a >2-fold increase (P<0.0001, n=4) in phosphorylation of Akt, a signalling protein required for initiating lactation. Akt influences oxidative phosphorylation and glycolysis, and we assessed these processes by measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), respectively. HMECs treated with 10nM insulin for ≤18hrs showed increased OCR (22 ± 0.9 vs. 17 ± 0.4 pmol O_2/min/10^6 cells for control HMECs, P<0.05, n=4) and ECAR (0.23 ± 0.003 vs. 0.18 ± 0.002mpH/min/10^6 cells for control HMECs, P<0.001, n=4), consistent with increased oxidative phosphorylation and glycolysis. HMECs treated with 10nM insulin for 8hrs significantly upregulated expression of glycolytic enzymes, namely hexokinase 2 (>4-fold increase, P<0.0001, n=4) and pyruvate kinase M1/2 (1.4-fold increase, P<0.05, n=4). However, RT-qPCR analysis of HMECs showed that insulin did not increase expression of genes mediating oxidative phosphorylation, suggesting an Akt-mediated post-transcriptional mechanism. In summary, increased insulin sensitivity together with insulin-stimulated oxidative phosphorylation and glycolysis may support mammary function and milk component synthesis at the onset of lactation.

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P205

UCP1 expression in human brown adipose tissue is inversely associated with cardiometabolic risk factors

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Introduction
Brown adipose tissue (BAT) increases energy expenditure and is a potential therapeutic target for obesity and associated cardiometabolic disease. It is unclear whether human BAT activity is reduced in obesity, as BAT ^{18}F-fluorodeoxyglucose uptake is reduced but BAT metabolic activity measured using ^{11}C-acetate PET is preserved. BAT thermogenesis relies on the presence of uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation from ATP synthesis. We hypothesized that BAT UCP1 levels are reduced in individuals with cardiometabolic disease.
Methods
BAT and WAT samples were obtained from 141 patients undergoing elective neck surgery. UCP1 mRNA levels were measured by quantitative real-time PCR in whole tissue (n=53) and differentiated pre-adipocytes (n=88). We tested whether UCP1 levels in whole tissue/adipocytes were associated with important cardiometabolic risk factors.
Results
Individuals with high UCP1 levels in whole BAT (threshold >2AU) were younger (44.1 ± 14.4y vs 55.7 ± 11.7y) with lower body mass index (26.5 ± 4.9 kg/m^2 vs 30.1 ± 6.0 kg/m^2), waist circumference (84.8 ± 19.1 cm vs 99.3 ± 18.6 cm), waist-hip ratio (0.86 ± 0.06 vs 0.92 ± 0.08), fat percentage (20.9 ± 9.1% vs 28.8 ± 11.4%), systolic (131 ± 25 mMHg vs 143 ± 22 mMHg) and diastolic blood pressure (79 ± 12 mMHg vs 86 ± 11 mMHg). BAT UCP1 levels were lower in subjects with pre-existing hypertension and those prescribed beta-blockers. BAT (but not WAT) UCP1 levels correlated negatively with age (r=-0.309), weight (r=-0.321), waist circumference (r=-0.315) and fat mass (r=-0.242). However, UCP1 levels in differentiated brown adipocytes were not associated with any of the above measurements.
Conclusion
BAT UCP1 levels are decreased in older, obese and hypertensive subjects, consistent with defective BAT thermogenesis. However, these subjects retain brown pre-adipocytes with the capacity to form new thermogenic adipocytes during appropriate stimulation. These data highlight the therapeutic potential of increasing BAT mass and activity in this patient group as a therapeutic strategy to ameliorate the metabolic consequences of obesity.

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P206

Circulating levels of adipose-derived lipokines correlate positively with fasting insulin in states of increased insulin insensitivity in humans

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Introduction
Palmitoleate, a proposed adipose tissue (AT)-derived lipokine, has been suggested to contribute to glucose homeostasis. However, data relating to the association between circulating palmitoleate and markers of insulin sensitivity in humans are equivocal. Recently, AT-derived fatty acid-hydroxy fatty acids (FAHFAs) have also been suggested to play a role in glucose homeostasis by increasing glucose uptake in AT. Again, data is conflicting for the association between circulating FAHFAs and markers of insulin sensitivity. The aim of the current work was to clarify the relationships between circulating lipokine concentrations and markers of insulin resistance, using a large cohort of individuals, across a spectrum of adiposity.
Methods
Fasting plasma samples (102 female and 77 male) from healthy, well-phenotyped and non-diabetic participants were stratified, based on the 75th centile of fasting plasma insulin concentrations, as normoinsuliaemic (NI) ($n=133$) or hyperinsulinaemic (HI) ($n=45$). Circulating concentrations of plasma palmitoleate were measured using gas chromatography and two FAHFA sub-families (PAHSAs and PAHPAs) were measured by liquid chromatography-mass spectrometry.
Results
We observed female sex-specific, positive correlations ($P<0.05$) between fasting insulin and PAHSAs and PAHPAs in the HI group only. In both sexes, similar, but non-significant, trends were also observed between circulating palmitoleate concentration and fasting insulin in the HI group, with no trends in the NI group. The HI group had higher relative fat mass, fasting glucose, plasma PAHSA and PAHPA but there were no differences in age, plasma total NEFA or palmitoleate.
Conclusion
Our data suggest that systemic concentrations of palmitoleate may be upregulated in response to insulin insensitivity and, although the same may true of PAHSAs and PAHPAs in females, there is a sexual dimorphic response. However, the usefulness of these lipokines as markers of insulin sensitivity is likely limited as plasma concentrations do not discriminate between individuals classed as NI and HI.

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P207

Vitamin D_3 supplementation improves glucose metabolism in the offspring of fructose-induced Sprague-Dawley rats

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Developmental programming of insulin resistance in the offspring of diabetic mothers have contributed significantly to the increased prevalence of type 2 diabetes mellitus and other metabolic disorders in the general population. Vitamin D has been reported to improve glucose metabolism, however its potential in reversing glucose intolerance programmed in the offspring of diabetic mothers has not been fully elucidated. The study therefore aimed to investigate the effect of vitamin D_3 supplementation on glucose tolerance in the offspring of fructose-induced diabetic Sprague-Dawley rats. Six female rats weighing 160-180g were fed on high fructose diet (25% w/v) for 12 weeks to induce hyperglycemia and hyperinsulinemia. The rats were subsequently mated after the successful induction of type 2 diabetes mellitus and were allowed to deliver at term. The offspring of the rats were weaned at 3 weeks and fed on normal rat chow till pubertal onset at 6 weeks. Separation of the offspring by sex was done and they were grouped into two namely (1) vitamin D_3 supplemented offspring, fed on a diet containing an additional 750 IU/Kg of vitamin D_3 for 6 weeks and (2) Standard rat chow fed (positive control) offspring. Oral glucose tolerance test was conducted, blood samples were obtained and assessed for fasting blood glucose, insulin, vitamin D_3 and lipid levels in both groups. Results showed that vitamin D_3 supplemented offspring of diabetic rats had a significant decrease in fasting blood glucose, insulin and triglyceride levels compared to the offspring on standard diet. Oral glucose tolerance test results also showed a significant enhancement of insulin sensitivity in the vitamin D_3 supplemented offspring compared to the positive control. These findings show that vitamin D_3 supplementation improves glucose homeostasis in the offspring of diabetic rat model.

Key words: glucose tolerance, vitamin D_3, maternal diabetes, developmental programming
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P208

Serum Bile Acid Measurements in Women of European and South Asian Descent with or without Gestational Diabetes Mellitus

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Introduction
Bile acid (BA)-feeding and genetic manipulation of BA receptors affect glucose tolerance in rodent pregnancy. In non-pregnant individuals, serum BA profiles depend on BMI and ethnicity. The interaction between serum BAs, ethnicity, and BMI in gestational diabetes mellitus (GDM) remains poorly understood.
Methods
Fasted serum samples were collected between 23-31 weeks' gestation. Experimental groups: lean or obese women of European (EU) or South Asian ancestry (SA), with or without GDM. Ethnicity-specific BMI thresholds: Obese >30 and >27 kg/m^2; Lean <25 and <23 kg/m^2 in European and SA women, respectively. Numbers per group: EU-Lean-Con ($n=63$), EU-Lean-GDM ($n=27$), EU-Ob-Con ($n=74$), EU-Ob-GDM ($n=73$), SA-Lean-Con ($n=62$), SA-Lean-GDM ($n=10$), SA-Ob-Con ($n=75$), SA-Ob-GDM ($n=40$). Serum BAs were measured with UPLC-MS/MS. Data were analysed using Mann-Whitney U tests/linear regression.
Results
Total serum BA were elevated in EU-Ob-GDM women compared to EU-Ob-Con (2.1 [1.4 – 3.8] vs. 1.3 [1.0 – 2.2] μmol/l, $p=0.0001$), but no GDM effect was seen in other groups. SA-Ob-Con women had elevated serum BA compared to SA-Lean-Con women (2.4 [1.2 – 4.7] vs. 1.6 [1.0 – 2.9] μmol/l, $p=0.0243$) as well as compared to EU-Ob-Con women ($P=0.0006$). Comparable results were obtained for primary, secondary, conjugated, unconjugated and 12α-hydroxylated BAs. There was no GDM effect on the relative contribution of primary, conjugated or 12α-hydroxylated BAs. Primary BAs correlated positively to fasting glucose ($r^2=0.12$, $p<0.0001$) and negatively to the quantitative insulin-sensitivity check index ($r^2=0.11$, $p=0.0032$) in GDM but not in control women. In SA (but not EU) women, C4 (7α-hydroxy-4-cholesten-3-one, BA synthesis measure) concentrations positively correlated to primary BA ($r^2=0.09$, $p<0.0001$).
Discussion/Conclusion
The correlation of BA concentrations to measures of glucose homeostasis and BA synthesis depend on GDM status, BMI, and ethnicity. These data stress the importance of studying women of different BMI and ethnicity separately to understand individualised risk factors for GDM.

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P209

Vitamin B12 deficiency induces *de novo* lipogenesis and lipid oxidation in human placental trophoblasts

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Background
Obesity-linked metabolic disorders are a worldwide health concern affecting about one third of women of reproductive age. The programming events in utero impact the risk of predisposition to obesity and metabolic diseases. Maternal B12 deficiency is associated with higher cord lipids. B12 has a potential epigenetic role and therefore may perpetuate an intergenerational cycle of obesity through its effects on placental function and fetal metabolism. Therefore, we hypothesize that

B12 deficiency could affect placental lipid metabolism and may alter fetal lipid levels, potentially influencing neonatal adiposity. Here, we assessed whether low B12 in human placental trophoblasts alters *de novo* fatty acid (FA) synthesis and oxidation.
Methods
Human trophoblastic choriocarcinoma cells (Bewo) were cultured using custom made Ham's F12 media supplemented with sufficient (500nM-Control) or low concentrations of B12 media (25pM-low B12) until confluence was achieved. RNA isolation, cDNA synthesis and gene expression assays using RT-qPCR were employed to examine the expression of genes required for FA synthesis and oxidation.
Results
Placental trophoblasts cultured in low B12 showed significantly increased gene expression of (1) nuclear transcription factors regulating FA synthesis (SREBF1), oxidation (LDLR), adipogenesis (PPARγ, CEBPα), (2) *de novo* FA synthesis (ACLY, ACACA, FASN), FA elongation (ELOVL6), (3) triglyceride biosynthesis (GPAT, AGPAT, Lipin1, DGAT2) and (4) downregulated gene expression in FA oxidation (CPT1A, SLC25A2, ACADS, HADHB, HADHA) compared to control ($P<0.05$). We also observed deregulated expression of leptin, a major adipokine of placental lipid metabolism.
Conclusion
Our data provide evidence that low B12 potentially impacts lipid metabolism and deregulates leptin in placental trophoblasts. Thus, indicating that B12 deficiency could alter placental lipid levels which may lead to placental dysfunction and subsequent dyslipidemia in offspring. Future studies to elucidate the epigenetic mechanisms will support the development of effective interventions to optimize maternal metabolism, placental function and health of the offspring.

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P210

Elucidating endothelial-derived molecules with potential anti-obesity properties via crosstalk with enterocytes and gut microbiota

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Introduction
Overweight and obesity is a worldwide chronic disease affecting 2 billion adults and millions of children. In diet-induced obesity (DIO), current treatments are not always effective or suitable for all patients due to the complexity of obesity and its associated health complications. Recently, the potential of developing weight loss therapy by targeting the gut microbiota has been raised. Previously, we have shown that mice overexpressing insulin-like growth factor-1 receptor in the endothelium (hIGFREO) are protected against DIO and glucose intolerance, which is associated with remodelling of the gut microbiota (1). *In vitro* experiments suggested endothelium-enterocyte crosstalk may be involved in elevating Regenerating Family Member 3 Gamma (REG3G) signalling and remodelling of gut microbiota in hIGFREO mice (1).
Hypothesis
Elevated enterocyte REG3G signalling is mediated by secreted factors from endothelial cells in diet-challenged hIGFREO mice.
Methods
At 8 weeks old, hIGFREO and wild-type (WT) mice were challenged with high fat diet for 8 weeks. Conditioned media from isolated endothelial cells were applied on differentiated Caco-2 enterocytes. Aqueous and lipid fractions of conditioned media were extracted using methanol/chloroform mixture. Untargeted metabolomics was performed on the conditioned media using UPLC/MS.
Results
Aqueous fraction of hIGFREO endothelial cell-conditioned media induced a 3-fold increase in *REG3G* gene expression in Caco-2 enterocytes. Caco-2 enterocytes treated with either unconditioned media, aqueous or lipid fractions of WT endothelial cell-conditioned media showed no difference in *REG3G* gene expression. Untargeted metabolomics revealed 3 upregulated and 3 downregulated aqueous features in hIGFREO conditioned media compared to the WT control.
Conclusion
hIGFREO endothelial cells can secrete aqueous factors to increase enterocyte REG3G signalling *in vitro*. Future work will focus on annotating upregulated aqueous metabolites from hIGFREO endothelial cells and exploring their ability to alter REG3G signalling in enterocytes.
Reference
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P211

Investigating the effect of obesity on gut damage, systemic inflammation, enhanced asthma severity due to gut derived bacteria, endotoxin

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Background
Obesity exacerbates a number of chronic inflammatory diseases including asthma, with increasing adiposity observed to worsen asthma severity and disease control. This exacerbation may arise as gut-derived bacterial fragments (endotoxin) and associated markers of endotoxin (lipopolysaccharide binding protein (LPB)), enter the circulation through a damaged gut barrier, provoking systemic inflammation. This study investigated the role of body weight on gut permeability and systemic inflammation, to influence asthma control and asthma status.
Methods
Fasted blood was collected from Caucasian men (age:52.72 ± 16.08yrs; BMI: 29.16 ± 5.69 Kg/m^2; $n=29$) and women (age: 46.42 ± 14.60yrs; BMI: 32.34 ± 7.48 Kg/m^2; $n=69$) with severe asthma, with and without obesity. Gut permeability marker Calprotectin, LBP and inflammatory markers (granzyme-A, IL-5, IL-6, CCL-4) were assessed in serum and plasma by ELISA. Anthropometric data and Asthma Control Questionnaire-6 (ACQ-6) data were collected.
Results
Our findings highlighted that BMI significantly correlated with self-reported impaired asthma control (ACQ-6score ≥ 1.5;$P<0.05$). Significant positive correlations were identified between BMI and pro-inflammatory biomarkers (granzyme A,$P<0.001$;IL-6, CCL-4, IL-5, all $P<0.0001$). In addition, analysis of circulating LBP showed that patients with poorly controlled asthma (ACQ-6 score ≥ 1.5) had increased LBP levels compared with well controlled patients with asthma (LBP:15.10 ± 7.88μg/mL Vs 10.95 ± 4.5 μg/mL; $P=0.0279$). Furthermore, irrespective of asthma control, LBP was increased in patients with obesity (LBP:17.06 ± 8.35μg/mL) compared with patients who were overweight (LPB:11.83 ± 6.6μg/mL; $P=0.0003$) or lean (LBP:11.36 ± 4.27μg/mL; $P=0.0004$). LBP levels were also significantly positively correlated with BMI ($P<0.0001$), permeability marker ($P<0.0001$) and inflammatory biomarkers ($P<0.05$).
Conclusion
In summary, patients with asthma and obesity were observed to experience impaired asthma control, with increased gut permeability and raised inflammatory mediators and markers. These data therefore suggest that reducing body weight, or therapeutically targeting the gut to reduce gut permeability, may offer people with obesity and severe asthma some improvement in their chronic inflammation conditions and disease management

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P212

Can improved glycaemic control improve NAFLD independent of weight loss in patients with type 2 diabetes?

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Aim
The current focus for the treatment of Non-Alcoholic Fatty Liver Disease (NAFLD) is lifestyle intervention with the aim of significant weight loss. NAFLD is tightly associated with type 2 diabetes (T2D) and obesity. In patients with T2D, glucose lowering agents that promote weight loss have shown a beneficial impact on NAFLD. However, it remains unclear as to whether glucose lowering can improve NALFD in patients with T2D, independent of weight loss.
Methods
In a retrospective analysis of data from 802 people with T2D, we examined the longitudinal impact of optimizing glycaemic control with DPP-IV inhibitors,

GLP-1RAs and SGLT2 inhibitors on Fatty liver index (FLI) and Fibrosis score 4 (Fib-4) adjusting for changes in BMI and choice of glucose lowering regimen over a 12-month period.
Results
At baseline, FLI correlated with glycated haemoglobin, even after adjustment for BMI ($r=0.734$, $P=0.014$). Linear regression analysis demonstrated a significant correlation between the change in glycated haemoglobin and change in FLI after adjustment for change in BMI, age, sex, and drug class ($r=0.467$, $P=0.031$). The greatest reduction in FLI was observed in patients with the largest reduction in glycated haemoglobin ($P<0.0001$). The probability of improvements in FLI with optimization of glycaemic control was similar with all 3 glucose lowering agents, despite differences in weight reduction. Similar relationships were observed examining the changes in glycaemic control and Fib-4.
Interpretation
Improvements in glucose control that are independent of weight loss are associated with improvement in NAFLD and should form an integral part of the management of patients with co-existent NAFLD and T2D.

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P213

Differentially expressed genes in insulin resistant macrophages are shared across multiple diabetes associated morbidities

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Background
Insulin resistance is the central defining feature of type 2 diabetes and increases with age. People with type 2 diabetes are at an increased risk of cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease and arthritis. Macrophages are phagocytotic leukocytes which play a central role in the development of type 2 diabetes and the chronic inflammatory diseases mentioned above.
Aim
Our aim was to determine if differentially expressed genes from aged insulin resistant macrophages may be conserved across macrophages from multiple diabetes associated morbidities.
Methods
Differentially expressed gene datasets from transcriptome analysis of bone marrow derived macrophages (BMDM) from aged insulin resistant mice gained through chronic hyper-stimulation of the PI3K arm of the insulin signalling pathway via hematopoietic SHIP2 knock-down (h-SHIP2KD) were compared to published transcriptome data sets of macrophages from mouse models of hyperglycaemia, atherosclerotic plaque progression and regression, NAFLD, Alzeimer's disease and arthritis.
Results
Upregulated and downregulated differentially expressed genes were found to be shared between h-SHIP2KD BMDM and all diabetes associated morbidity macrophage datasets analysed. Ongoing analyses are revealing common intracellular signalling pathway regulation between these morbidities.
Conclusion
These data reveal signalling pathways in insulin resistant macrophages which may have the potential to be targeted by new therapeutic strategies to impact diabetes associated chronic inflammatory disease progression.

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P214

C-peptide assessments- are we doing it correctly?

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Background
C-peptide is an amino-acid chain which is an equimolar marker of endogenous insulin. It is used to investigate the cause of non-diabetic hypoglycaemia and classification of diabetes. C-peptide can only be interpreted with a paired venous glucose <3 mmol/l for non-diabetic hypoglycaemia, and >4 mmol/l for diabetes classification.
Aims and Objectives
To determine if: 1. C-peptide tests were requested for appropriate indication 2. Tests were requested with clear information 3. Samples were sent with a paired venous glucose 4. Tests were analysed appropriately as indicated by paired glucose 5. Tests were done with paired insulin for investigation of hypoglycaemia.
Methodology
We completed an audit using data collected from the Royal Bournemouth Hospital (RBH) laboratory. We obtained 320 C-peptide requests, for 130 patients, over 35-month period and analysed according to the objectives.
Results
92.3% of patients had an appropriate indication for C-peptide test; investigation for hypoglycaemia (29.2%) or classification of diabetes (61.5%). Only 91.6% had a clear description on request form. From the 320 C-peptide requests, only 83.5% were sent with a paired glucose. Of the 196 requests for hypoglycaemia, 19.4% were analysed with a glucose >3 mmol/l or without a paired glucose, and 16.7% weren't paired with insulin. As for diabetes classification, of the 90 C-peptide requests, only 67.8% were analysed with a glucose >4 mmol/l.
Conclusion
We found that none of our objectives met the gold standard of 100%. In response, we have discussed our results with the RBH laboratory, to update their glucose cut-off for C-peptide analysis in both hypoglycaemia and diabetes. This audit aims to educate both medical and laboratory staff to request C-peptides only for appropriate indications, to describe clear clinical details, to send all tests with a paired glucose (and insulin for hypoglycaemia) and to process all investigations with an appropriate glucose level.

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P215

Metabolic syndrome and obesity in IBD patients: how common?

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Introduction
Although patients with inflammatory bowel disease (IBD) -Crohn's disease (CD) and ulcerative colitis (UC)- are considered prone to malnutrition, studies have shown an increased risk for obesity, especially visceral obesity and metabolic syndrome (MetS). Possible mechanisms involved include dysbiosis, gut microbiome and chronic inflammation. The aim of the study was to assess the prevalence of MetS and obesity in a group of IBD patients.
Methods
Anthropometric data were collected, and all patients underwent blood tests and body composition data using dual-energy X-ray assessment (DXA) whole body. MetS was diagnosed using IDF criteria.
Results
81 adult patients (48 with CD and 33 with UC), median age 42 (IQR 23), were included in the study. 65% were younger than 50 years. Their median BMI was 24.5 (7.5) kg/m^2, range 12.4-41.3 kg/m^2. Of them, 40.7% had a BMI >25 kg/m^2, 23% were overweight, and 17% had obesity. Only 2% of them were underweight. MetS was present in 20.9% of the patients, with a higher prevalence in UC than CD patients (30.3% vs14.5%). However, approximately 47% were younger than 50 years. Comparative analysis between UC and CD did not show significant differences in weight, BMI, waist or hip circumference. As for the metabolic parameters, triglycerides were statistically higher in CD patients (103 (65) vs 79 (57) mg/dl, $P<0.001$). Moreover, although not included in MetS, VAT was higher in CD than UC patients (807 (1337) vs 549 (1337) mm3, $P=0.05$).
Conclusions
MetS is common in IBD patients, even in younger ones. Although higher prevalence in UC, CD patients seemed to have a higher risk for visceral obesity, which could lead to increased cardiovascular risk. Follow-up studies should be considered.

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P216

Simvastatin regulates *Il10* gene expression in male and female murine macrophages

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Statins are among the most widely prescribed medications worldwide, decreasing the risk of cardiovascular diseases by reducing cholesterol levels. However,

statins also increase the risk of incident type 2 diabetes (T2D), disproportionately affecting women compared to men. Inflammation has emerged as a central factor underpinning T2D pathology, with macrophages playing a significant role. Statins have been found to influence macrophage inflammatory responses, and this has been linked to statin-induced insulin resistance in murine adipose tissue. However, whether sex differences exist in statin-mediated macrophage inflammatory responses and the potential underlying mechanism(s) that drive differential responses has yet to be defined. Treatment of bone-marrow derived macrophages from wild-type c57bl/6 male and female mice with 10 μM simvastatin for 24h decreased *Il10* mRNA expression in both male (0.22-fold, $P=0.0002$, $n=3$) and female BMDMs (0.13-fold, $P<0.0001$, $n=3$) whilst increasing *Il1b* mRNA levels (10.45-fold in males and 4.83-fold in females, $n=4$). These findings demonstrate that statins stimulate a pro-inflammatory response in both male and female macrophages, which may contribute to the diabetogenic action of statins. Ongoing analysis will reveal further statin-mediated macrophage responses, the impact of sex and how these factors may contribute to women's increased statin-induced diabetes risk.

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P217

Ethnic differences in diabetes remission following bariatric surgery

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Background and Aim
Type 2 diabetes mellitus (T2DM) disparately affects ethnic groups. Prevalence is higher in Asian and Black ethnicities, and these patients suffer increased rates of some diabetes-related complications. Bariatric surgery is an effective treatment for T2DM and can lead to complete diabetes remission. The aim of this study was to assess if T2DM remission rates at 1-year following bariatric surgery vary between different ethnicities.
Methods
We retrospectively reviewed electronic records of 946 patients undergoing bariatric surgery at a UK tertiary centre (2015-2021), identifying 293 patients with T2DM. Data was collected on ethnicity, diabetes duration, diabetes-related complications, and pre- and post-operative weight, HbA1c and use of hypoglycaemic medications. Diabetes remission was defined as HbA1c <48 mmol/mol at least 3 months after cessation of hypoglycaemic medication. Odds ratio (OR) of remission was compared using a chi-squared test.
Results
Our cohort was ethnically diverse; including White (39.3%), mixed (2.7%), Asian (17.8%), Black (14.3%) and other ethnicities (14.7%). Weight loss did not differ between ethnicities. Overall diabetes remission rate at 1-year was 42.3%. Asian patients were least likely to remit (OR 0.84 [95% CI 0.43-1.67]), whilst Black patients were most likely to remit (OR 1.63 [95% CI 0.79-3.21]) as compared to White patients. Logistic regression showed diabetes duration, pre-operative use of insulin and pre-operative HbA1c predicted diabetes remission at 1-year.
Conclusions
At 1-year post-bariatric surgery, T2DM remission rates were highest in Black patients and lowest in Asian patients. However, a more precise estimate of effect size would require a larger sample size. Considering the higher prevalence and complication rates of T2DM in these ethnic minorities, understanding differences in metabolic response to bariatric surgery is invaluable in prioritizing surgery. Further assessment of the role of ethnicity in diabetes remission following bariatric surgery in a multi-centre cohort would be vital to develop our initial findings.

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P218

Remote Blood Glucose Level monitoring amongst women with Gestational Diabetes Mellitus during COVID-19

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Introduction
Gestational diabetes mellitus (GDM) is any degree of glucose intolerance developed during pregnancy[1]. Remote Blood Glucose Monitoring (BGM) may facilitate more effective communication between women with GDM and physicians.
Objectives
To evaluate the effectiveness of remote BGM (using OneTouch Verio system) in the management of women with GDM during COVID-19 and assess the impact on delivery modality. Diabetes in pregnancy NICE guidelines were applied.
Methodology
This retrospective study was performed on 217 women with GDM attending Sligo University Hospital (95 in 2019 and 122 in 2021). Data on HbA1c, treatment modality and OneTouch Verio usage were collected using the diabetes Prowellness database. Data on delivery modality were collected using the Euroking database.
Results
In 2019, (pre-pandemic and remote BGM unavailable), majority of women with GDM were diet controlled (39%). 33% required metformin, 11% on insulin and 17% on metformin and insulin. In 2021, majority (43%) were diet controlled, 28% on metformin, 17% on insulin and 12% on both. In 2021(during pandemic), we compared treatment modality amongst women with GDM using remote BGM (58%) vs those not using same. In the remote BGM subgroup, 38% were diet controlled, 30% on metformin, 12% on insulin and 20% on both. The mode of delivery in 47% of these women was caesarean section (34% elective and 13% emergency). In the subgroup of women not using remote BGM in 2021; 49% diet controlled, 25% on metformin, 24% on insulin and 2% on both. The mode of delivery in 28% of these women was caesarean section (6% elective and 22% emergency).
Conclusion
During the COVID-19 pandemic, the use of remote BGM resulted in more women being treated with insulin. Of note, there were less emergency caesarean sections amongst women using remote BGM.
Reference
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P219

Clinical profile and risk factors for severity and mortality of post-COVID-19 mucormycosis

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Background
Mucormycosis is a serious but rare angio-invasive fungal infection in high-risk patients with diabetes, organ transplantation, neutropenia, and hemochromatosis. The COVID-19 pandemic has been associated with increased incidence of mucormycosis and the incidence has risen more rapidly during the second wave of pandemic in India. The clinical profiles and risk factors for severity and mortality are not very clear among patients with COVID-19 infected with mucormycosis.
Methods
Data was collected from patients hospitalized to PSG Hospitals and Research Centre, Coimbatore, Tamilnadu, India, with mucormycosis infection, during the period April 2021 to August 2021. Patients were managed surgically and medically with amphotericin B (conventional/ liposomal) for 3 weeks, followed by oral antifungal therapy for 3 weeks. We aimed to analyse the clinical profile and the risk factors for severity and mortality among these patients.
Results
104 patients with COVID-19–associated rhino-orbito-cerebral mucormycosis (CAM) with a mean age (SD) of 53.7 (11.8) years were included in the analysis. 88 (84.6%) were men. All were type 2 diabetics (11.6% newly diagnosed). 80.8% of them had HbA1C level > 6.4% proving the risk of mucormycosis in uncontrolled diabetes ($P<0.001$). Endoscopic sinus surgery (ESS) with debridement was performed in 51.92% of patients. ESS with debridement, along with orbital compression was done in 21% of patients. Of the 104 patients with CAM, 16.35% died, 35.5% underwent maxillectomy, 1.92% evisceration, whereas 7.6% underwent exenteration. 81.7% had intravenous amphotericin B and 18.3% had retro-orbital amphotericin B. On multivariate analysis, intravenous amphotericin B administration (Estimate: 1.48; P = .029) and HbA1C levels (Estimate: 4.24; $P=0.039$) showed significant association with disease outcome.
Conclusion
Increased morbidity and mortality from mucormycosis are associated with uncontrolled diabetes mellitus and systemic steroid use. Precautions necessary to

manage patients with mucormycosis in COVID-19 are control of diabetes and judicious use of steroids.

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P220

Endotoxin Impairs Brown Fat Phenotype and Mitochondrial Function in 2D and 3D Brown Adipocytes Models

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Background
Dysfunctional adipose tissue in obesity is known to contribute to metabolic diseases, including type 2 diabetes mellitus (T2DM). This may be due to increased gut-derived endotoxemia (LPS) reducing brown adipose tissue (BAT) activity and altering mitochondrial function. However, the effect of LPS on BAT activity in 3D culture models has not been studied, despite giving a better representation of in-vivo tissue. Therefore, this study investigated the effects of LPS on 2D and 3D brown adipocyte biology and mitochondrial function.
Methods
Immortalized murine brown adipocyte 2D and 3D (spheroid) cultures were differentiated with/without LPS (100 ng/ml). β3-adrenergic stimulator CL316,243 (CL) (10 μM), was used to induce BAT activity via UCP1. Gene and protein expression were analysed using qRT-PCR and immunohistochemistry.
Results
LPS reduced expression of browning genes in 2D and 3D models: CIDEA (2D: FC = -14.11, $P < 0.0001$; 3D: FC = -26.21, $P < 0.0001$), ELOVL3 (2D: FC = -24.84, $P < 0.0001$; 3D: FC = -59.82, $P < 0.001$), PLIN5 (2D: FC = -24.18, $P < 0.01$; 3D: FC = -20.32, $P < 0.0001$). Moreover, LPS decreased UCP1 gene expression in basal conditions (2D: FC = -56.38, $P < 0.05$; 3D: FC = -25, $P < 0.05$) and following CL treatment (2D: FC = -2.82, $P < 0.01$; 3D: FC = -7.41, $P < 0.0001$). Immunohistochemistry identified reduced UCP1 expression in LPS-differentiated 3D spheroids ($P < 0.0001$). Mitochondrial genes were also reduced with LPS including (a) dynamic genes: DRP1 and MFN2, with a maximum reduction of FC = -3.2 ($P < 0.001$) in 2D and FC = -6.03 ($P < 0.0001$) in 3D models, (b) biogenesis genes: PGC1α and POLG with a maximum reduction of FC = -3.31 ($P < 0.0001$) in 2D and FC = -8.67 ($P < 0.0001$) in 3D model, and other key functional genes CPT1β, CS, COX4I1.
Conclusion
This study identified LPS as an inhibitor of brown adipocytes phenotype and mitochondrial function, with more potency in 3D spheroids. This highlights that gut-derived endotoxemia may contribute to individual brown adipocyte dysfunction and reduced browning capacity of the adipocyte cell population. Therefore, targeting this inflammatory pathway may therefore reduce obesity-associated metabolic dysfunction.

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P221

Pregnancy following islet cell transplantation in a woman with type 1 diabetes and autoimmune Addison's disease

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A 33-year-old woman with type 1 diabetes and autoimmune Addison's disease conceived in September 2021 following careful preconception counselling. The patient had a history of recurrent, severe hypoglycaemia requiring intensive care admission and had previously received two allogenic islet cell transplants (January 2020 and November 2020). The patient had no severe hypoglycaemia following transplantation, although she continued to experience overnight hypoglycaemia, while in a steroid deficient state. Total daily dose of insulin required post-transplantation was < 10 units. The pregnancy was complicated by hyperemesis and recurrent adrenal crises, despite careful monitoring of glucocorticoid and mineralocorticoid replacement. Tacrolimus was continued throughout the pregnancy as immunosuppressive therapy, with escalating doses required for therapeutic effect. Crucially, from 18 weeks of pregnancy, when women with diabetes typically experience rising insulin resistance because of placental hormone production, this patient's insulin requirements did not increase. Overnight hypoglycaemia in the context of autoimmune Addison's disease remained a clinical concern. C-peptide secretion was measured throughout each trimester and did not significantly change across the course of the pregnancy (*latest biochemistry results pending)*. In the third trimester, the patient developed pre-eclampsia. This complication occurred in the setting of an apparently 'normal' blood pressure: a consequence of mineralocorticoid depletion and her medical comorbidities. A Caesarean section was performed at 35 + 3 weeks. The neonate developed severe hypoglycaemia and required ventilation during the first day of life. Both mother and baby recovered quickly and were discharged home one week later. This case illustrates a complex pregnancy with a successful outcome in the rare and challenging setting of type 1 diabetes with islet cell transplantation and concurrent Addison's disease. Importantly, biochemical surveillance reveals that the function of the transplanted islet cells has not been negatively impacted upon by the profound insulin resistance of pregnancy.

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P222

Investigating the effects of 5.5 mmoL vs 25 mmoL glucose concentration in culture media on LHCN-M^2 cell viability, proliferation, metabolism and differentiation

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Introduction
In vitro skeletal muscle cell models are vitally important for investigating the molecular mechanisms of skeletal muscle in metabolic and endocrine diseases, such as obesity and type 2 diabetes. Culture media for skeletal muscle cells can often contain glucose concentrations (GC) five times higher than what's considered normal in fasting human plasma, thus is not representative of the *in vivo* environment. Hyperglycaemia in culture media may negatively impact metabolic function, by creating a model of cell toxicity that's representative of diseases such as *diabetes mellitus*. The aim of these experiments was to determine the impact of media containing GC of 5.5 mmol (physiological) vs 25 mmol (supraphysiological) on cell viability, proliferation, ATP production and differentiation in human LHCN-m^2 myoblasts.
Methods
LHCN-m^2 myoblasts were cultured in 5.5 mmol or 25 mmol glucose growth media and cell viability, ATP production, and proliferation were determined. Differentiation of LHCN-m^2 myoblasts into multinucleated myotubes was induced by reducing levels of human serum within the culture media and analysed by immunofluorescence following 10 days of differentiation.
Results
We observed no differences in the viability, proliferation or basal ATP production rates of LHCN-m^2 cells grown in 5.5 mmol compared to 25 mmol glucose ($P > 0.05$ for all). However cells had a trend of higher ATP production rates and faster proliferation in 5.5 mmol compared to 25 mmol. Fluorescence microscopy revealed the formation of multinucleated myotubes differentiated in 5.5 mmol glucose media containing various concentrations of human serum (0.5%, 1% and 2%).
Conclusions
Our data demonstrates the ability to differentiate LHCN-m^2 cells in 5.5 mmol GC, which allows our *in vitro* model to be more physiologically-relevant and more comparable to what is observed *in vivo* in humans. Further work is required to determine the implications of GC on the wider metabolic function in LHCN-m^2 myoblasts.

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P223

Micronutrient concentrations and their associations with BMI in bariatric surgery patients

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Purpose
Obesity and/or bariatric surgery can be associated with micronutrient deficiencies. We studied whether there was a correlation between body mass index (BMI) and micronutrient levels pre- and post-bariatric surgery.

Methods
We performed a retrospective cohort study of 745 patients who underwent bariatric surgery in a Northwest England teaching hospital. Patients were recommended standard postoperative supplements consistent with national guidelines. Data on concentrations of folate, iron, vitamin B12 and vitamin D and BMI were collected from electronic patient records before surgery and at 4-,12-,24-,36- and 48-months of follow-up.
Results
The patients included 514 (69.0%) women; 496 (66.6%) underwent gastric bypass, 240 (32.2%) sleeve gastrectomy and 10 (1.3%) gastric band surgery. At baseline, mean ± SD age was 47.0 ± 10.5 years, weight 135.1 ± 23.6 kg and BMI 51.2 ± 7.7 kg/m^2; folate was 8.0 ± 3.9 µg/l, iron 12.2 ± 4.6 µmol/l, vitamin B12 411.4 ± 269.1 ng/l and vitamin D 32.6 ± 24.1 nmol/l. BMI at baseline was inversely correlated with serum folate (coefficient, -0.221) and vitamin D (-0.269), and weakly correlated with vitamin B12 (-0.069) and iron (-0.077) concentrations Mean concentrations of folate, iron, vitamin B12 and vitamin D increased with supplementation at follow-up.
Conclusion
The continued increase in micronutrient concentration and weakening negative correlation found between BMI, folate and vitamin D after follow-up appointments indicates the effectiveness of micronutrient supplementation. Investigations into the effect of other variables on micronutrient concentrations post-bariatric surgery are necessary to comprehend the BMI–micronutrient relationship further.

	12 months	24 months	48 months
Folate (µg/l)	12.28	12.83	13.15
Iron (µmol/l)	14.80	15.14	13.90
Vitamin B12 (ng/l)	638.76	691.90	711.97
Vitamin D (nmol/l)	52.28	56.82	53.75

Table of mean micronutrient concentration before bariatric surgery at follow-up.

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P224

The importance of identifying severe hyponatraemia early in hospitalised patients and early referral to endocrinology. Our experience in a large secondary care teaching hospital

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Background
Hyponatraemia is known to be associated with significantly increased mortality in hospitalised patients. We identified the number of cases of hyponatraemia referred for an endocrine opinion in our hospital, examined the causes present, and assessed how the speed of referral to endocrinology could affect the management.
Methods
Inpatient referrals were audited over a 6-month period from 1st October 2021 to 30th April 2022. Data regarding the condition being referred, time taken to refer, and initial blood test investigations were obtained using the Cerner electronic patient database.
Results
Over the 6-month period, there were 103 referrals (64 female, 39 male, age range 22 to 95 years; mean age 73 years) with hyponatraemia. Of these, 34 were severe cases (sodium less than 125 mmol/l), 47 were moderate cases (sodium 125-129 mmol/l) and 22 were mild cases (sodium 130-135 mmol/l). 49 cases were due to hypervolaemic hyponatraemia, 33 cases were euvolaemic hyponatraemia due to the Syndrome of Inappropriate ADH (SIADH) secretion, and 21 were due to hypovolaemic hyponatraemia. 44% of referrals were sent within 48 hrs of the condition being identified, and 56% over 48 hrs. Appropriate initial investigations had been completed (paired serum and urine osmolality, 9am cortisol and thyroid function tests) in 46% of cases referred. 72% of patients referred for an endocrine review within 48 hrs had a gradual improvement in sodium within 72 hours, compared to 43% of patients referred more than 48 hrs after identifying hyponatraemia.
Conclusion
The early identification of hyponatraemia and early referral for an endocrine opinion increases the probability of hyponatraemia improving within 72 hours. We will provide education to our junior doctors during a quality improvement project to emphasise the importance of referring severe hyponatraemia to endocrinology in a timely manner, with appropriate initial investigations to enable earlier treatment.

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P225

Characterisation of the mechanism of long-chain fatty acid uptake in human-derived pancreatic beta cells

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Background
It is widely believed that increased circulatory concentrations of long-chain saturated fatty acids (LC-SFA) significantly contribute to the death and dysfunction of pancreatic β-cells in the development of type 2 diabetes (T2D). The mechanism by which LC-SFA cross the β-cell plasma membrane has not been fully established. This work aims to characterise the mechanism underpinning this uptake. Ultimately, regulation of LC-SFA entry may maintain β-cellviability, thereby slowing, or potentially halting, the progression of T2D.
Methodology
To determine whether the fluorescent LC-SFA analogue, BODIPY FL C_{16}, crosses plasma membranes using simple diffusion, cell-sized giant unilamellar vesicles (GUVs) were formed using microfluidics. RNA-seq analysis, with differential gene expression analysis of six transcriptomics datasets of human-derived EndoC-βH1 β-cells, human islets, adipocytes, and hepatocytes, determined quantitative differences in the expression of candidate LC-SFA transport proteins (CTPs). Changes in CTP gene expression was assessed using qRT-PCR in EndoC-βH1 cells following a 6h exposure to LC-FFA C16:0, C18:0 and C18:1 in low (5.5 mM) and high (20 mM) glucose. The rate of uptake of LC-SFA in EndoC-βH1 cells was assessed using a pHrodo™ Green AM intracellular pH indicator and dynamin inhibited with Dyngo™-4a.
Results
BODIPY FL C_{16} rapidly permeated GUV membranes. The profile expressions of LC-FFA transport proteins in hepatocytes and adipocytes significantly differed to those of human islets and EndoC-βH1 cells indicating that the mechanism of uptake differs in these cell types. Human islets and EndoC-βH1 cells had a similar pattern of expression with CD36, ACSL1-4 and FATP4 being upregulated in both. Exposure to LC-FFA in high and low glucose did not alter CTP expression. There was a rapid ($<$20s) uptake of LC-SFA, which was inhibited when the cells were pre-incubated with the dynamin inhibitor.
Conclusion
LC-FFA can cross artificial membranes using simple diffusion, and LC-FFA uptake seemingly occurs via a dynamin-mediated process in β-cells.

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P226

Use of Freestyle Libre® In People with Type 2 Diabetes Mellitus in Specialist Diabetes Clinic

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Introduction
Flash glucose monitoring has been widely used for people with T1DM over the last 10 years. In March 2022 NICE guidelines recommended extending use to people with T2DM on insulin, previously use was limited to people on dialysis and those self-funding.
Aim
To examine the use and outcomes of flash glucose monitoring in people with T2DM.
Methods
People with T2DM locally who have used flash glucose monitoring for more than 90 days were identified on Libreview®. We used hospital records to identify HbA1c prior to initiation and at least 60 days post initiation. Sensor data were evaluated using Libreview.
Results
Using LibreView, we identified 25 people with T2DM, mean age 57.9 (± 10.53) who used flash monitoring for > 90 days between March 2021 and April 2022. All patients were on insulin, 14 were on basal-bolus, 4 on mixed insulin and 7 on basal only. 6 were on injectable GLP-1 agonists and 8 were on oral hypoglycaemic medications. 7 people were on haemodialysis and 3 were post renal transplant. We have pre and post HbA1c for 18 people. The median HbA1c

reduction was 0.45% (4.9 mmol/l) (IQR -1.5% to +0.26%). The median Time In Range (TIR) was 63% (range 0% - 96%), with 32% having TIR over 70%. Median Time Below Range was 0% (range 0% - 6%), median Time Above Range was 37% (range 1% - 100%). Mean GMI was 7.87 (± 1.64).
Conclusions
Flash glucose monitoring has similar reductions in HbA1c in T2DM as in T1DM. Wider use as per newer NICE guidance will help a wider population of people with insulin treated diabetes.

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P227

Covid - 19 Vaccination Acceptance Among Type 2 Diabetes Patients In University of Medical Science Teaching Southwest Nigeria

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Background
The mortality from COVID-19 is higher in DM patients compared to the general population. Hence, it is highly desirable that diabetic patients are vaccinated against COVID-19 infection in order to reduce their risk of contracting the disease and having devasting consequences from the infection.
Aim
The aim of this study is to determine the willingness of type 2 DM patients to accept COVID-19 vaccine and the factors that influence their decision and to provide useful information to address their concerns about COVID-19 vaccines and improve its uptake
Materials and Methods
This cross-sectional descriptive study was carried out between February and May 2022 in which consecutive diabetes patients were administered questionaire after an informed consent. Descriptive statistical analysis was employed for categorical and continuous variables and multivariable logistic regression was used assessed willingness to receive vaccine and its determinants.
Results
Of the 302 diabetes patients that participated in the study. (65.9%) were 60 years and above and majority were male (68.9%) and married (67.9%). Though majority perceived COVID-19 to be a serious disease; 33.5% considered themselves to be at risk of contracting COVID-19 despite being diabetic. Acceptances of the COVID-19 vaccination was high in the study participants (70.2%). Factors associated with the willingness to be vaccinated include, perceived seriousness of the disease, previous vaccination and level of education ($P < 0.001$). Age ($P = 0.367$), marital status ($P = 0.292$), religion ($P = 0.3570$ and participants occupation ($P = 0.468$) were not significantly associated with the willingness to receive COVID-19 vaccine.
Conclusion
Despite the perceived seriousness of Covid 19 infection in diabetes patients, 30% of the study participants were not willing to receive COVID-19 vaccination, education and awareness campaign are necessary to bridge this gap so that all diabetes patients can be vaccinated to reduce mortality associated with COVID-19.

Keywords: Covid 19, Vaccine, acceptance type 2 diabetes, Nigeria
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P228

Self-care pattern in patient living with type 2 diabetes Southwest, Nigeria

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Background
Self-care practices in patient living with diabetes are important to effectively prevent, manage, and limit complications associated with diabetes as patients spend more time alone than they spent with health care providers in managing their health conditions.
Aims
The aim of the study was to evaluate self-cate practices and their determinants in patients living with type 2 diabetes. Hence, this study aimed at assessing self-care practices and their determinants among patients with type 2 diabetes.
Materials and Methods
This cross-sectional, descriptive, multi-center study was conducted among 348 type 2 diabetes patients selected from six tertiary hospitals in Southwest Nigeria. Descriptive statistical analysis was employed for categorical and continuous variables and multivariable logistic regression assessed association between determinant factors and adherence to self-monitoring of blood glucose (SMBG).
Results
Of the study participants, 83.1%, 66.9%, 28.4%, and 27.9% adhered to prescribed medications, physical exercise, had meal plans incorporated into their diabetes management and SMBG, respectively. There was a statistically significant association between male gender, duration of diabetes, and previous episode of hypoglycemia with adherence to SMBG practices while lower educational level and use of insulin were associated with less likelihood of adherence to prescribed medications.
Conclusion
The degree to which patients living with diabetes adhered to recommended self-care practice components were less than satisfactory especially SMBG, physical activity, and having meal plans.

Keywords: Determinants, Nigeria, self-care practices, type 2 diabetes
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P229

FreeStyle Libre 2 use in non-diabetes setting – A case of post-bariatric surgery dumping syndrome causing severe hypoglycaemia in pregnancy

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Flash glucose monitoring has increased dramatically in patients with diabetes since the introduction of the FreeStyle libre 2 (FSL) incorporating hypoglycaemia predictive features and an alarm system. A 31-year-old lady, gravida 2, para 1 presented at 26 weeks' gestation following a car accident where she fractured clavicle and navicular. She reported blurred vision and subsequent collapse whilst driving (with her daughter as a passenger) prior to the accident. Paramedics at the accident scene documented severe hypoglycaemia with a blood glucose of 1.6 mmol/l which was appropriately treated. Five years previously she underwent Roux-en-Y gastric bypass surgery with a consequent drop in BMI from 47.7 kg/m^2 to 29.9 kg/m^2. Whilst she reported minor post prandial hypoglycaemic symptoms pre pregnancy these had not required medical advice, but she had noticed these more frequently in preceding weeks. A 2-hour glucose of 2 mmol/l was noted from a 24-week OGTT to exclude gestational diabetes. Despite intensive dietary advice she continued to suffer severe hypoglycaemic episodes for the next 2 weeks with glucose values below 2 mmol/l. She had severe hypoglycaemia during her OGTT done at 24 weeks gestation. A FSL-2 with hypoglycaemia alarm was inserted to reduce the risk of further seizures and maternal harm. The frequency and severity of hypoglycaemia was reduced but not completely eradicated following the FSL-2. Within 24 hours of delivery the severe hypoglycaemic episodes were eradicated but the patient continues to flash monitor for 4 weeks for reassurance and to obtain evidence to restart driving. Severe hypoglycaemia during pregnancy should be recognised as a complication following Roux-en-Y bypass surgery. Such patients with low 2-hour glucose values at OGTT should receive further dietary advice. In non-diabetic patients with severe hypoglycaemia e.g., dumping and insulinoma flash monitoring can be invaluable in reducing harm from hypoglycaemia.

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P230

Impact of COVID-19 Lockdown on Biomarkers of Diabetes and Dyslipidaemia

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Introduction
Impact of COVID -19 lockdown on care of patients with chronic disorders such as dyslipidaemia and diabetes still being realized. We examined if care was impacted by assessing biomarkers for diabetes and dyslipidaemia management as well as for vitamin D status, often monitored in general practice.
Methods
Retrospective laboratory data for total cholesterol, glycated haemoglobin (A1c) and for vitamin D levels were obtained for late (October to December) for 2019 (prior to COVID-19 lockdown), and for early (January to April) 2020, early 2021, late 2021, and early 2022. Laboratory results were analysed for abnormality and significance using NCSS statistical software.
Results
Results from 59,782 patients, aged 4 to 97 yrs (median 53) including 36,260 females were analysed. Median cholesterol levels were 4.7, 4.87, 4.67, 4.94, 4.89 mmol/l, mean A1c were 6.8, 6.9, 6.9, 6.8, and 6.9 %, and Vitamin D levels; 23.4, 21.6, 23.1, 26.45, and 22.3 ng/mL for late 2019, early 2020, early 2021, late 2021, and early 2022 respectively. There was no significant difference ($P > 0.54$) in cholesterol levels between late 2019, early 2020, and early 2021, however, levels were higher in late 2021 ($P = 0.05$). Similarly, for A1c, no significant changes ($P > 0.35$) were observed except for higher levels in late 2021 ($P < 0.005$). As for vitamin D status a significant ($P < 0.005\%$) decline in early 2020 from late 2019 reflects seasonal variation, however, in contrast to the other biomarkers, levels in late 2021 were significantly higher ($P < 0.005\%$).
Conclusion
The increase in total cholesterol and A1c levels suggests a decline in care by late 2021 consistent with prolonged COVID-19 lockdown in 2020 and 2021. Vitamin D status suggests either active intake possibly influenced by media or by exposure to outdoor activities. Limited access to routine healthcare may have had unfavourable outcomes on diabetes and dyslipidaemia.

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P231

Relationship between gestational diabetes mellitus and incidence of post-delivery dysglycaemia

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Background
Gestational diabetes mellitus (GDM) is defined as glucose intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. GDM is a risk factor for dysglycaemia in later life. The objective of the study was to determine the impact of GDM on glucose tolerance in the short term post-delivery in a cohort of women who attended the Lagos University Teaching Hospital (LUTH)
Study Design
This was a prospective observational study.
Methods
One hundred and twenty-eight pregnant women who attended LUTH antenatal clinics and who had no history of pre-gestational glucose intolerance were recruited in the first trimester of pregnancy. Pertinent data were collected via a questionnaire. The participants underwent a 75g oral glucose tolerance test (OGTT) at 24-28 weeks gestational age. Venous plasma glucose was measured via the glucose oxidase method. GDM was diagnosed using the World Health Organization (WHO) 2013 criteria. The participants were followed up and OGTT repeated at 6-12 weeks post-delivery.
Statistical Analysis
Descriptive statistics were presented using mean and standard deviation. P-value ≤ 0.05 was considered statistically significant.
Results
Among the participants with GDM, the incidence rate of dysglycaemia at 6-12 weeks post-delivery, was 333 per 1000 person-years. Impaired glucose tolerance (IGT) was the most common (77.8%) dysglycaemia observed. Presence of hypertension ($P = 0.004$) and use of insulin during pregnancy ($P = 0.024$) were significantly associated with post-delivery dysglycaemia.
Conclusions
GDM had a significant impact on the incidence of dysglycaemia in the short-term, 6-12 weeks post-delivery, in women who accessed care at LUTH. Hypertension and requirement of insulin for glucose control increased the likelihood of abnormal glucose metabolism following delivery, in a pregnancy complicated by GDM.
Keywords: Gestational diabetes mellitus, post-delivery dysglycaemia, Lagos.

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P232

Transient Diabetes mellitus post Covid 19 vaccination

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Background
Covid 19 infection has previously been reported to be associated with worsening of pre-existing and new onset diabetes mellitus1. However, the association of new onset autoimmune diabetes mellitus after Covid vaccination is not fully recognised in the literature.
History
We report the case of a 58-year-old healthy woman who received a Covid 19 vaccination on 14th of Nov 2021. 2 weeks subsequently she was admitted with headache, blurred vision and visual disturbances and was diagnosed with migraine. Random blood glucose was noted to be 15.3 mmol/l and HbA1c 129 mmol/l confirmed a diagnosis of diabetes mellitus. She had past medical history of Ehlers-Danlos syndrome, factor V Leiden mutation and recurrent venous thromboembolism (VTE) but not diabetes mellitus. HbA1c performed 6 months previously showed a normal result, 37 mmol/l. Her prescribed medications were Warfarin, Quetiapine 300 mg OD, Venlafaxine 75 mg OD and Tapentadol. CT scan of abdomen was done which showed no evidence of any pancreatic abnormalities. Patient was commenced on Metformin and discharged home. Glutamic Acid Decarboxylase, IA-2, and Zinc transporter-8 antibodies were checked and all of them were negative. She was readmitted to hospital 3 months following her initial admission with right leg pain and swelling. On this occasion, HbA1C was 36 mmol/l. Her weight had been steady. Metformin was withdrawn.
Conclusion
It was thought to be a case of DM secondary to some immunological phenomenon after COVID vaccination.
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P233

Hyperglycemia and clinical outcomes among patients with acute ischemic stroke

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Introduction
Hyperglycemia is common in acute ischemic stroke and is associated with worse neurological outcomes. This study aims explore the association between hyperglycemia and short-term stroke outcomes.
Methods
We retrospectively reviewed the records of 97 consecutive patients with acute ischemic stroke managed in a cardiovascular hospital. Hyperglycemia was defined as RBG $>$ 7.8 mmol/l on admission, and was considered sustained if it persisted beyond 24 hours. HbA1c was done in patients with diabetes or hyperglycemia An NIHSS score $>$ 10 was classified as severe stroke and modified Rankin Scale (mRS) score $>$ 2 as stroke-disability. Seventh-day neurological improvement (SDNI) was defined as a $\geq$ 2-point improvement in NIHSS score by day-7. The association between diabetes status, hyperglycemia, HbA1c and the stroke severity, disability, improvement and 30-day mortality was analyzed.
Results
Insulin was required in 29 patients, most commonly basal + supplemental insulin regimen. Patients with diabetes were more likely to have significant stroke-disability (Or=2.54 CI 1.07 – 6.04), but it was not significantly associated with stroke severity, SDNI or 30-day mortality. Patients with admission hyperglycemia had a trend for high-mortality (Or=3.05, CI = 0.99 – 9.5), but was only significant amongst patients with sustained hyperglycemia (Or=4.78, CI = 1.46 – 15.68). Hyperglycemia was not significantly associated with the other stroke indices. HbA1c level was not associated with stroke severity, disability, improvement or mortality.

Variable	Mean or Frequency	Variable	Frequency
Age	61.4 ± 12.5 years	Males	61 (62.9%)
Hypertension	87 (89.7%)	Diabetes	41 (42.3%)
Initial hyperglycemia	36 (37.1%)	Sustained Hyperglycemia	28 (28.9%).
Initial blood glucose	8.2 ± 4.4 mmol/l	HbA1c > 6.5%	40 of 61 patients.
Duration of Admission	7.1 ± 6.4 days	30-day mortality	15.5%.

Conclusion
Poor neurological outcomes are common amongst stroke patients with diabetes. Hyperglycemia portends a high-risk, especially when sustained while HbA1c does not have any apparent short-term prognostic implications.

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P234

Hyperglycaemia in patients with Acute Coronary syndromes (ACS): Retrospective audit data from Barnsley Hospital NHS Foundation Trust

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Hyperglycaemia is common in patients (~65%) when they are admitted to hospital with ACS. It is recognised to be one of the important prognostic indicators for all-cause mortality in patients who present with ACS, regardless of pre-existing diabetes1. NICE guidelines recommend to keep blood glucose (BG) levels below 11 mmol/l2 and offer all people with hyperglycaemia after ACS (without known diabetes) for HbA1c 3 check before discharge. We were interested to see whether we followed our national guidelines.
Methodology
Retrospective electronic data collection over a period of 5 months. 31 patients who presented with ACS with BG of >11 mmol/l and trend of BG levels monitored.
Results
93.5% of the patients had pre-existing diabetes with BG ranges 11-20 mmol/l. 6.5% noted with new hyperglycaemia. None of these patients met the target glucose levels of <11 mmol/l whilst in-patients. Subcutaneous Insulin added to their original treatment in21 %, however dose titration not optimised to achieve the required BG target level. 79% there is no changes were made in their usual diabetes control method despite high BS. 41.9% had their HbA1c levels checked prior to hospital discharge.
Conclusion
Hyperglycaemia is common during ACS which should be effectively managed by clinical team to minimise adverse clinical outcome. It is vital to establish "best practice" guidelines within the hospital with appropriate follow up.
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P235

Diabetic Ketoacidosis (DKA) in Maturity Onset Diabetes of Young (MODY) associated with Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

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Introduction
DKA is often seen in people with Diabetes Mellitus I and seldom in Diabetes Mellitus II but rarely seen in Maturity Onset Diabetes of Young (MODY) and even more rare in association with SGLT2i.
Case history
44 years female, genetically confirmed Hepatocyte Nuclear Factor 1 alpha (HNF1A) MODY since 2004 initially treated with maximum doses of metformin and gliclazide and then lost to follow-up. GP initiated Empagliflozin a year before presentation due to suboptimal diabetes control. There was no previous history of DKA. Her mother and grandmother also had MODY. She presented to accident and emergency with nausea, vomiting, abdominal pain and unable to tolerate any fluids. She was hemodynamically stable but her blood results confirmed severe DKA (with hyperglycaemia). Empagliflozin (SGLT2i) was stopped and local DKA protocol was commenced. She was later transferred to high dependency area for monitoring purposes due to severity of DKA and very slow resolution of ketosis but did not require cardiovascular or respiratory support. She gradually improved clinically and biochemically without any complications and discharged on gliclazide and metformin with stable glycaemic control on out-patient follow-up.
Investigations
Full blood count showed raised white cells count but normal C-reactive protein. Renal, liver, coagulation profile and Chest X-Ray were normal. Blood glucose: 21.9 mmol/l; pH: 6.83; HCO3: 1.9 mmol/l; Ketones: 5.2 mmol/l Pre-admission HbA1c: 39 mmol/mol 3 month post-admission HbA1c: 44 mmol/mol
Results and treatment
Local DKA protocol resulted in complete resolution of DKA without any complications and SGLT2i was discontinued.
Conclusions and points for discussion
- Historically, DKA was considered as one of the exclusion criteria for MODY but several reported cases resulted in omission of this criterion.
- MODY patients are equally at risk of DKA therefore decision regarding SGLT-2i like empagliflozin should be cautiously considered.
- Management remains same as for standard DKA besides discontinuing SGLT2i.

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P236

Specialist Weight Management Service: COVID19 did not break our spirit

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Background
The COVID19 pandemic greatly affected the delivery of outpatient clinics. Tier 3 specialist weight management services (SWMS) aim to help obese patients lose weight through holistic lifestyle modification delivered by a multidisciplinary team consisting of specialist physicians, dieticians, physiotherapists, psychologists, and support workers. Prior to the pandemic, the service was delivered mainly through in person consultations. The nature of the pandemic necessitated a switch to virtual consultation. We hypothesise that this change may have negatively affected the success and efficacy of the service.
Aim
To determine the extent of the impact COVID19 and the change from in person to virtual consultations had on the efficacy of our SWMS.
Methods
Data from two 6-month periods was collected retrospectively from case notes. The first period was October 2018 – March 2019 (pre-COVID19 group) and the second was March – August 2020 (COVID19 group). All consecutive patients initiated from a single centre were included for analysis. Outcome measures were percentage of patients $>5\%$ weight loss, percentage of patients $>10\%$ weight loss, and length of time spent under care of our service.
Results
71 patients were initiated in the pre-COVID19 group and 76 patients in the COVID19 group. Average age was 46.1 and 41.4 years for pre-COVID19 and COVID19 respectively. Both groups were mainly female (85.9% pre-COVID19, 75% COVID19). Percentage of patients with $>5\%$ weight loss was not significantly different between groups (30% pre-COVID19, 36% COVID19). Percentage of patients with $>10\%$ weight loss was significantly different (6.7% pre-COVID19, 15.3% COVID19). Length of time under care was not significantly different between groups (417 days pre-COVID19, 436 days COVID19).
Conclusion
COVID19 and the switch to virtual consultations did not worsen the performance of our SWMS.

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P324

Metformin inefficiency in vitamin B12 deficient hepatocytes to lower lipids is alleviated via Adiponectin-AMPK axis

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Introduction
Non-alcoholic fatty-liver disease and T2DM remain a global burden. Metformin is the first-line drug for T2DM that decreases glucose and lipid levels. However, prolonged metformin treatment decreases vitamin B12(B12), whereas low B12 is associated with obesity and dyslipidaemia. Clinical studies showed that metformin treatment increases circulating adiponectin and adiponectin improves NAFLD. Others suggested that metformin has no effect on intrahepatic triglyceride (TG) levels. We hypothesised that low B12 might impede metformin-induced intrahepatic lipid lowering effect. We tested this hypothesis and assessed whether low B12 impairs the beneficial effect of metformin on hepatic lipid metabolism and the potential underlying mechanisms.
Methods
HepG2 cells were cultured using custom-made B12 deficient EMEM-media and seeded with different concentrations of B12: 500nM(control), 1000pM(1nM), 100pM and 25pM(lowB12), followed by 24-hour metformin/adiponectin treatment. Western-blotting, RT-qPCR, total intracellular TG, radiochemical analysis of TG synthesis and seahorse mitochondria-stress assays were undertaken.
Results
In low-B12 hepatocytes, total intracellular TG and synthesized radiolabelled TG were increased. Regulators of lipogenesis-(SREBF1), cholesterol-(LDLR) and genes regulating lipogenesis, TG and cholesterol biosynthesis were increased. Genes regulating fatty acid oxidation-(FAO) and mitochondrial function were decreased. We also observed decreased pAMPKα and pACC levels. Following metformin treatment in low B12-hepatocytes, we found that the gene and protein expression of above targets were not alleviated. However, adiponectin independently decreased intrahepatic lipid levels even in low B12 conditions via upregulated pAMPKα and pACC levels. Combined adiponectin and metformin treatment ameliorated the low B12 effect and resulted in increased pAMPKα and pACC, with subsequent reduction in lipogenesis, increased FAO and mitochondria function.
Conclusion
Low B12 impaired the lipid lowering effect of metformin. Adiponectin independently decreased intrahepatic lipids even in low B12 conditions. Co-administration with adiponectin ameliorated the low B12 effect with metformin treatment and induced a higher intrahepatic lipid lowering effect.

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P325

A potential role for the Wnt signalling pathway in the development of obesity: insights from animal models

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Background
Obesity is a global health concern and a recognised risk factor for several prevalent diseases. Genetic variation can influence susceptibility to the development of obesity. Existing work in humans explains a limited proportion of the heritability of obesity-related traits and prioritisation of variants on which to focus mechanistic studies is challenging. Novel insights can be obtained from species such as the domestic dog and the pig in which obesity occurs spontaneously and gene mapping is more tractable as a consequence of selective breeding.
Methods
A genome wide association study in 241 Labrador Retrievers identified obesity-associated loci harbouring 19 positional candidate genes which were subjected to a novel analysis pipeline designed to assess their plausibility in influencing obesity risk. Multiple lines of evidence were used including: i) the identification of statistically overrepresented signalling pathways; ii) tissue-specific expression data; iii) *in vivo* modelling databases; iv) data from existing human studies. In pigs, we interrogated publicly available data from GWAS and linkage studies of adipose related traits to focus on loci consistently associated with adipose accumulation.
Results
The Wnt signalling pathway was overrepresented amongst the canine candidate genes when compared to the genome as a whole ($\chi^2(1, n=20700) = 16.5881$, $P < 0.000001$), with *csnk1a1*, *cdh8,* and *sdk1* falling within chromosomal regions of interest. Similarly, in pigs, the Wnt signalling-associated gene *lrp5* was found within the chromosomal region most strongly associated with adiposity. This aligns with previously identified associations between obesity in humans and the gene *lgr4,* which encodes a receptor involved in Wnt signalling.
Conclusions
This investigation suggests that genetic variants within the Wnt signalling pathway may influence obesity risk in multiple species. This *in silico* approach will be supplemented with work *in vitro* and *in vivo* to determine how the Wnt signalling pathway may influence obesity risk.

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P326

Examining the relationship between gestational diabetes, maternal pre-pregnancy body mass index (BMI) and large for gestation age neonates by ethnicity

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Objective
To determine if the impact of pre-pregnancy body mass index (BMI), fasting glucose levels and post load glucose levels on large for gestational age neonates varies with ethnicity.
Data sources
Electronic health records of all eligible pregnant women in an inner city service.
Study design
Retrospective analysis of pregnant women at risk of developing gestational diabetes mellitus (2016-2019) of.
Population or sample
Eligible pregnant women.
Synthesis method
Maternal and fetal characteristics were compared across five ethnic groups: White, Black African-Caribbean, South Asian, Mixed/Other Asian and other/Unknown. A customized birth centile calculator was used to determine prevalence of LGA in each ethnic group by category of maternal BMI, fasting glucose and 120-minutes plasma glucose. Association between fetal macrosomia and maternal BMI, fasting and 120-minutes plasma glucose were assessed across ethnic groups using multilinear regression analyses (with White ethnicity as the reference group).
Results
Among the 16788 participants, 36.8% were women of white origin, 21.8% Black African Caribbean, 8.8%South Asian, 20.9% Mixed origin and 12.1% originated from other ethnic groups. Mothers of Black and African Caribbean, South Asian and Mixed origin delivered a higher proportion of LGA neonates at low pre pregnancy maternal BMI categories (< 18.5) and high BMI categories (only for black).
Conclusions
Ethnicity influences percentage of large for gestational age neonates. Glucose threshold to define LGA risk differs in each ethnic groups. Ethnic specific glucose threshold to define LGA could be indicated.

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P327

'Don't Let them dry'—Hyponatraemia in Covid-19 (a real-world analysis)

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Background
The aetiology of hyponatraemia in SARS-CoV-2 (COVID-19) is complex. Early studies have suggested a syndrome of inappropriate anti-diuretic hormone picture. We undertook a real-world retrospective analysis of patients with hyponatraemia and COVID-19 hospitalised over a 12-month period and evaluated practice against European hyponatraemia guidelines to see if initial investigations and management were appropriate. Additionally, we evaluated whether hyponatraemia in COVID-19 was associated with adverse outcomes and other associations with poor prognosis in this cohort.
Methods
We retrospectively analysed data from 229 patients with confirmed serum sodium <130 mmol/l and positive reverse-transcriptase polymerase chain reaction COVID-19 test over a 12-month period. Additionally, we used binary logistic regression to evaluate associations between patient characteristics and mortality.
Results
Records of volume status (46.7%), serum osmolality (29.3%), urine osmolality and sodium (24.5%), serum cortisol (22.3%), and thyroid stimulating hormone (52.8%) were sub-optimal. Hypovolaemia was the prominent aetiology of hyponatraemia in COVID-19 patients. Thirty-day mortality (34.5%) in those with hyponatraemia and COVID-19 was similar to overall 30-day mortality for COVID-19 patients attending hospital over the same period (34.1%). Logistic regression demonstrated female gender (OR 3.88, 95% CI 1.78–8.46, $P<.001$), lower nadir sodium (OR .797, 95% CI .702–.905, $P<.001$) and higher Charlson comorbidity index (OR 1.355, 95% CI 1.159–1.583, $P<.001$) were associated with increased likelihood of mortality.

Discussion
In those with COVID-19, hyponatraemia was not associated with increased 30-day mortality in comparison with patients who had normal sodium levels. Recognition of hypovolaemia as a common presentation of hyponatraemia in patients with COVID-19 is important to prevent inappropriate fluid restriction and ensure timely fluid management in these patients. Female gender, lower nadir sodium and the number of comorbidities were predictors of poor outcomes in our cohort. Excess mortality seen in females is likely explained by the higher mean age (76.8 vs 72.1).

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P328

Vernonia amygdalina Alleviates Neurodegenerative Effects of High Fat Diet and Streptozotocin-Induced Type 2 Diabetes Mellitus in the Hippocampi of Adult Male Wistar Rats

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Cognitive impairment and neurodegeneration are a few hallmarks of brain insulin resistance, a core feature of Type 2 diabetes mellitus (T2DM). Using a Wistar rat model of a high-fat diet and streptozotocin-induced T2DM, we aimed to determine the potential of Vernonia amygdalina (VA) as a possible treatment for the accompanied neurodegenerative effects of this condition on hippocampal structure and function. T2DM adult rats were prepared by a combination of a high-fat diet and intraperitoneal injection of 35 mg/kg streptozocin. The elevated plus and Barnes maze tests were used to evaluate anxiety, learning, and memory functions, followed by H&E and cresyl violet staining, immunohistochemical staining for hippocampal amyloid beta, synaptophysin, and glial fibrillary acid protein (GFAP), and RNA analysis of P53, P21, glutathione (GSH) and glutathione peroxidase (GPX-1) genes expression levels. T2DM model animals had significantly reduced open arm entries and duration and higher escape latencies, depicting increased anxiety and decreased spatial memory and learning abilities($P<0.05$). Expression changes were evident for P53, GSH, P21, and GPX-1 genes, which included an increased expression of P53 and P21 in the hippocampus of T2DM model animals and a slight reduction of these genes in VA groups, and an increased expression of GSH in T2DM and VA groups. Also, photomicrographs revealed a fragmented pyramidal cell layer with visible pyknotic cells and a gross reduction in cytoplasmic Nissl proteins across the Cornus Ammonis and dentate gyrus regions of the hippocampi. Similarly, increased expression of amyloid-beta, synaptophysin, and GFAP was seen in these regions. However, V. amygdalina was able to enhance the learning and memory abilities of T2DM rats, replenish hippocampal pyramidal neurons, and help improve hippocampal synapses, while improving the brain's antioxidant defense system. These findings may provide helpful insights into the treatment of T2DM-induced brain insulin resistance.

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P329

POMC mutation in a canine obesity model: dogs with β-MSH and β-endorphin deletion have increased hunger and low resting metabolic rate

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Background
A mutation in POMC in retriever dogs prevents production of the POMC-derived peptides β-MSH and β-endorphin but not α-MSH and is associated with weight, adiposity and owner-reported food motivation (Raffan *et al*, 2016). Melanocortin signalling is central to the control of energy homeostasis but the relative contribution of the POMC derived neuropeptides is not well understood because rodents produce only α-MSH whereas humans, like dogs, produce α-MSH and β-MSH.
Methods & Results
We recruited adult, healthy pet dogs and tested their eating behaviour and energy expenditure. An inaccessible food task showed dogs heterozygous for the mutation had greater incentive salience in response to a food stimulus (increased hunger). Voluntary food intake at a modified ad libitum meal was high (~2 kg) but there was no significant difference between genotypes. Vomiting/regurgitation occurred in 9/16 wild type dogs and 1/12 heterozygous dogs, which could imply different physiological responses to overfeeding. There was no measurable difference in the hedonic response to food. Resting energy expenditure measured using indirect calorimetry in the post-absorptive state was approximately 20% lower in dogs homozygous for the mutation than for wild type dogs (MR/hour = 123 + βBM*Weight in Kg + βhomozygousPOMC*1 where βhomozygous-POMC = -42.3 (95% CI -62.9 to -21.7, $P=0.0005$) and βBM = 2.484 (-0.58 - 5.55, $P=0.1$).
Conclusion
Dogs bearing a POMC mutation which disrupts production of β-MSH and β-endorphin display increased hunger and markedly lower resting energy expenditure but normal satiety and hedonic responses. Although it remains possible β-endorphin deletion is in part responsible, these data implicate β-MSH as important in determining hunger and moderating energy expenditure, and that this role is independent of the presence of α-MSH.

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P330

Glicentin concentrations following Liraglutide treatment in patients with overweight/obesity

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Background
Liraglutide is a long-acting glucagon-like peptide-1(GLP-1) receptor agonist that promotes weight loss. The minimum adequate/good response to liraglutide (≥5% weight loss at 3 months) is not achievable in all patients. Currently there are no biomarkers to predict good response. Enhanced postprandial glicentin concentration was recently considered as superior to GLP-1 in predicting weight loss following bariatric surgeries.
Objective
1) To assess the effect of liraglutide on fasting glicentin concentration in patients with overweight/obesity 2) To evaluate the difference in baseline fasting glicentin concentrations between good and poor responders to liraglutide (≥5% vs. <5% weight loss from baseline).
Methods
Validation of glicentin ELISA kit (Mercodia, Sweden) was performed and fasting glicentin concentrations from 34 patients collected at baseline (pre-treatment), 2, 4 and 6 months post treatment were analysed. Statistical analysis was done using Analyse-It v5.40.2. T-test was used to examine the difference between baseline and post-treatment glicentin concentrations. ANOVA-test was used to examine the difference in baseline glicentin between good and poor responders. Level of significance is 5%.
Results
Glicentin concentration decreased following liraglutide (mean difference -11.8 mmol/l, 95% CI: -18.1 to-4.16, P: 0.001) There was no difference in glicentin between good and poor responders at baseline ($n=17$ in each group).
Conclusion
Liraglutide treatment is associated with a significant reduction in fasting glicentin concentration. Possible explanation is that liraglutide can downregulate glicentin in a manner similar to endogenous GLP-1. Larger studies maybe needed using both fasting and postprandial samples (where glicentin concentration is higher) to better assess the clinical utility of glicentin as a predictor of good weight loss response to liraglutide.

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P331

Mass Spectrometry Imaging to Investigate Carnitine Metabolism during Brain Ageing

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Ageing is associated with decline in mitochondrial function whereby dysregulation in carnitine metabolism is highly correlated to poor ageing phenotypes. L-Carnitine transports activated long-chain fatty-acids (FAs) across mitochondrial membranes for β-oxidation and energy production. It is hypothesised that accumulation of long-chain FAs within cells is related to disordered transportation and reflects lower cellular energy upon ageing. Our global aim is to determine the differences in composition and distribution of L-carnitine and acyl-L-carnitines (ACs) within aged mouse brains. Mass spectrometry imaging (MSI) allows concomitant spatial measurement of multiple molecules with direct histopathological correlation. Here we developed a universal MSI protocol to image L-carnitine (C0) and ACs of various chain lengths; acetyl-(C2), butyryl-(C4), hexanoyl-(C6), decanoyl-(C10), lauroyl-(C12), myristoyl-(C14), palmitoyl-(C16) and stearoyl-(C18). Matrix assisted laser desorption ionisation (MALDI)-MSI was performed on Synapt-G2Si-QToF and Bruker-12T-SolariX-Fourier-transform–ion-cyclotron-resonance (FT-ICR)-MS. Brains (male, C57BL6J, aged 3m) were cryosectioned (12 μm) and imaged (100 μm resolution). ACs (C0-C18) standards were used for method optimisation and validation. Carnitines readily ionised as $[M+H]^+$ ions. 2,5-Dihydroxybenzoic acid (DHB) was selected as MALDI matrix achieving x5 intense signals than α-cyano-4-hydroxycinnamic acid. Ionisation efficiency changed with chain length as follows; C16 > C12 > C10 > C6 > C4 > C2 > C0, reflected in different limits of detection (LODs). Solvent compositions (90%-50% aqueous methanol) were compared for DHB application and 50% selected improving LODs two-fold for long-chain ACs; C16(<0.1ug/mL) > C12(~0.1ug/mL) > C10(~0.2ug/mL) > C6(~0.2ug/mL) > C4(~1ug/mL) > C2(~5ug/mL) > C0(~100ug/mL). Using optimised parameters ACs were successfully imaged in control mouse brain tissue. Carnitine was more abundant in grey-matter, in contrast long-chain ACs (C14-18) were in white-matter. Identity was confirmed at high-mass resolution using FT-ICR-MS, which also offered improved LODs. MALDI-MSI represents a useful approach for imaging ACs (C0-C18) in brain tissue. Future work will investigate effects of age on composition and distribution of these ACs.

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P332

Digital Communication through Covid – A free NHS App for patients with Type 1 diabetes improves accessibility and self-management

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Introduction
Self-management of chronic disease is increasingly being recognised as an essential tool in chronic disease management. During the pandemic, face-to-face diabetes clinics were suspended, and resources were focussed on delivery of urgent care. A free NHS app was created to virtually deliver information on all aspects of type 1 diabetes management and to support patients in their self-management during an increasingly difficult period. The App included an 'Alerts' function to keep patients up to date with changes to the service. The aim of this study is to investigate patient perceptions of the application.
Methods
A questionnaire-based cross-sectional study was designed by the diabetes team to obtain quantitative data. The survey was performed via "Google Forms" and was piloted with independent medical colleagues in different departments to ensure the questions were relevant and without bias. All patients who were registered on the App were invited to complete the survey over a 4 week period.
Results
108 patients of the 900 registered users completed the survey. The mean score of patient accessibility to diabetes information and services before using the App was 5.1, and after using the App was 8.8 ($P<0.001$). 91% of patients would recommend the App, the NPS is +89. 57.2% of patients "agreed" or "strongly agreed" that the App helped them schedule and attend their screening appointments, and 73.7% "agreed" or "strongly agreed" that the App has improved their self-management of type 1 diabetes.
Conclusion
Overall, patients agree the App has improved accessibility to diabetes information and services and improved self-management of their condition. Patients are likely to recommend the App to friends and family who have diabetes. The authors recommend a free NHS app can be beneficial in delivering patient information in type 1 diabetes and is a useful tool in improving self-management within chronic disease management.

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P333

SIMBA for Students – teaching endocrinology to pre-clinical medical and pharmacy students through online simulation: a pilot study

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Introduction
Simulation via Instant Messaging – Birmingham Advance (SIMBA) for Students is an online education model used to teach endocrine topics to pre-clinical medical and pharmacy students using simulated clinical cases delivered over WhatsApp. This study investigated the efficacy and acceptability of SIMBA for students compared with traditional small group teaching (SGT).
Methods
The SIMBA sessions focussed on curriculum learning objectives and included three interactive clinical cases covering an area of endocrinology, followed by a Q&A session with an expert. All students were asked to fill out a survey which included 12-15 multiple choice questions (MCQs) following SIMBA and SGT. Median MCQ results as percentages were compared between groups using Wilcoxon signed rank test. The answers to Likert scale questions were expressed as percentages. Open-ended questions from surveys underwent thematic analysis.
Results
132 year 1, year 2 medical and year 1 pharmacy students attended nine SIMBA sessions in 2021-2022 covering adrenal, metabolic bone, thyroid, diabetes, and reproductive endocrinology. The median MCQ result was significantly higher in the SIMBA only group than the SGT only group ($P=0.0059$). There was no significant difference in score between the SIMBA and SIMBA + SGT groups ($P=0.3083$). Most students agreed that SIMBA was easy to follow (96%), engaging and interactive (83%), stimulated their interest in endocrinology (86%), promoted new knowledge (94%), and provided an in-depth understanding on the topic (96%). 90% enjoyed the session overall and 80% would like to have SIMBA alongside SGT. Positive themes from thematic analysis were knowledge application through case-based learning, interaction, and instantaneous feedback.
Conclusions
SIMBA is a good alternative model for SGT to teach endocrinology to pre-clinical medical and pharmacy students by providing engaging, interactive, and interesting sessions. A study is currently underway to assess improvements to the model and wider impacts on academic performance in a larger cohort.

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P334

Epidemiology of Diabetes Mellitus in Children in Kazakhstan: Data from Unified National Electronic Health System 2014-2019

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Background and aims
We aimed to explore the epidemiology of Diabetes Mellitus (DM) Type 1 and 2 in children aged 0-18 in Kazakhstan based on the aggregated large-scale healthcare

data from the Unified National Electronic Healthcare System (UNEHS) in 2014-2019.
Methods
10,134 incident Type 1 and Type 2 DM pediatric patients were identified through UNEHS. Incidence, period prevalence, and mortality rates per 100,000 population at risk were calculated. The follow-up period was from the initial date of DM diagnosis until death or the end of the follow-up (December 31st, 2019). Cox proportional hazards regression modeling was used to assess the associations between demographic factors with all-cause mortality.
Results
Among 10,134 patients there were 9,310 and 824 children with Type 1 and Type 2 DM, respectively. Median age at diagnosis was 10.0 (interquartile range (IQR) 6.0 – 13.4)) and 13.0 (IQR 8.4 – 15.7) for Type 1 and Type 2 DM, respectively. Retinopathy was the most common complication for both DM types. The incidence rate of DM Type 1 and 2 decreased from 28.1 to 22.0 per 100,000 population and from 3.5 to 2.0, respectively. The period prevalence rate increased from 48.8 to 143.8 per 100,000 population in DM Type 1, and from 4.9 to 12.4 in DM Type 2 patients. Mortality increased twice for DM Type 1 patients but remained consistent for the DM Type 2 patients over the follow-up period. Among DM Type 1 children, female sex, older age, and Kazakh ethnicity were associated with a higher risk of death. Among DM Type 2 patients, only older age was a significant determinant for higher all-cause mortality.
Conclusions
While the incidence of both types of DM in children has been decreasing in Kazakhstan over 2014-2019, the prevalence remains high, with the mortality increasing for DM Type 1 patients.

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P335

Assessing GLP-1 Agonists and DPP-IV Inhibitor Prescribing in the Management of Type 2 Diabetes during COVID-19

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This study assesses adherence to the NICE guidance of GLP-1 agonist and DPP-IV inhibitor prescribing from 2021-2022, during the COVID-19 pandemic, in primary care. We took a group of 86 patients with type 2 diabetes mellitus (T2DM) and monitored HbA1c, BMI, frequency of diabetic reviews, medication changes and symptoms throughout the pandemic. Evaluation of adherence to the NICE guidance during COVID-19 and the effects on these patients was made. The intervention was an MDT meeting reviewing NICE guidelines and reviewing records with diabetes specialist nurses. Results showed that as the pandemic progressed, there were direct negative effects on the number of appropriate medication changes made and therefore a lack of adherence to NICE guidelines. However, the intervention had a positive effect on adherence. HbA1c levels worsened overall throughout the pandemic even when adherence was improving, possibly due to factors such as isolation and limited healthcare access. This highlighted the number of challenges the pandemic presented for patients and healthcare staff. Diabetic patients were unable to access frequent appointments meaning medication changes may not have been possible and there was more reliance on patients to self-manage their condition. As for healthcare staff, there was difficulty reaching patients and adaptations to the way in which care was delivered had to be made. Improving and increasing scalability of further interventions in primary care should be encouraged as the study showed they are likely to benefit patient health, but also reduce costs and have wider impacts on the community. Further data from different groups of patients will allow assessment of how groups were affected differently during the pandemic to help target care. Further cycles of larger patient cohorts within Tower Hamlets will allow greater significance of data.

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P336

Comparison of global rating scale scores of Simulation via Instant Messaging -Birmingham Advance (SIMBA) participants from high- and low- and middle-income countries of residence

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Introduction
Simulation via Instant Messaging -Birmingham Advance (SIMBA) is a virtual platform which simulates anonymised, real-life clinical cases to train healthcare professionals. Participants' competence is assessed using an adapted version of the global rating scale (GRS) commonly used in medical schools.
Aims
To compare GRS scores of participants according to country of residence and domains assessed as part of simulation.
Methods
Endocrine sessions conducted from July 2020 to October 2021 were considered. Participants' performance was scored from 1 (poor) to 5 (excellent) according to various domains – namely, history-taking, physical examination, investigations, result interpretation, clinical judgment and management. Performance was also grouped according to participants' country of residence into high-income countries (HIC) and low- and middle- income countries (LMICs) based on the 2022 World Bank report. Difference in performance was compared using the Chi-square test.
Results
6 SIMBA sessions (thyroid, pituitary, diabetes, metabolic bone, gonadal and diabetic microvascular complications) with a total of 293 participants are included in the analysis. 91 (31%) participants were from LMICs. Median (IQR) GRS scores for the domains assessed are as follows: history-taking 4.0 (3.0-5.0), physical examination 4.0 (3.0 - 4.6), investigations requested 3.3 (3.0 - 4.0), result interpretation 2.6 (1.6 - 3.3), clinical judgment 3.3 (2.6 - 4.0) and management 2.6 (2.0 - 3.3). On comparing HICs and LMICs, scores were similar for history-taking (HIC 3.81, LMIC 3.79; $P=0.05$), physical examination (HIC 3.67, LMIC 3.68; $P=0.19$), investigations requested (HIC 3.35, LMIC 3.33; $P=0.27$) and result interpretation (HIC 2.63, LMIC 2.61; $P=0.74$). HICs scored higher for clinical judgment (HIC 3.23, LMIC 3.18; $P=0.008$) and management (HIC 2.66, LMIC 6.42; $P=0.001$).
Conclusion
In general, SIMBA participants scored lower for result interpretation, clinical judgment and management. Scores were particularly low among participants from LMICs. This highlights the need for cost-effective and more accessible training programmes for clinicians.

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P337

A case of GLP-1 RA-induced hypoglycaemia following RYGB in a patient with Type II Diabetes and autonomic dysfunction

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Background
Increased endogenous post-prandial GLP-1 release is a key mediator of improved glycaemic control following Roux-en-Y gastric bypass (RYGB) surgery. GLP-1 receptor agonists (GLP-1 RA) augment glucose-stimulated-insulin-release and suppress glucagon release, and do not usually cause hypoglycaemia. The use of GLP-1 RA have been shown to be safe for patients requiring additional glycaemic control following RYGB. We present a case of severe recurrent fasting nocturnal hypoglycaemia with semaglutide use following RYGB in a patient with autonomic dysfunction and hepatic fibrosis.
Case
A 54 year old Caucasian woman with obesity (BMI 44.9 kg/m^2), T2DM (7 year duration), peripheral neuropathy and autonomic dysfunction, non-alcoholic steatohepatitis with F2 fibrosis, hypertension, bile salt malabsorption, GORD, and sleep apnoea underwent RYGB surgery. Pre-operatively she was treated with metformin, empagliflozin, liraglutide and pre-mixed insulin. 18 months post-operatively, her weight plateaued at 16 kg (13.6%) weight loss. Metformin and empagliflozin provided suboptimal glycaemic control with HbA1c 55 mmol/mol. She commenced semaglutide 0.5 mg subcutaneously once weekly. This augmented her weight loss (further 10 kg loss in subsequent 18 months) but she began reporting symptoms of hypoglycaemia that were unrelated to eating.

Results
Continuous glucose monitoring captured a pattern of recurrent severe nocturnal hypoglycaemia. This abated upon stopping all diabetic medication, and re-appeared on re-introduction of semaglutide 0.5 mg SC OW alone.
Discussion
We postulate that the presence of autonomic dysfunction in this case may inhibit counter-regulatory hormones protecting against hypoglycaemia. Clinicians using GLP-1 RA following RYGB should be alert to the possibility of impaired protection against hypoglycaemia.

Diabetes Medication	Mean Glucose (mmol/l)	% TIR 4-10 mmol/l	% TIR <3.9 mmol/l	% TIR <3 mmol/l	% TIR <2.8 mmol/l
Metformin 1g OD, Semaglutide 0.5 mg OW	5.3	69	24.6	7.5	5.2
Nil	7.2	85.9	0.7	0	0
Semaglutide 0.5 mg OW	5.8	79.8	12.2	3.7	2.6

% TIR: Percentage time in range

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P338

Unusual late presentation of maturity onset diabetes of young (MODY)

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Background
Maturity-onset diabetes of the young (MODY) is a group of 13 monogenic forms of diabetes transmitted in an autosomal dominant pattern and is characterized by a primary defect in pancreatic β-cell function. This disease has an early onset, usually before 25 years of age. It may present with mild asymptomatic hyperglycemia with progressive development to clinical diabetes mellitus. First-line treatment relies on sulphonylureas or insulin according to MODY subtype.
Case Presentation
This is a case of 55 years old lady who was diagnosed with type 1 diabetes at the age of 29 years. She was started on basal-bolus insulin initially and moved onto insulin pump later. At that time, type 1 diabetes was diagnosed on the clinical grounds, high HbA1c and high insulin requirement. Recently her sister got diagnosed with MODY (HNF-1 Alpha gene defect) at the age of 48 years. Due to family history, our patient was tested for MODY. She was 55 years old at the time. Relevant investigations like insulin auto antibodies, C- peptide and Insulin level was requested which was followed by genetic testing. Her daily insulin requirement and glycemic control was reviewed. Blood results showed that her antibodies to Glutamic acid decarboxylase and Islet cell came back negative with a healthy C-peptide and Insulin level, which points towards a probable diagnosis of MODY. Subsequently, her genetic testing showed HNF-4 Alpha gene defect. On careful review of her glycemic control, we found that her insulin requirement were consistently about 0.3 units/kg, which is not expected of type 1 diabetes 25 years into the diagnosis. Her HbA1c was maintained around 51 mmol/mol (6.8%).
Conclusion
We can say that MODY can present above the age of 45 years. In our clinical practice, we should always review the diagnosis of diabetes if there are clinical concerns.

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P339

Diabetic striatopathy: A rare presentation as stroke mimic and focal seizure

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Introduction
Diabetes striatopathy (DS) is an extremely rare hyperglycaemic complication of diabetes with a prevalence reported as 1 in 100,000[1]. Though DS is commonly associated with a non-ketotic hyperglycaemic hyperosmolar state (HHS), it is occasionally reported in diabetic ketoacidosis (DKA). DS is known as non-ketotic hemichorea-hemiballismus due to its presentation with hyperkinetic movements but rarely presents as stroke-mimic[2]. Here we present an extremely rare case of DKA-associated DS in a patient who presented with unilateral hemiparesis and focal seizures.
Case report
78 M, known T2DM, presented with acute right-sided weakness, facial droop, slurring of speech, and right-sided focal seizures along with acute decompensation of glycemic control (HbA1C 6.1%–>17%). His blood tests showed DKA (CBG>47, PH-7.23) with ketones of 5.4. CT head showed left-sided diabetes striatopathy. He was treated as per DKA protocol and was started on Humulin I twice daily. His neurological deficits and focal seizures got resolved in 3 days and he got discharged on regular insulin.
Conclusion
The term Diabetes striatopathy (DS) was introduced in 2009 to denote a condition with the radiological finding of striatal hyperintensity, and contralateral movement disorder in poorly controlled diabetes patients. DS is commonly known as non-ketotic hemichorea/hemiballismus, predominantly reported in elderly Asian females with poorly controlled T2DM[3]. Literature reviews have shown its varied presentation from hyperkinesia to hemiparesis. While hyperkinesis was mostly reported in nonketotic hyperglycaemic conditions, hemiparesis was found in patients with ketosis. Hyperglycaemia promotes cerebral autoregulation failure, hypoperfusion, and activation of anaerobic metabolism, resulting in depletion of GABA in the basal ganglia in non-ketosis hyperglycemia[4]. However, in hyperglycaemia with ketosis, the inhibitory neurotransmitter GABA is re-synthesized from acetoacetate and hence hyperkinetic movements are controlled. DS is a reversible condition with normalisation of hyperglycaemia. DS should be suspected in patients with uncontrolled diabetes and abnormal basal ganglia imaging.

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P340

"Severe Lipaemia" with triglyceride levels above 100 mmol/L: successfully treated with insulin therapy alone

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Introduction
Commonest causes of pancreatitis are alcohol and gallstones but less common causes like hypertriglyceridemia should also be considered as management may differ.
Case history
47 years old gentleman with history of pancreatitis and hyperlipidaemia type1 taking atorvastatin and bezafibrate, admitted with severe abdominal pain and vomiting. He was non-smoker and non-drinker. No history of cholelithiasis or medications causing pancreatitis. He was haemodynamically stable and systemically well except epigastric tenderness. After excluding diabetic ketoacidosis (DKA), he was initially managed conservatively for acute pancreatitis but bloods showed severe lipaemia therefore insulin/dextrose infusion was started in view of hypertriglyceridemia induced pancreatitis with successful resolution of hypertriglyceridemia without requiring plasmapheresis but required intensive care for active monitoring.
Investigations
Blood sample after hypercentrifugation (due to severe lipaemia) showed: Urea: 9.3 (2.8-7.2 mmol/l), Creatinine: 184(59-104umol/l), Sodium, Potassium and Magnesium were normal but hypocalcaemia 1.91(2.20-2.60 mmol/l) Triglycerides: 103.2 (<1.7 mmol/l), Cholesterol 26.9 (<5 mmol/l) CT Abdomen: Acute severe pancreatitis with severe oedema and extensive peripancreatic fluid but no frank necrosis.
Results and treatment:
1. Conventional management of acute pancreatitis with fluid resuscitation and analgesia. 2. Insulin (0.05units/kg/hour) and 5% dextrose (100-150ml/hour) infusion, given severe hypertriglyceridemia. 3. High dose prophylactic anticoagulation (Enoxaparin 40 mg twice/day) due to hyperviscosity from hypertriglyceridemia. 4. Patient also required calcium infusions for recurrent hypocalcaemia. (Likely because of excessive free fatty acids or saponification). Within 6 days, hypertriglyceridemia improved from 103 mmol/l to 5.4 mmol/l without plasmapheresis and cholesterol dropped to <6.1 mmol/l.
Learning Points:
1. Hypertriglyceridemia should be considered as differential of acute pancreatitis as management varies. 2. Insulin and dextrose infusion should be initiated early if hypertriglyceridemia is the cause as this can reduce complications by effectively lowering triglycerides. 3. Effective thrombo-prophylaxis is essential due to high

risk of thromboembolism. 4. Patient may develop severe and recurrent hypocalcaemia therefore active monitoring and management is needed.

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P341

New onset diabetes triggered by use of growth hormone secretogogue for body building, a case report

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Introduction
Growth hormone secretogogues (GHS) are popular among body building communities as muscle bulking agents. We present an interesting case of new onset diabetes induced by a combination of GHS and selective androgen receptor modulators (SARMs).
Case report
A 34-years body builder was referred by his GP due to a 3-week history of polyuria, polydipsia and fatigue. He had recently used one cycle of a combination tablet which contained Ibutamoren 20 mg (MK-677), Testolone 20 mg (RAD-140) and Ligandrol 8 mg (LGD) for 26 days. He was otherwise well with no significant past medical history. His mother, grandmother and sister have type 2 diabetes. On examination, BMI was 38.2 kg/m^2. His blood glucose was 27.5 mmol/l and ketones was 0.1 mmol/l. HbA1c was 102 mmol/mol. Anti-GAD, Zinc transporter and pancreatic islet cell antibodies were negative. C peptide was 611 pmol/l (range 190-990). TSH and anti- tissue transglutaminase antibodies were normal. He was started on Metformin 500 mg BD which was later increased to 1 gram BD and Gliclazide 80 mg BD. His capillary glucose improved one week after starting treatment but did not normalise and ranged between 8-12 mmol/l. He was advised not to use GHS.
Discussion
Ibutamoren is an orally active non-peptide growth hormone (GH) secretagogue, mimicking the GH stimulating action of ghrelin. It has the potential to cause sustained activation of GH-IGF-1 axis. Available studies indicate that GHSs could raise blood glucose and HBA1c due to decrease in insulin sensitivity. In our case, onset of diabetes coincided with the use of GHS along with SARMs.
Learning points
1. This case report shows the importance of taking thorough drug history including over the counter drugs and supplements. 2. Physicians should be mindful of the side effects of over-the-counter drugs used for body building.

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Neuroendocrinology and Pituitary

P88

Cabergoline in acromegaly – a multicenter, retrospective, cohort study of non-irradiated patients using current criteria for disease control

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Background
Cabergoline monotherapy or in combination with somatostatin analogue (SSA) has been reported in few studies with IGF-1-normalization-rates 0%-100%(monotherapy) and 42%-60%(combination therapy). However, in these studies, inclusion of irradiated patients is a potential confounder and currently proposed disease control criteria (normal IGF-1, GH $<$ 1 mg/l) have not been applied.
Aim
Investigate the efficacy of cabergoline monotherapy or as add-on to ongoing SSA-therapy in achieving biochemical control in non-irradiated patients with acromegaly.
Patients and methods
Multicenter, retrospective cohort study involving non-irradiated patients offered cabergoline monotherapy or add-on to SSA for uncontrolled acromegaly from four UK Pituitary centers (Birmingham, Bristol, Leicester and Oxford). Clinical/laboratory data were analyzed.
Results
Patients on cabergoline monotherapy ($n=69$): Median IGF-1$_{\text{pre-cabergoline}}$ 2.13xupper limit of normal (ULN) (1.02-8.54) and median duration of cabergoline treatment 23 months (3-252). Normal IGF-1 was achieved in 31.9% of patients. Latest median weekly cabergoline dose was 2.5 mg (0.25-4) (responders), 3 mg (0.25-7) (non-responders), ($P=0.39$). On univariate regression analysis, IGF-1-normalisation was related with prolactin co-secreting adenoma (B 1.50, $P=0.019$) and lower IGF-1$_{\text{pre-cabergoline}}$ (B-0.70, $P=0.015$). On ROC analysis, IGF-1 $<$ 1.97ULN had sensitivity 71% and specificity 65% in predicting IGF-1 normalisation (AUC 0.745). GH $<$ 1 mg/l was found in 25.8% and normal IGF-1 + GH $<$ 1 mg/l in 12.9% of patients. Patients on combination therapy ($n=26$): Median duration of SSA-treatment before cabergoline 18 months (2-118), IGF-1$_{\text{pre-cabergoline}}$1.70xULN (1.03-2.92), median duration of SSA + cabergoline 36 months (4-139). Normal IGF-1 was achieved in 23.1% of the patients. Latest median weekly cabergoline dose was 1.25 mg (0.5-3) (responders), 3 mg (0.5-4.5) (non-responders), ($P=0.134$). GH $<$ 1 mg/l was found in 39.1% and normal IGF-1 + GH $<$ 1 mg/l in 17.4% of patients.
Conclusions
IGF-1 levels normalized in 32% (monotherapy) and in 23% (combination-therapy) of patients. For monotherapy lower IGF-1$_{\text{pre-cabergoline}}$ and prolactin co-secreting adenoma were associated with IGF-1 normalization. The response rate to combination-therapy was lower compared to previous reports, possibly due to the exclusion of irradiated patients.

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P89

Somatic sequencing in an enriched cohort of recurrent non-functioning pituitary adenomas

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Background
Sporadic non-functioning pituitary adenomas (NFPAs) are described as having quiet mutational landscapes. Genes with recurrent somatic alterations have not been identified by previous studies examining heterogeneous pituitary tumour populations. Existing biomarkers have limited ability to discriminate NFPAs with a predisposition for regrowth from those that will follow a more indolent course after primary surgery. We undertook somatic sequencing, in an enriched cohort of NFPAs with a propensity for recurrence, in order to identify variants with potential prognostic or therapeutic utility.
Methods
36 formalin-fixed paraffin-embedded NFPA tumour samples from 21 patients that had required multiple therapeutic interventions (revision surgery and/or radiotherapy) or demonstrated radiological recurrence / regrowth following primary surgery (median time to recurrence 31.5 months), were recruited. Tumour and paired germline DNA samples were sequenced using a custom 92 gene '*pan-endocrine and oncology*' panel. Variants were filtered for non-synonymous changes and a driver variant was defined as a pathogenic or likely pathogenic variant with a VAF $>$5%.
Results
12 of 40 potential driver variants were within genes relating to the PI3K/AKT signalling pathway (PIK3CA, PTEN, HRAS, NRAS, EGFR, SRC). 7 of 36 [19.4%] tumour samples were identified to have a potential somatic driver variant within constituents of the PI3K/AKT signalling pathway, 4 within PIK3CA. Amongst patients with recurrent tumours, those with variants in PI3K/AKT pathway constituents in the first resected tumour sample, had a tendency to a longer median time to progression (41.3 months [24.2 – 58.3]) vs 30.2 [22.5 – 40.0]), although this did not reach statistical significance.
Discussion
In NFPAs with a predisposition for regrowth following primary surgery, variants in the PI3K/AKT pathway are commonly encountered. Further studies will help to elucidate the potential prognostic and/or therapeutic value of this finding.

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P90

Phosphoproteomics analysis of aryl hydrocarbon receptor interacting protein (AIP) knockout cells reveals AIP-mediated kinase signalling cascades

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Introduction
Aryl hydrocarbon receptor interacting protein (AIP) is a multifunctional co-chaperone protein: it behaves as a tumour suppressor in the pituitary, but may have other roles including oncogenic function in other tissues. Protein phosphorylation is an important posttranslational modification that regulates protein activity, which is crucial for understanding protein function. To understand the molecular pathways altered in AIP deficient cells, we have performed global phosphoproteomics analysis of Aip-knockout mouse embryonic fibroblasts (Aip-KO MEFs) cells.
Aim
The aim of this study was to discover altered protein phosphorylation-related signalling pathways in Aip-KO MEFs.
Method
Phosphoproteomics analysis was performed by mass spectrometry (MS). Lysates were collected in four replicates from 5x106 MEFs (WT and Aip-KO cells). Phosphopeptides were enriched using titanium dioxide (TiO2) and subsequently analysed by LC-MS/MS. Ingenuity pathway analysis (IPA) was used for pathway analysis.
Results
We have identified 352 significantly altered phosphopeptides (200 hyper- and 152-hypophosphorylated) in Aip-KO MEFs compared to wild type cells. Among the hyperphosphorylated peptides, 10 were kinases and five were phosphatases. IPA analysis revealed two significantly activated pathways. The 'Endocannabinoid cancer inhibition pathway' (Camkk2, Map2k7, Prkab2, Smpd3, Tcf4 and Twist1) was not previously suggested to be involved with AIP. The 'Epithelial adherens junction signalling' pathway (key altered proteins) which we have previously identified in gene expression and protein data of AIPpos human and mouse pituitary tumours.
Conclusions
This study revealed novel insights into AIP-mediated signalling events and can be used as a valuable resource for further understanding of its function in invasive pituitary tumour development which might lead to novel therapeutic targets.

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P91

Diabetes insipidus safety: Automated electronic records alert to identify patients with diabetes insipidus in hospital

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Background
Cranial diabetes insipidus (DI) is characterised by the inability to produce vasopressin leading to uncontrolled diuresis. Management includes administering synthetic vasopressin analogue desmopressin (DDAVP). Recently, there have been several national reports of DDAVP omission causing serious patient harm. This study aims to evaluate the feasibility of an automated alert system using Natural Language Processing (NLP) in electronic health records (EHR) to detect DI cases in a large tertiary hospital.
Methods
Retrospective analysis of data (February 1st-28th, 2022) of an automated search using Cogstack NLP for the following words "DDAVP", "desmopressin" and "insipidus" in patients' EHR, to generate daily alerts sent to a dedicated email inbox. We included all adult inpatients ($\geq$18 years).
Results
97 alerts were detected corresponding to 41 patients. On average, 2.7 alerts where generated each day. 16 of them (8 patients) met the inclusion criteria. No patients experienced adverse outcomes secondary to inappropriate DI management. The endocrinology team was aware or involved in 6 of the 8 cases (75%). In 43 alerts, DDAVP was used for other indications. 34 were paediatric patients. We were unable to identify what word triggered 4 alerts.
Conclusions
This preliminary study shows promising potential for the use of NLP to help identify DI inpatients in clinical practice. If used as a real-time alert system, it would alert the inpatient team to the 25% of DI inpatients currently unidentified. Given the high risk of deterioration if these patients are inappropriately managed, it is crucial for them to be referred to the specialist team early in the admission. Further work is required to refine the alert system to facilitate its implementation in a clinical setting.

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P92

Natural history of non-functioning pituitary microadenomas – results from the UK NFA consortium

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Background
The published data on the natural history of (presumed) non-functioning pituitary microadenomas (micro-NFAs) is possibly compromised by small

sample sizes, short follow-up and inclusion of cases with other pathologies in the analyses.
Objective
To clarify the long-term outcomes of micro-NFAs in a large cohort of patients.
Methods
We conducted a multi-centre, retrospective, cohort study involving 22 UK endocrine departments (UK NFA consortium). Cases of (presumed) micro-NFAs detected by MRI and seen in participating departments were included. Clinical, imaging and hormonal data were collected. Statistical analyses were performed by Kaplan-Meier survival curves and Cox-regression.
Results
453 patients were included. Median age at tumour detection was 44 years (IQR 31-57). At baseline, 35 (7.1%), 8 (1.8%) and 7 (1.5%) patients had secondary hypogonadism, hypothyroidism and hypoadrenalism (not attributable to other causes), respectively. For 413 patients with $\geq$ 2 follow-up MRIs, median monitoring was 3.5 years (IQR 1.7 – 6.1). 49 (11.9%) micro-NFAs grew, 79 (19.1%) reduced in size and 285 (69%) remained stable. Cumulative probability of growth was 7.6% (95%CI 4.7 – 10.5%), 14.3% (95%CI 10.0 – 18.6%) and 18.1% (95%CI 12.8% – 23.4%) at 3, 5 and 7 years, respectively; age at diagnosis, sex, tumour size ($<$5 mm or $\geq$ 5 mm) were not predictive factors. Two patients developed clinical apoplexy. Twenty-five (6.1%) micro-NFAs became macro-adenomas (24/25 were $>$ 5 mm at diagnosis), 7 (28%) of which had surgery. Two patients (0.5%) (who also had tumour growth) developed new hypopituitarism.
Conclusions
In this UK NFA consortium study, we have shown that the 5-year probability of micro-NFA growth is low (14%), and development of new hypopituitarism is exceptionally rare. Progression to macroadenoma is an unusual event. Need for surgical intervention during follow-up is very uncommon. Following detection, surveillance imaging for micro-NFAs $<$5 mm can be delayed by at least 3 years and additional hormonal testing is necessary only if tumour growth.

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P93

Circadian/diurnal rhythm profiles of serum and salivary melatonin, cortisol and cortisone, determined by liquid chromatography tandem mass spectrometry (LC-MS/MS)

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Background
Melatonin and cortisol production demonstrate circadian rhythms; disruption of these rhythms feature in endocrine and neurodegenerative disorders, such as Addison's disease, Huntington's disease (HD) and Alzheimer's disease (AD). Measuring serum and saliva concentrations at nadir is challenging using immunoassays. We have developed LC-MSMS methods for measuring serum and saliva melatonin, cortisol and cortisone to analyse 24hr profile samples obtained from sleep studies.
Methods
4 hourly serum samples ($n=231$) collected over a 24hr period were obtained with consent from 28 HD patients and 14 controls. Hourly saliva samples ($n=523$) from 30 individuals with APOE- $\varepsilon^{3/3}$ and APOE- $\varepsilon^{3/4}$ genotypes at higher risk of developing AD having undergone partial sleep deprivation (sleep restricted to 4hrs) or multi-nap cycles (4hrs 160min sleep,80min wake). LC-MSMS methods were developed using a Waters Xevo TQ-XS LC-MSMS. The method was compared against commercial ELISA (IBL, Germany).
Results
The LC-MSMS method showed intra/inter-assay precision (CV%) of $<$8.1% and $<$9.6% across the assay range for melatonin(0.1-430 pmo/l), cortisol and cortisone (saliva/serum) of (1.3-165 nmol/l/28.5-806 nmol/l), (2.76-259/2.87-108 nmol/l), respectively. LLoQ and LLoD for melatonin were 2.7 pmo/l and 0.3 nmol/l for cortisol and cortisone. Comparison of LC-MS/MS melatonin values against ELISA showed a negatively biased correlation in serum ($y=0.5738x-10.667$, $r^2=0.7265$) ; no correlation was observed in saliva ($y=0.2273x+8.719$, $r^2=0.1927$). The sleep studies showed significant rhythm observed in serum melatonin (time, conc) peak (3:30am, 162.1 pmo/l), nadir (2:45pm, 0.8 pmo/l); cortisol peak (7:00am, 456.6 nmol/l), nadir (11:00pm, 99.3 nmol/l). HD patients exhibited lower concentrations of melatonin and cortisol across all time points compared to the controls. Saliva in APOE carriers showed circadian rhythm in the sleep-deprived group, but not in the multi-nap group.
Conclusion
Our LC-MSMS methods were able to detect circadian rhythms of melatonin, cortisol and cortisone in serum and saliva samples. Salivary method advancement has clinical applications and offers an alternative to venous samples in research studies.

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P94

Gene-chromatin regulatory circuits driving stemness in the anterior pituitary

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The pituitary gland is a dynamic organ that adapts its cellular architecture throughout life, making it an ideal model for the study of stem cells (SCs), their commitment and differentiation. *Sox2*-expressing cells are *bona fide* anterior pituitary stem cells (PSCs), which through genetic lineage tracing have been shown to give rise to all anterior pituitary hormone-producing cells both in the embryo and adult. The YAP/TAZ signalling pathway has been previously shown to promote PSC self-renewal, but the molecular mechanisms controlling this process remain unknown, as are additional key factors controlling the stem cell state. To explore these mechanisms, we utilised an inducible mouse model of YAP over-activation, mis-expressing constitutive active YAP in all endocrine cells of the anterior pituitary, compared to uninduced controls. *In vivo*, failure to downregulate YAP leads to PSC expansion, inability to upregulate lineage determining factors, and a subsequent failure of PSCs to differentiate. Pituitaries were dissociated and single cells sequenced using a multi-omic approach allowing simultaneous mRNA and global chromatin accessibility profiling for each individual cell. Individual cell types were identified based on gene and TF expression, as well as accessibility of TF binding motifs in the underlying DNA regions, thereby allowing characterisation of transcription dynamics. We present here the construction and analysis of gene-chromatin regulatory circuits predicted to be implicated in the regulation of PSC self-renewal. We focus on three members of the Nuclear Family I (NFI) family of TFs, previously undescribed in the pituitary gland, and identify these as putative regulators of PSCs in mice and humans. The study of novel PSC regulators is highly relevant to regenerative approaches, and to investigations on the underlying causes of disease including hypopituitarism and pituitary tumours.

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P95

Optimising the Insulin Tolerance Test: Cortisol Thresholds on Abbott Platforms should be lowered to 416 nmol/L

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Background
Adrenal insufficiency (AI) is a life-threatening condition which requires long term glucocorticoid (GC) replacement. Patient misdiagnosis results in inappropriate GC use, which has significant adverse effects and is associated with an increased mortality risk. The insulin tolerance test (ITT) is the gold standard test for diagnosis, but the widely accepted cut-off value of $\leq$550 nmol/l used to diagnose AI is founded on outdated immunoassays. Use of this cut-off in an era of more specific immunoassays therefore risks misdiagnosis and subsequent unnecessary GC exposure.
Methodology
This retrospective analysis assessed 297 ITT cortisol responses using the Abbott-Alinity analyser platform in patients with suspected AI over a period of approximately 12 years (August 2010-January 2022). Patients were classified as

having AI or not, based on a comprehensive clinical review of electronic patient records from the point of test to the present day by a panel of adrenal specialists.
Results
Using the current institutional cut-off value of 500 nmol/l, receiver operating characteristic (ROC) analysis identified a 100.0% sensitivity and 43.4% specificity (area under the curve 0.9812). This gave a negative predictive value (NPV) of 100.0% and a positive predictive value (PPV) of 28.6%. Using a lower cortisol threshold value of 416 nmol/l on the Abbott analyser platform maintained a sensitivity of 100.0% and improved specificity to 87.2%, improving the PPV to 64.0%
Conclusion
This is the largest review of ITT data in AI patients to date. Data supports lowering the Abbott analyser ITT cortisol threshold to 416ce:hsp sp="0.25" />nmol/l. Use of this improved cut-off avoids unnecessary glucocorticoid replacement therapy in 106 (41.6%) individuals in this study.

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P96

A case of chronic hyponatremia secondary to SIADH treated with low dose Tolvaptan to prevent recurrent hospital admission and proven cost effective

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Introduction
Tolvaptan, a selective vasopressin 2 receptor antagonist is proving beneficial in managing hyponatremia secondary to SIADH.
Case report
A 75-year-old male with history of traumatic SAH developed hyponatremia secondary to SIADH. He had multiple admissions with symptomatic hyponatremia. His sodium level kept dropping despite putting on fluid restriction and trial of sodium chloride tablets. He was started on Tolvaptan 7.5 once weekly initially. His sodium level improved but started becoming symptomatic a day before next dose. His Tolvaptan dose was increased to one and a half of tablet each week. He became symptomatic after cutting his dose to one tablet. He was then again commenced back to previous one and half tablets per week. He is successfully maintaining his sodium level didn't have further hospital admissions due to hyponatremia for a long time.
Investigations
Patients' sodium level during first hospital admission was 120 mmol/l. Serum osmolality 242 mOsmol/kg, urine osmolality 656 mOsmol/kg and urinary sodium 76 mmol/l. After starting on Tolvaptan his sodium level maintained between 133-141 mmol/l. He has undergone serial serum and urine osmolality measurements.
Progress
Tolvaptan improved serum sodium and decreased hyponatremia symptoms for this patient and subsequently prevented recurrent hospital admission.
Discussion and Learning Points
1. This was the first case in KGH where Tolvaptan was used for a longer term with regular monitoring and prescribing arrangement remained in secondary care. 2. We have calculated roughly that his Tolvaptan is costing 2950 pounds a year (One and half tablets/ week), but his each hospital admission costs even more with 4-5 days of average stay. 3. Although Tolvaptan use in daily clinical practice is still limited due to the potential risk of overcorrections and its cost, but it can be an effective treatment option in carefully selected and monitored patient population.

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P97

Aberrant cyclic GMP-AMP synthase stimulator of interferon genes signalling in an *AIP* mutant cell line

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Background
The cyclic GMP-AMP synthase stimulator of interferon genes (cGAS-STING) signalling pathway is an element of the innate immune response and is activated by the presence of DNA in the cytosol. Triggering of this immune response may occur in the setting of infection or neoplasia. Activation of this pathway results in phosphorylation of interferon regulatory factor 3 and downstream transcription of cytokines such as interferon β and interleukin-6. Polyinosinic:polycytidylic acid (Poly (I:C)) is a synthetic double-stranded RNA analogue which activates the innate immune system. Previous research suggests that the phenotype of *AIP*-mutated pituitary tumours is shaped by their tumour microenvironment.
Aim
The aim of this work was to assess the expression of genes involved in cGAS-STING signalling in an *Aip* knockout cell line.
Methods
RT-qPCR was used to assess gene expression in wild-type and Aip knockout mouse embryonic fibroblasts following six hours of treatment with Poly(I:C) or vehicle.
Results
Aip knockout was first successfully confirmed by qPCR and western blotting. Knockout cells treated with vehicle showed significantly increased expression levels of *Irf3* ($P=0.0002$), *Ifnb* ($P=0.004$) and *Il6* ($P=0.003$) compared to wild-type vehicle treated cells. In addition, following treatment with Poly(I:C), there appeared to be further significant enhanced expression of the cGAS-STING pathway downstream gene *Irf3* ($P=0.02$) in *Aip* knockout cells versus wild-type cells. *Ifnb* downstream of *Irf3* and *Il6* downstream of *Nfkb1* showed a trend for enhanced expression in *Aip* knockout versus wild-type cells treated with Poly(I:C), but this did not reach significance.
Conclusions
The data suggest that lack of *Aip* results in increased inflammatory cytokine gene expression with increased responsiveness to the Poly(I:C) STING agonist. This would correspond with our previous data with more inflammatory infiltration in *AIP* mutant human and mouse tumours.

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P98

The pituitary patients' experiences pre and during the Covid-19 pandemic

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Background
Patient experience is a crucial part of patient care, but is not systematically assessed. In light of this we performed a UK-wide survey to understand the care experiences of patients with pituitary conditions over the preceding three years.
Methods
In collaboration with patients and pituitary experts a web-based survey was designed, aimed at patients 18yrs and over. Specific topics included: assessment of information provision, communication between health care professionals, effectiveness of emergency care protocols for adrenal insufficiency (AI) and overall management of Arginine Vasopressin Deficiency - AVP-D (cranial diabetes insipidus) Participants answered each question rating from 'poor' to 'excellent' on a five-point scale, with free text comments. The survey was available electronically between August and December 2021.
Results
A total of 982 patients, all with confirmed pituitary diagnosis, (70.93% female) completed survey forms, 700 provided free text comments. For those with AI or AVP-D, experiencing an in hospital or A&E episode, 72.47% were not confident staff understood or managed their condition properly. Those with AVP-D, 75.61% couldn't recall being given information at diagnosis about desmopressin, or the risk of changes in serum sodium. Only 63% of patients with AI were given information about sick day rules at diagnosis. 68.84% said their experience of care was worse since pandemic. Free text comments reported support from endocrine teams to be inadequate, with quality of care ranging from: poor 16.50% to excellent 29.74%.
Conclusions
Care for patients with pituitary disease is highly variable in the UK. These data mandate an urgent need for improvements in care of patients with pituitary disease by three main steps: 1) increasing awareness and education of pituitary conditions for patients and health care professionals; 2) improving communication between health care professionals and patients; 3) signposting support available from the Pituitary Foundation.

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P99

Pseudo-Cushing's syndrome in the context of intense physical exercise and underlying eating disorder - pitfalls of interpreting investigations in patients with body dysmorphia

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Introduction
Pseudo-Cushing's syndromes are a heterogeneous group of disorders and include alcoholism, obesity, anorexia nervosa (AN), depression and intense physical exercise. These share biochemical features of Cushing's syndrome (CS) causing ACTH-dependent hypercortisolism. Distorted body image is a prominent feature of eating disorders. We describe the case of patient with AN who was convinced she had CS. This led to investigations that confirmed hypercortisolism which perpetuated anxiety about an underlying endocrine condition.
Case Study
A 37-year-old woman with a prior history of AN was referred with concerns about facial swelling and elevated random cortisol levels. Investigations showed raised free cortisol excretion and non-suppression on dexamethasone testing. On examination, she was underweight (BMI 17.50) with no features of CS. Facial puffiness in the region of the parotid glands was noted which is well recognised with eating disorders. A history of daily intense prolonged physical exercise was elicited. Pituitary and adrenal imaging were normal. Pseudo-Cushing's syndrome secondary to AN and intense physical exercise was diagnosed. The patient was asked to reduce exercise and aim for an ideal body weight of 53 kg.
Discussion
Pseudo-Cushing's syndrome is due to physiologic overactivity of the HPA axis. Mechanisms include reduced cortisol clearance, changes in CBG affinity and glucocorticoid resistance. The latter explains hypercortisolism and lack of clinical signs of cortisol excess in underweight women. This case highlights that performing endocrine tests for 'reassurance' and exclusion may be counter-productive as this perpetuates anxiety in already psychologically vulnerable individuals when spurious abnormal results are found. This leads to unnecessary additional investigations. The patient's perception of facial puffiness was disproportionate to clinical findings and indicated body dysmorphia. Treatment of underlying causes ameliorates biochemical abnormalities. However, body dysmorphia may pose barriers and patients' may not always be receptive to this. Psychological support remains the mainstay of therapy.

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P100

Adipose tissue and glycemic changes in patients with surgically treated acromegaly

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Introduction
Excess GH in acromegaly has lipolytic action and detrimental effect on glucose metabolism and insulin signaling. Recent studies have suggested a specific lipodystrophy in patients with acromegaly. Paradoxically, although the visceral adipose tissue (VAT) and intrahepatic lipid were reduced in active acromegaly compared to controls, insulin resistance was increased. Fat was redistributed from subcutaneous and visceral depots to muscle; weight and VAT depots rose with surgical or medical therapy. The aim of our study was to assess the weight and glycemic changes in Romanian patients treated with surgery for acromegaly.
Patients and methods
Retrospective evaluation of weight, height, body mass index (BMI), blood glucose levels in 26 patients (6 men, 20 women) with active acromegaly, not treated with somatostatin analogs, before and at 3 to 6 months after surgery.
Results
Mean age before surgery was 51 $\pm$ 12 years. In 12 patients (46%) IGF1 and/or GH levels were controlled after surgery (IGF1 $<$ 1.3xULN). Pituitary insufficiency was recorded in 3 patients (11.5%) and diabetes mellitus in 5 (19%) before surgery, and in 4 (15.3%) and 6 (23%), respectively, after surgery (p = NS). Overall, mean body weight increased significantly after surgery, from 79.7 to 82.3 kg ($P < 0.01$), BMI tended to increase (27.5 to 29.5 kg/sqm, $P = 0.055$). In contrast to other studies, weight increased significantly only in patients not controlled after surgery: 80.5 to 82.5 kg, $P < 0.01$, 2 (14%) with glucocorticoid replacement after surgery. Mean glycemia (mg/dL) decreased after surgery from 124.3 to 102.5 ($P < 0.01$), notably in controlled patients (106 to 91.5, $P < 0.01$) and borderline in uncontrolled ones (105 to 96.5, $P = 0.058$).
Conclusion
In patients with acromegaly, although body weight increased after surgery, blood glucose levels improved, suggesting different pathophysiologic mechanisms regulating fat and glucose metabolism, as compared to non-acromegalic patients with metabolic syndrome.

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P101

A rare case of silent Gonadotroph Adenoma presenting with secondary infertility, oligomenorrhea in a female patient with a history of polycystic ovarian syndrome

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Background
Gonadotroph adenomas are usually clinically non-functioning and hypersecretion of FSH or LH is unusual, and no distinct hormone-dependent clinical phenotype is present. Positive immunostaining for nuclear transcription factor SF1 is usually sufficient to diagnose gonadotroph adenoma.
Case History
A 37-year-old lady with Asian background presented with tiredness, headaches, weight gain, poor sleep, secondary amenorrhea and infertility for 2 years. She previously conceived twice with one live birth and a miscarriage. She had a past medical history of PCOS.
Examination
She had no galactorrhea or visual field defects. Rest was unremarkable. Weight 87.2 kg Height 162 cm -BMI 33.2 kg/m^2.
Investigations
FSH -3.6 IU/l (2.5-10.2 IU/l). LH-1.1 IU/l (1.9-12.5) with increased FSH/lH ratio in the setting of high oestradiol of 2156 pmo/l, testosterone 2.7 nmol/l(0.5-2.5 pmo/l), free testosterone 59 pmo/l (10-50) and prolactin $>$4237 mIU/l (102-496 mIU/l). TSH and Cortisol levels-normal. Serum prolactin was undetectable 2 weeks after commencing cabergoline therapy, consistent with stalk effect. US Pelvis-Both ovaries had normal ultrasound appearances. No cysts or mass seen in pelvis. MRI Head-Large sellar/suprasellar mass, measuring **25 x19**mm, partly encasing the right internal carotid artery. Some radiological compression of the chiasm.
Management
Under the combined endocrine and neurosurgery pituitary multidisciplinary team, trans-sphenoidal surgery was performed without post-operative complications. She was commenced on Hydrocortisone 10/5/5 mg, which was discontinued after a normal response to an insulin stress test. Histology result showed a predominant hormone negative pituitary adenoma with variably intense nuclear positivity for SF1 transcription factor and a few FSH and pan α-subunit positive cells, consistent with a gonadotroph adenoma.
Conclusion
Gonadotroph adenoma should be considered in the differential diagnosis of patients harboring pituitary adenoma with reproductive dysfunction. Trans-sphenoidal resection is the initial treatment of choice although recurrence remains a significant possibility long-term and continued surveillance is essential.

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P102

Early Onset Neurosarcoidosis with Delayed Severe Hypercalcaemia

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Sarcoidosis is a multiorgan disease often affecting the lungs and lymphatic system. Neurological involvement occurs in sarcoidosis as granulomas infiltrate the nervous system. Here, we present a case of neurosarcoidosis diagnosed following non-specific neurological symptoms and delayed hypercalcaemia. A 32-year-old female presents with headaches, vomiting and acute confusion. During admission she developed unresponsive episodes. She has a background of type 1 diabetes and hypothyroidism. A CT-head scan only showed lytic lesions. Lumbar puncture was sterile with high proteins. She was treated for meningoencephalitis. Further abdominal imaging showed splenomegaly with infiltrates. 8 weeks later she presented with severe hypercalcaemia, suggesting a potential underlying sarcoidosis. The CT-thorax scan done at the time showed mediastinal lymphadenopathy, but bronchoscopic biopsies were non-specific. A

multidisciplinary team meeting concluded that the diagnosis was sarcoidosis with extrapulmonary manifestations based on the clinical picture. The diagnosis of neurosarcoidosis is dependent on clinical suspicion of the diagnosis followed by finding of granuloma in biopsy sample. The presence of both clinical symptoms and granuloma on biopsy confirms the diagnosis. This case report discusses neurological involvement and the non-specific presenting symptoms that make the diagnosis of neurosarcoidosis difficult.

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P103

A rare case of Erdheim-Chester disease as the underlying cause of cranial diabetes insipidus

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Introduction
Erdheim-Chester disease is a rare form of non-Langerhans' cell histiocytosis characterised by foamy histiocyte infiltration with multi-systemic manifestations. Roughly 550 cases have been described in the literature, most frequently affecting men aged 40-60. Bony pain is the most common symptom, resulting from osteosclerotic lesions of the long bones of the lower limbs. Extra-skeletal manifestations are varied and include diabetes insipidus resulting from pituitary infiltration.
Case History
A 65-year-old female presented in 2010 with a short history of polyuria and polydipsia. She had a fluid intake of 7-8 litres, passing equal amounts of dilute urine. Cranial diabetes insipidus was confirmed with the hypertonic saline test. Baseline serum osmolality increased from 295 mOsmol/kg 313 mOsmol/kg. Peak AVP level was 0.4 pmo/l from a baseline of 0.3 pmo/l. There was prompt concentration of urine with Desmopressin (baseline urine osmolality 63 mOsmol/kg increased to 580 mOsmol/kg) confirming cranial diabetes insipidus. Short Synacthen test was normal. The patient had a history of primary hypothyroidism treated with Levothyroxine but had no other systemic symptoms. Idiopathic cranial diabetes insipidus was diagnosed in the absence of a structural pituitary lesion on MRI scanning. X-Rays in 2021 for persistent knee pain showed radiological features and lesions consistent with Erdheim-Chester disease, confirmed on bone biopsy. 10 years after initial presentation, it was established that the diabetes insipidus was secondary to Erdheim-Chester disease.
Discussion
Erdheim-Chester disease is a rare cause of cranial diabetes insipidus. Due to its rarity and non-specific multi-systemic manifestations, there is often a diagnostic delay. It should be considered in patients presenting with cranial diabetes insipidus of unclear aetiology alongside bony pain or other unexplained multi-systemic complaints.

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P104

Patient-reported use of physiotherapy services in rare endocrine conditions – a quantitative study

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Background
Recent research on experiences of adults with a rare endocrine condition/disease (RED) indicate a preference for greater access to allied health professionals including physiotherapists.
Objective
To explore experiences of musculoskeletal (MSK) symptoms (typically managed by physiotherapy) of adults living with a RED and investigate their reported usage and satisfaction of MSK physiotherapy services.
Method
Ethically approved, quantitative survey disseminated via social media and UK online support groups. 256 participants (232 from the UK, 24 outside the UK) aged 18+ with a RED diagnosis of $\geq$3 months (RED defined as affecting $\leq$1 per 2,000 of the population).
Results
78.1% of participants (n=200) experienced $\geq$5 MSK symptoms, from a maximum of 14 symptoms compiled from case studies/RED symptom checklists. The most common symptom was fatigue 92.2% (n=236). 43.0% of total participants (n=110) were referred to physiotherapy. Of 232 UK participants, 41.8% (n=97) saw/were referred to 136 UK physiotherapy settings: 59.8% (n=58) NHS physiotherapy, 17.5% (n=17) private physiotherapy and 22.7% (n=22) both private and NHS physiotherapy. 54.0% (n=82) of 152 UK participants without a referral (mode $\geq$7 symptoms) would have liked a referral. Over 73% of participants rated NHS community (n=14), NHS inpatient (n=15), private community (n=3) and private outpatient services (n=35) as good quality and helpful for managing their condition and 57.4% rated NHS outpatients (n=68) as good quality. NHS inpatient physiotherapists were most highly rated for understanding of RED, (73.3% good) with NHS outpatients at 29.4%.
Conclusions
This is a novel study exploring experiences and perceptions of physiotherapy from people living with REDs. Findings indicate that physiotherapy can be helpful in managing symptoms and corroborates a growing area of research, suggesting access to wider multi-disciplinary healthcare teams may be beneficial. Therapists' knowledge of RED may be dependent on setting and further research is required.

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P105

Case Series: Primary / neo-adjuvant ^{131}I-MIBG therapy as a safe and effect treatment in the management of pheochromocytoma / paraganglioma

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Background
As per 2014 Endocrine Society guidelines, ^{131}I-MIBG therapy is usually reserved for metastatic or unresectable disease in patients with pheochromocytoma / paraganglioma. In this series, we describe three patients effectively treated with primary ^{131}I-MIBG therapy. The indications were primary neo-adjuvant therapy prior to surgery, or palliative.
Case series
Case 1 – 18-year-old male with a 60 mm para-aortic paraganglioma on CT scan after a presentation with trauma. Urinary catecholamines were elevated and alpha blockade commenced. Surgical intervention was deemed of unacceptably high risk due to proximity to major mesenteric vessels. One cycle of primary ^{131}I-MIBG therapy was administered. The lesion reduced to 53 mm on repeat imaging, now clear of vessels and amenable to resection. No complications were encountered. Case 2 – 31-year-old female with SDHB mutation, diagnosed with a 56 mm pelvic paraganglioma after presentation with a crisis. Plasma metanephrines were elevated and alpha blockade commenced. Due to a COVID-19 related surgical delay, she received a single cycle of primary ^{131}I-MIBG therapy prior to resection, which was well tolerated. No repeat imaging was performed but the surgical specimen appeared similar in diameter to radiological measurements. Case 3 – 79-year-old female diagnosed with a 150 mm mesenteric paraganglioma after presenting with urinary discomfort. Plasma metanephrines were normal and surgery was considered too high risk due to proximity to mesenteric vessels. The lesion reduced to 120 mm after three cycles of ^{131}I-MIBG therapy. After multidisciplinary team review, surgery was considered feasible, but conservative management was pursued due to comorbidities.
Discussion
In the cases described primary^{131}I-MIBG therapy was well tolerated without significant side effects or precipitation of pheochromocytoma crisis. In two cases significant reduction of tumour volume was achieved. These outcomes suggest primary ^{131}I-MIBG therapy may be a safe and effective treatment approach pre-surgery (neo-adjuvant) or for palliation without the presence of metastasis.

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P106

Identifying and characterising variants in patients with pachydermoperiostosis

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Introduction

Pachydermoperiostosis (primary hypertrophic osteoarthropathy, PHOA) is a rare genetic condition characterised by digital clubbing, pachydermia, hyperhidrosis, cutis verticis gyrata and periostosis. The *SLCO2A1* transporter and *HPGD* enzyme genes play an important role in prostaglandin metabolism, hence loss of function mutations in them causes PHOA. To date, according to the VarSome database 101 and 41 variants have been identified in the *SLCO2A1* and *HPGD* genes respectively. The signs and symptoms of PHOA can be confused or overlap with some conditions like acromegaly, thyroid acropachy, psoriatic/rheumatoid arthritis and secondary hypertrophic osteoarthrpathy. Although certain symptoms can help differentiate from these other conditions, they are not always apparent due to the variable penetrance of PHOA. Hence it is important to identify known or novel variants in patients.

Aim

The aim of this project is to examine both disease-causing genes (*HPGD* and *SLCO2A1*) in PHOA patients to identify and characterise known and novel variants.

Methods

Performed Sanger Sequencing for *HPGD* (seven exons) and *SLCO2A1* (14 exons) on peripheral blood DNA. The identified variants on both genes were classified using the American College of Medical Genetics (ACMG) classification guidelines that combine a series of functional, genetic, population and in silico evidence and calculating their strength.

Results and discussion

We identified a total of 14 variants in 14 patients or family members of probands. Six of the 14 variants were novel. The novel variant in the *HPGD* gene was g.30009_30012delGTAA. Novel variants in the *SLCO2A1* gene were: c.822_823insA (p.Phe275IlefsTer21), c.724_725insCCTGCCAC, c.161G>A (p.Ser54Asn), c.165C>G (p.Ser55Arg) and c.1604C>G (p Pro535Arg). Our in-silico analysis of these variants including protein properties and functional outcomes suggest a likely pathogenic or pathogenic effect. These findings could further the genotype database for PHOA, and the genotype-phenotype correlations can provide insights to clinicians and help future genetic diagnosis and counselling.

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P107

Severe hyponatremia-A manifestation of new Pituitary metastases in Renal Cell Cancer

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It is very rare to have Pituitary metastasis in Renal Cell cancer (RCC). Prevalence of Pituitary metastasis varies from 1-4% in all cancers and about 2.6% in RCC. Most common cancers with pituitary metastasis are breast (33%) and lung (36%). We present a rare case of RCC with pituitary Metastasis presented with severe Hyponatraemia. A 71 years old male with history of renal cell cancer who underwent Right nephrectomy in 2017. He was found to have intrathoracic metastases in 2018 and started on Tivozanib treatment. He was referred with severe hyponatremia (Sodium-120 mmol). His cortisol was low and had central hypothyroidism. MRI head shown a focal metastatic deposit from RCC and pituitary metastasis. His pituitary functions also revealed a pan hypopituitarism picture as below: His hormones are being replaced. Hyponatremia was a combination of corticotroph and thyrotroph deficiency. He underwent Stereotactic radiosurgery for metastatic disease and is under regular follow up of endocrine team.

Conclusion

Severe hyponatremia can also be a manifestation of Pituitary metastasis. This is a rare clinical condition and difficult to diagnose. However, stepwise approach enables the appropriate diagnosis. It is important to check Cortisol and Thyroid function in hyponatremia.

TSH (mU/l)	0.12
Free T4 (pmol/l)	4.6
Free T3 (pmol/l)	2.0
Prolactin (m IU/l)	736
Testosterone (nmol/l)	<4
Cortisol (nmol/l)	38

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P108

Dopamine agonist intolerance in prolactinoma- A management challenge to endocrinologist

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Introduction

Typically, patients with a microprolactinoma will have serum prolactin level between 2,000-4,000mIU/l. The primary goal of treatment is to normalise prolactin level and thereby improve symptoms associated with a raised prolactin. Dopamine (D2) agonists are the main stay of treatment with some patients unable to tolerate dopamine agonists rather than being resistant to the medication.

Case report

A 26-year-old lady with a history of anxiety and depression, hypersomnia, obesity class 3, PCOS, presented with galactorrhoea and secondary amenorrhoea. Her prolactin level was 1670 mU/l, with suppressed gonadotrophins (Table:1) She was on venlafaxine, modafinil. MRI pituitary in 2018 revealed 5x6 mm pituitary microadenoma. In 2018, she was commenced on Cabergoline and subsequently Bromocriptine, but unable to tolerate standard doses. She continued to have symptomatic hyperprolactinaemia despite discontinuation venlafaxine. Later she was restarted on Duloxetine for her other medical conditions. Repeat pituitary MRI in 2019 time revealed slight increase in size of the adenoma measuring 1.34 cm X 1.24 cm, with no compression of the optic chiasm. Due to her poor response and intolerance to D2 blockers she was initiated on Lanreotide 30 mg monthly injections in January 2021 (prolactin 4,558)., In December 2021, prolactin fell to 1,843 (>50% reduction). Given an insufficient response Lanreotide was discontinued and prolactin rose in January 2022 (figure-1).

Conclusions

Dopamine agonist intolerance poses a management challenge with Prolactinomas. There is insufficient evidence with Somatostatin receptor agonists.

Table 1

Date	FSH(IU/l)	LH(IU/l)	Prolactin(mU/l)	Estragen(pmol/l)
1/22	4	11	2525	128
11/21	2	3	1863	70
12/20	<1	<1	4558	62
2/20	<1	<1	2343	<50
03/19	2	2	1860	<50

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P109

A TSH-secreting pituitary adenoma cured from SSA monotherapy alone: Disease free more than three years after stopping treatment

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Introduction

TSH-secreting pituitary adenomas (TSHomas) are rare pituitary tumours treated primarily with surgery; in cases of surgical failure, somatostatin analogue (SSA) or radiotherapy are further options. SSAs are rarely used as monotherapy; if responsive and in the absence of radiotherapy, the requirement of life-long medical treatment, is unknown. Herein, we present a patient with a TSHoma who remains in remission three years after SSA withdrawal.

Case

A 29-year-old female was referred to the Endocrine Department in 2002 with deranged thyroid function tests; TSH 1.4mIU/l (0.4-5.5), FT4 30.2 pmo/l (9.0-20.0), and FT3 10.9 pmo/l (3.5-6.5). She initially presented to her GP with fatigue and hot flushes; her medical, family, drug history was unremarkable. Positive examination findings included mild tremor and a small palpable goitre only. Repeat testing confirmed hyperthyroxinaemia with inappropriate TSH secretion; screening for antibodies, analytical interference or familial dysalbuminaemia hyperthyroxinaemia was negative. FT4 by equilibrium dialysis was 55.6 pmo/l (10-36 pmo/l). Alpha subunit (α-SU) was 0.45IU/l (<1.0). Anterior pituitary screen was otherwise unremarkable. MRI pituitary demonstrated a 7x7x9 mm adenoma. A trial of octreotide 50 mg subcutaneously thrice daily was started; three weeks later, TSH, T4 and T3 fell from 3.2 mU/l, 28.2 pmo/l, and 10.8 pmo/l to 0.6 mIU/l, 16.5 pmo/l and 5.7 pmo/l,

respectively, suggesting a TSHoma. The patient declined pituitary surgery, instead choosing monthly long-acting SSA injections. On this treatment, she remained euthyroid for 16 years and MRI surveillance showed tumour shrinkage with no identifiable surgical target. In 2019, SSA was withdrawn; three years later, she remains biochemically euthyroid with stable MRI appearances.

Discussion

To our knowledge, this is the second reported case of a TSHoma with sustained remission after SSA monotherapy withdrawal. Given limited experience on this management approach, optimal treatment duration is unknown; our case demonstrates that re-assessment of the long-term requirement of SSA monotherapy needs to be considered in these cases.

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P110

Retrospective analysis of clinical, biochemical, radiological features of Craniopharyngioma

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Craniopharyngioma is a rare embryonic malformation of the Sellar/parasellar region. This harbors BRAF-V600E mutations. There are 2 Subtypes-Adamantinomatous and Papillary. Point prevalence of CP is around 2/100,000 with no variance by gender or race. CP has bimodal age distribution with peak incidence in the ages of 5-14 and 65-74 years. CP presents with following clinical features: Symptoms due to increased intracranial pressure-Nausea, headaches, visual impairments, hormone deficiencies, growth retardation, hypothalamic obesity. Hypopituitarism is due to tumour and/or treatment-related lesions to the hypothalamic-pituitary axis. This affects the secretion of Growth hormone (GH, 75%), Gonadotropins (LH/FSH, 40%), Thyroid-stimulating hormone (TSH, 25%), Adrenocorticotropic hormone (ACTH, 25%). Diagnosis is made via neuroimaging. A detailed neuroophthalmological examination is required once diagnosis is made. An experienced multidisciplinary team (neurosurgery, radiation oncology, neuro-oncology, endocrinology, ophthalmology, neuroradiology, and neuropathology) is essential for the optimal treatment of both paediatric and adult patients with craniopharyngiomas. Aggressive surgery with an attempt to achieve complete resection at diagnosis versus a more conservative surgical approach that used radiation therapy (RT) to treat residual disease is suggested. We have undertaken a retrospective review of Craniopharyngioma patients over the 10 years. Clinical, radiological, biochemical features were analysed. Data from 20 patients with craniopharyngioma were collected. Average age of patients was 61.2 years, female and male accounted for 70% and 30 % respectively. Many patients (75%) required Hydrocortisone while 40% and 15% required levothyroxine and desmopressin respectively post-surgery. 12 had histopathological diagnosis of craniopharyngioma. Histologically 3 had adenomatous, 2 had papillary and 6 had grade 1 craniopharyngioma with only 1 patient had recurrence during follow up.

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P111

A rare Presentation of Carcinoid Crisis Following Radioactive Iodine Treatment for Thyroid Cancer in a Patient with Metastatic Midgut Neuroendocrine Tumour

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Introduction

Carcinoid crisis represents a rare medical emergency with potentially fatal manifestations that can occur in patients with neuroendocrine tumours (NETs). The condition is caused by a substantial release of vasoactive metabolites from the NETs during diagnostic or therapeutic interventions. However, in rare instances, it can occur spontaneously. Here, we report a patient who developed a carcinoid crisis following radioactive iodine ^{131}I (RAI) treatment for thyroid cancer.

Case report

A 72-year-old male known to have metastatic midgut NET with mediastinal and para-aortic lymphadenopathy and peritoneal disease, on long-acting somatostatin analogue therapy. He is also known to have metastatic follicular variant papillary thyroid cancer with lung nodules (pT3a NX M1 R1). The thyroid cancer was treated with thyroidectomy followed by ablative RAI ^{131}I treatment. The patient received two cycles of RAI ^{131}I treatment with no complications recorded. However, one week post receiving the third cycle, he developed clinical features of carcinoid crisis and presented with facial flushing, fever, wheezy chest, palpitations, and frequent watery diarrhoea up to 20 times per day. The patient was hyperthermic, tachycardic, hypotensive and had signs of bronchospasm. He was immediately resuscitated with intravenous fluid and commenced on intravenous Octreotide infusion as per the European Neuroendocrine Tumour Society guidelines. Rapid reversal of carcinoid crisis was achieved, and Octreotide infusion was gradually titrated down based on patient response. A complete biochemical and radiological assessment revealed no other potential precipitant of carcinoid crisis. The patient made a full recovery and was discharged.

Discussion

Early recognition and treatment of carcinoid crisis is imperative to avoid adverse consequences. Successful patient outcome greatly relies on the availability of clinical expertise and effective management. RAI might have induced carcinoid crisis in this patient; up to our knowledge, this has not been reported in the literature.

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P112

Primary papillary epithelial tumor of the pituitary- a challenge to diagnosis; first reported case from Sri Lanka

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Background

While pituitary adenomas are the commonest Sella neoplasm, number of other entities should be considered in the differential diagnosis and the diagnosis is based on histopathological and immunohistochemical characteristics. Pituitary tumors with papillary architecture are uncommon and have limited differential diagnoses. Primary papillary epithelial tumor of the pituitary is a recently described histopathological entity with striking papillary architecture and TTF1 positivity.

Case

A 60-year-old male presented with a 1-year history of gradual visual deterioration, mild hypothyroid symptoms and erectile dysfunction without any constitutional symptoms, systemic symptoms and features of diabetes insipidus. A pituitary adenoma was suspected and imaging revealed 2.8*2.4*2.5 cm solid mass involving pituitary fossa and suprasellar region causing displacement of the optic chiasm. Endocrine evaluation revealed evidence of central hypothyroidism and hypogonadism. The patient had undergone transcranial surgery and histological evaluation revealed a neoplasm predominantly composed of papillary structures without any aggressive features. Immunohistochemistry revealed positive staining for Cytokeratin 7, Pan-Cytokeratin, and occasional expression of TTF1 with Ki 67 index of 1%. Extensive evaluation for the possibility of metastatic deposit from papillary adenocarcinoma was negative. After excluding other causes for similar histopathological appearance, the lesion was diagnosed as a primary papillary epithelial tumor of the Sella. The patient was offered radiotherapy following the surgery and had a residual tumor on imaging at 3 months. Re-evaluation at 1 year revealed no interval change of residual lesion and the patient was well.

Conclusions

Primary papillary epithelial tumor of the Sella is a novel described histopathological entity. It needs to be considered in the differential diagnosis of Sella tumors with papillary architecture after excluding other causes for similar histopathological appearance including extensive evaluation for a possibility of metastatic deposit. Prognosis seems to be favorable, however, long term follow-up studies are required to assess the behavior and the best therapeutic option.

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P113

A Rare Case of Radiation-Induced Sarcoma in Acromegaly – Diagnostic challenges

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Introduction

Acromegaly is a rare, progressive disease characterised by excess growth hormone. The recommended treatment is surgery. Radiotherapy and somatostatin analogues are

used as adjuncts. The risk of post-radiotherapy osteosarcoma is 0.01% to 0.03% among all irradiated patients. We report a case of radiation-induced osteosarcoma that developed 22 years after radiotherapy for acromegaly.
Case report
In 1997, a 53-year-old gentleman with acromegaly due to an extensive sellar/parasellar/suprasellar tumour was treated with transsphenoidal surgery and radiotherapy, followed by gamma-knife in 2002. At annual reviews, he remained clinically well. His IGF1 was normal on lanreotide and cabergoline. He required hydrocortisone, thyroxine, and testosterone replacement. MRI of pituitary in 2010 and 2015 showed the right parasellar residuum had shrunken, and no residual pituitary fossa tumour compared to 2005. In 2019, he was seen in eye clinic due to headaches, sudden onset 6th nerve palsy. MRI pituitary showed normal sella but an enhancing clival lesion, extending to cavernous sinuses. A CT guided biopsy was non-diagnostic, and the consensus was either post radiation changes or a low-grade tumour. The skull-base MDT proceeded with an endoscopic transnasal biopsy due to worsening headaches and left sided third nerve palsy. The histopathology showed osteoblastic lesion raising suspicion of radiation-induced osteosarcoma, later confirmed by regional sarcoma MDT, but he deteriorated rapidly and died.
Conclusion
Our patient developed rapidly progressive radiation-induced osteosarcoma in the setting of normal IGF1. This case has the longest latency recorded (22 years) for patients developing radiation-induced osteosarcoma following radiation therapy in acromegaly. IGF1 monitoring or visual field surveillance is unlikely to identify this rare complication. Moreover, in treated cases of acromegaly, MRI surveillance is not usual clinical practice unless there is biochemical recurrence. Clinicians should be vigilant in suspecting late development of secondary tumours in patients who received cranial irradiation.

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P114

Skull base lymphoma causing hypopituitarism

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A 69-year-old lady presented to the ophthalmologists in view of a right 6th cranial nerve palsy and headache. Neuroimaging showed a central and right sided base of skull tumour with involvement of multiple cranial nerves (3rd, 4th, 6th). An endoscopic biopsy was inconclusive. She presented to the medical team few days later with drowsiness, lethargy, and her sodium was found to be 117 mmol/l with a potassium of 5.5 mmol/l. Serum osmolality was 267 mOsm/kg, urine osmolality was 559 mOsm/kg and urinary sodium was 46 mmol/l. Thyroid function tests and cortisol levels were not done at this time. She was on amitriptyline, and the hyponatraemia was attributed to the drug, and this was stopped. She was managed as SIADH with fluid restriction, and thereafter her sodium improved to 125 mmol/l and she was discharged. She presented 48 hours later with reduced mobility. This time her random cortisol was 147nmol/l, with a low FT4 of 6.0 pmo/l, and low TSH of 0.06 mIU/l. Prolactin levels were normal. Her FSH was unusually low at 1.8 IU/l and her LH was $<$ 0.2 IU/l despite her post-menopausal status. A clinical diagnosis of hypopituitarism was made and she was prescribed stress doses of oral steroids, but she had a cardiac arrest shortly thereafter probably secondary to the adrenal insufficiency, and was intubated. After improvement and stabilisation, she was kept on oral hydrocortisone for possible secondary adrenal insufficiency. Transnasal biopsy of the tumour done some weeks later suggested a lymphoma. MRI of the pituitary showed that the enhancing tumour was involving the cavernous sinus on the right and was inseparable from the pituitary gland, the stalk remained central and was not thickened. The pituitary gland was not enlarged. She is currently on chemotherapy which includes dexamethasone.

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P115

Pituicytoma mimicking as a Non-functioning pituitary macroadenoma

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Background
Pituitary adenomas are the commonest Sellar neoplasm, there are number of other differential diagnosis based on histopathological features and immune histochemical characteristics. Pituicytomas are rare tumours of sellar and suprasellar region which originate from pituicytes which are specialised glial cells of neurohypophysis and infundibulum.
Case report
A 63-year-old lady with a background history of bilateral cataract corrected with surgery and astigmatism presented with 1 year history of worsening occipital headache and progressive visual deterioration. CT brain done for evaluation of headache revealed pituitary macroadenoma and subsequent MRI pituitary revealed intra and supra sellar mass of 2.1 cm in cranio-caudal diameter, extending to the third ventricle and compressing the optic chiasm. She had bilateral slightly reduced visual fields on perimetry. Endocrine evaluation revealed prolactin of 760 mU/l and hypogonado-tropic hypogonadism with normal thyroid, adrenal and growth hormone axis. With the preoperative diagnosis of non-functioning pituitary adenoma patient has undergone uncomplicated transsphenoidal adenectomy and post-operative recovery was uneventful. Histology revealed a vascular tumour comprising of spindle cells arranged in storiform pattern with inconspicuous mitotic figures. Immunohistochemistry was positive for vimentin, s100 and TTF1 and negative for synaptophysin, Cam5-2, pituitary hormones, pituitary transcription factors and EMA. There was occasional positivity for GFAP. Ki-67 index was 5% and BRAF mutation was negative. With the characteristic immunohistological features the tumour was diagnosed as pituicytoma. Patient is awaiting post operative MRI to decide on subsequent management.
Conclusions
Clinical presentation and radiological characteristics of pituicytomas are nonspecific, and diagnosis typically made based on immunohistopathological results. Tumours are usually slow growing and benign and amenable to surgery; however, surgical treatment may be challenging due to the hypervascularity. Prognosis seems to be favourable, long term follow-up studies are required to assess the behaviour and the best therapeutic option.

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P116

Insulinoma presenting as Seizures - Case Report of a 16-year-old young woman

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Introduction
Insulinomas are rare pancreatic neuroendocrine tumours (PETS), which are usually benign and sporadic. They secrete insulin, and hence present with hypoglycaemia. We report a case of insulinoma presenting as seizures.
Case Presentation
The patient, a 16-year-old female, first had an episode of convulsion a year prior to referral to the Endocrine Clinic. She was managed at a private clinic with intravenous fluid (name unknown) and later commenced on Carbamazepine when convulsion recurred few days later. Convulsions were generalized, with dizziness and altered sensorium. Symptoms were often preceded by physical exercise and hunger, and were relieved, and prevented by intake of carbonated drinks and fruit juice. She was referred to the Neurology clinic when symptoms persisted despite use of anti-convulsant. She was later referred to the Endocrine clinic on suspicion of insulinoma when her random blood glucose was found to be low, during one of the episodes of convulsion, which occurred at the Neurology clinic. There were no symptoms suggestive of hypothyroidism or Cushing's syndrome, and she was not on other regular drugs. She was moderately obese; other examinations were normal. She had a 72-hour prolonged fasting done, which was terminated when hypoglycaemia occurred after 12 hours: blood glucose 2.2 mmol/l, elevated serum insulin - 52.5u/ml and C-peptide - 5.85ng/ml. Other biochemical investigations and abdominal ultrasononography were normal. Abdominal Magnetic Resonance Imaging (MRI) showed an oval, well-marginated T2 hyperintense mass at the tail of the pancreas, measuring 3.64 x 3.72 x 2.63 cm in H x T x AP diameter, and suggestive of insulinoma. She subsequently had distal pancreatectomy done with complete resolution of symptoms.
Conclusion
Unusual presentations of insulinoma may delay diagnosis, result in wastage of health resources, and increase morbidities and mortalities. A high index of suspicion is needed for early detection and proper management.

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P237

Acetate ameliorates depressive-like behaviour in a rat model of PCOS through suppression of HDAC2 expression and DNA methylation

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Background
Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. PCOS has been demonstrated to induce depressive-like behavior. Epigenetic alterations such as histone deacetylation (HDAC) and DNA methylation have been suggested in major depression. However, their effects with respect to neuroinflammation are not clear. This study, therefore, investigated the pathogenic role of epigenetic modification in PCOS-associated depression and the therapeutic potential of HDACi, acetate.
Materials and Methods
Adult female Wistar rats (120-150 g) were allotted into groups ($n=6$/group) namely: control (vehicle; p.o.), acetate-treated (200 mg/kg), letrozole (LET)-treated (1 mg/kg) and LET + Acetate-treated. Letrozole was administered for 21 days to induce PCOS and acetate was administered concomitantly. Biochemical analysis (NF- kB, lipid profile, acetylcholine, malondialdehyde etcetera), gene expression (HDAC2 and DNA methyltransferase), and histological evaluation were performed with appropriate methods.
Results
Treatment with letrozole caused hyperandrogenism, hyperinsulinemia, and disrupted ovarian morphology with evidence of degenerated follicles. In addition, these animals showed depressive-like behavior and increased expression of HDAC2 and DNA methyltransferase in PFC and hippocampal tissues. Biochemical analyses showed elevated NF-kB and acetylcholine levels in PFC and hippocampus as well as plasma lipid peroxidation and impaired antioxidant system in LET-treated animals. Histological analysis of PFC and hippocampus showed neurodegeneration in LET-treated animals compared with control. However, these alterations were attenuated when treated with acetate.
Conclusion
The study demonstrates that PCOS-associated depression is characterized by neuroinflammation and elevated acetylcholine levels, and this is associated with increased expression of HDAC2 and DNA hypermethylation in the PFC and hippocampus. Besides, the study suggests that acetate ameliorates PCOS-associated depression through the suppression of prefrontal and hippocampal DNA methyltransferase and prefrontal but not hippocampal HDAC2 expression.
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P238

Anticoagulation practice for venous thromboembolism prophylaxis in patients with Cushing's Syndrome - a Society for Endocrinology survey of UK Centres

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Background
Cushing's syndrome (CS) is estimated to have a 10-fold increased risk of venous thromboembolism (VTE) compared with the normal population with VTE accounting for 3.6-11% deaths in CS patients. There are no specific guidelines for VTE prophylaxis in CS other than that it should be considered given the increasingly recognised risk.
Methods
Via the Society for Endocrinology, we surveyed current VTE anticoagulation practice across UK Endocrinology centres.
Results
50/129 centres participated in the online survey. Less than half (48%) anticoagulated CS patients with the rest (26/50) stating they did not routinely anticoagulate at any point in the management pathway. In those centres that did anticoagulate, practice varied across patient selection, type of anticoagulation administered, timing of initiation of anticoagulation and the duration of anticoagulation. Seven centres anticoagulated for the duration of hypercortisolaemia, 66,7% anticoagulated perioperatively and 2 centres did not specify their thromboprophylaxis regime. Most of the centres that anticoagulated, did so for both adrenal and pituitary origin Cushing's patients (19/26 centres); 4 centres anticoagulated only pituitary origin, none anticoagulated adrenal Cushing's only. 26% use mechanical thromboprophylaxis (stockings) routinely. The duration of anticoagulation varies widely ranging from hospital stay until 12 weeks post-operatively. Most centres (24/26) use LMWH at a prophylactic dose, but 2 centres use Rivaroxaban. 30% of centres have changed their anticoagulation practice in recent years as a result of published data on VTE risk in CS, but also after experience of patients suffering VTEs in the perioperative period.
Conclusions
Despite well recognised incidence and mortality only 48% of surveyed UK Endocrinology centres are routinely advising VTE prophylaxis in CS patients. Clearer guidelines on VTE regimes are needed to help standardise practice. Large multi-centre studies are needed to inform such recommendations on type, timing of initiation and duration of anticoagulation indicated for CS patients.
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P239

A zebrafish model of *AIP* loss of function

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Background
Aryl hydrocarbon receptor-interacting protein (*AIP*) has been identified as a tumour suppressor gene in pituitary gland, causing 10% of all familial isolated pituitary adenoma. Patients with heterozygous loss-of-function germline mutation of *AIP* develop young-onset growth hormone and/or prolactin-secreting pituitary tumours. Homozygous loss of *AIP* leads to embryonic lethality in several animal models (mouse, fruit fly, round worm). Mouse embryos show cardiac developmental abnormalities.
Objective
The aim of the current study was to generate a zebrafish loss-of-function model for *aip* in which to explore the cell biological processes affected by heterozygous and homozygous loss of this gene.
Methods
The EMBOSS Needle was used to identify the zebrafish homologue of the human *AIP*. We used CRISPR/Cas9 gene editing to generate a line of fish carrying loss of function mutations targeting exon 2 in the zebrafish *aip* gene. *Aip* RNA expression was examined using *in situ* hybridisation and qPCR. *Aip* heterozygote and homozygote fish were assessed for growth rate and cardiac function using transmission microscopy and morphological analysis in Image J. Antisense *in situ* hybridisation with probes to growth hormone 1 (*gh1*), prolactin (*prl*) and proopiomelanocortin a (*pomca*) was used to assess pituitary phenotypes.
Results
Zebrafish *aip* showed 78.8% of homology to human *AIP* with conservation of all known interacting sites. *Aip* mRNA was expressed throughout the developing zebrafish embryo until 28 hours post fertilisation (hpf) stage when it became more strongly expressed in the head. *Aip* loss-of-function mutant animals showed reduced AIP expression. No significant differences in gross morphology were observed at 48 hpf. We report preliminary morphological characterisation of growth rate and cardiac function from 24 hpf to 7 days post fertilisation and development of the pituitary from 48 hours.
Conclusion
We have generated an *aip* loss-of-function zebrafish line providing ideal opportunity to study pituitary phenotype and cardiac phenotype.
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P240

UK practice on incidental (presumed) non-functioning pituitary microadenomas: a 13-year interval comparison

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Introduction
The optimal management approach for incidental non-functioning pituitary microadenomas (micro-NFAs) is unclear. We aimed to capture current UK practice and identify changes following a 13-year interval.
Methods
Two surveys on micro-NFAs were conducted in 2009 and 2022 (advertised by Society for Endocrinology). Hormonal/imaging evaluations were explored.

Results
2022: 150 clinicians participated. At baseline, ≥142 (95%) would measure prolactin, IGF-1, TSH/fT4, gonadal hormones and in 131 (87.9%), morning cortisol. 19 (12.8%) would check 24-hour UFC or ONDST. 67/142 (47.2%) would reassess pituitary function annually until discharge, 74/142 (52.1%) would only reassess if tumour growth/new symptoms of hypopituitarism. 23/149 (15.4%) would check visual fields in all. 6/148 (4.1%) would discharge after baseline imaging; 44 (31.0%), 26 (18.3%), 26 (18.3%) and 7 (4.9%) would discharge if MRI stable after 1, 2, 3 or 5 years, respectively. 10 (7.0%) would scan beyond 5 years and 20 (14.1%) at 1 and 2 years with life-long clinical follow-up. 2009: 214 clinicians participated; 204/213 (95.8%), 193/209 (92.3%), 155/204 (76.0%), 152/205 (74.1%), 124/198 (62.6%), 44/190 (23.2%) and 41/191 (21.5%) would measure prolactin, fT4, gonadotrophins, IGF-1, morning cortisol, 24-hour UFC, and LDDST, respectively. 47/190 (24.7%) would plot baseline visual fields. 197 (94.7%) would repeat MRI; 7 (3.6%), 68 (34.5%), 102 (51.8%), 19 (9.6%) and 1 (0.5%) would image after <6 months, 6-12 months, 1 year, >1 year, or non-specified interval, respectively. Responses on subsequent imaging strategies were highly variable. Compared to 2009, 2022 respondents were more likely to measure IGF-1 (96.0% vs 74.1%, $P<0.0001$) and morning cortisol (87.9% vs 62.6%, $P<0.0001$), whilst less likely to dynamically assess adrenal reserve (11.4% vs 30.4% $P<0.0001$).
Conclusions
Biochemical evaluation of micro-NFAs has changed with time, now in concordance with current guidelines. Frequency of imaging surveillance remains variable, warranting generation of further evidence on the natural history of micro-NFAs.

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P241

Understanding the molecular pathophysiology of stress on the developing and adult brain

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The hypothalamic-pituitary-adrenal (HPA) axis is the main stress-responsive neuroendocrine system in humans. Glucocorticoids (GC) constitute the principal systemic mediators of HPA axis function by governingmetabolic and behavioural responses to stress. Those include the modulation of transcriptional processes through the coordinated action of glucocorticoid (GR) and mineralocorticoid (MR) receptors. To study the effects of systemic malfunctioning of the HPA axis on the developing and adult brain, we are using zebrafish as the *in vivo* model of choice due to their highly conserved neuroendocrine systems. We are employing bioinformatic approaches (RNAseq analysis) to characterise transcriptomes of zebrafish mutants with disrupted functioning of the GC receptors, generated with CRISPR/cas9 gene-editing technology. Additionally, we are performing whole-mount *in situ* hybridisation, RT-qPCR and behavioural tests. We hypothesise that we will identify a novel set of differentially expressed genes in the brains of our mutants (MR and GR), establish how these are developmentally regulated by these receptors, as well as provide insights into which subset of genes might be co-regulated by MR/GR. Ultimately, we wish to identify the GC-inducible mediators that play roles in neuronal plasticity and thus may contribute to the pathophysiology of human stress-induced disorders. Our recent *in silico* analysis confirms altered GC signalling in zebrafish with mutations in MR and/or GR. We reveal novel stress-induced mediators and we highlight the neuroendocrine pathways that may contribute to stress-induced alterations in the brain. Going forward, we will perform whole-mount *in situ* hybridisation to spatially map expression patterns in both adulthood and during different stages of development. These experiments will be complemented by quantification of behavioural phenotypes using different stress paradigms and pharmacological treatments. A combination of the approaches discussed above is likely to bring new insights into these processes, which will be necessary in order to find more effective treatments of stress-related disorders.

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P242

FUZ is required for SHH-mediated pituitary development

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The primary cilium of cells detects and transduces extracellular signals, in particular, amplifying the SHH pathway, a key pathway required for pituitary development. FUZ is a planar cell polarity (PCP) effector, which is essential for normal ciliogenesis, required for recruiting retrograde intraflagellar transport proteins to the base of the organelle. The primary cilia of *Fuz*$^{-/-}$ mutants are shorter or non-functional. Previous work has reported ciliopathy phenotypes in *Fuz*$^{-/-}$ homozygous null mutants, including neural tube defects, craniofacial abnormalities and polydactyly, alongside PCP defects including kinked or curly tails and heart defects. Furthermore, in patients, FUZ variants are associated with a risk of neural tube defects and craniosynostosis. Interestingly, mouse mutants have no pituitary gland by 14.5dpc, but the cause of this phenotype has not been investigated. We analysed pituitary development in *Fuz*$^{-/-}$ mouse mutants from the onset of Rathke's pouch (RP) specification at 9.0dpc. Histological analyses reveal initial RP induction; however, RP fails to expand demonstrating elevated apoptosis and hypoplasia. Essential markers such as LHX3 and LHX4 are absent by 11.5dpc, indicating failure of anlage specification. Analyses of FGF, BMP and SHH signalling reveal reduced SHH pathway activation in the mutant, affecting anterior pituitary fate specification and normal development. Our findings suggests that primary cilia are required for normal pituitary development to mediate SHH pathway activity, and that mutations in FUZ may underly abnormal pituitary development and hypopituitarism.

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P243

Imaging surveillance of completely resected gastroenteropancreatic neuroendocrine tumors is associated with high levels of radiation exposure

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Background & Aims
Neuroendocrine tumours (NET) are a heterogenous group of neoplasms that secrete peptides and neuroamines. For potentially malignant gastroenteropancreatic (GEP) NET, surgical resection represents the only curative option. Ten-year imaging surveillance programs using cross sectional imaging are recommended due to long time-to-recurrence following resection. We performed a retrospective chart review to evaluate radiation exposure associated with surveillance of completely resected GEP NET and characterize local practice patterns.
Methods
We reviewed records from patients diagnosed with well-differentiated GEP NET from January 2005 to July 2020. Eligible cases were identified by a data analyst and manually screened for eligibility. Location of primary, modality of surveillance imaging, and duration of follow-up were collected [JC1]. Dosimetry data was collected to calculate total effective dose and mean effective dose per year.
Results
Sixty-two cases met inclusion criteria with 422 surveillance scans performed. Cross sectional imaging was used in 82% and functional imaging was used in 18% of scans. Mean number of surveillance scans per year was 1.25 (0.42 – 3). Mean total effective dose was 59.37mSv (SD 46.20; 0 to 203.62mSv) while mean total effective dose per year was 11.19mSv (SD 9.55; 0 to 45.25mSv). Over the recommended 10 years of surveillance, the estimated total effective dose was 112mSv. Age at diagnosis and location of primary were not significant predictors of effective dose per year.
Conclusions
Imaging surveillance of completely resected GEP NET results in cumulative radiation doses in the range associated with secondary malignancy development. Strategies to minimize radiation exposure in long term surveillance should be considered in future guideline development.

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P244

Neuroendocrine tumour (NETs) patient experience of switching to generic somatostatin analogue during the COVID-19 pandemic

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Introduction
In patients with neuroendocrine tumours (NETs) somatostatin analogues are used to control symptoms in patients with functioning tumours and as antiproliferative agents in those with non-functioning tumours. During COVID-19, the 'Sandostatin Your Choice' service was terminated by Novartis, removing home care nurses from administering the analogue in patients' homes. The first generic

version of depot octreotide was Olatuton® produced by Teva, and this was commissioned at a dose of 30 mg per month. At a given dose a generic should have the same clinical and side effect profile. We conducted a patient survey to assess clinical changes, side effects and satisfaction with Olatuton®.
Method
Paper questionnaires with prepaid return envelopes, were sent out in February 2022 to all 90 neuroendocrine patients switched to Olatuton® who are under the care of Sheffield Teaching Hospitals NHS Foundation Trust. These consisted of 14 MCQs that assessed side effects, tolerance and service satisfaction.
Results
There was a 59% response rate. 34% of patients noted new symptoms with the switch to Olatuton®. 36% stated new injection site symptoms, 55% noticed gastrointestinal symptoms and 36% noticed hyperglycaemic symptoms. 68% of all patients stated they were "very satisfied" with the home care nursing team.
Conclusions
Two thirds of patients tolerated the switch to Olatuton® without any problems or dosage issues. However, 21% required a change to an alternative somatostatin analogue , with yellow cards completed in these instances due to an exacerbation of the expected GI side effect profile (very much like a de novo start), increased pain at injection site and loss of control of symptoms. In some cases, this experience generated concern of clinical disease progression for the patients. However, patients were highly satisfied with the home care service provided, which is of paramount importance in pandemic times.

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P245

An investigation into discrepancies between serum insulin-like growth factor 1 (IGF-1) concentrations and clinical presentation in the assessment of acromegaly

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Background
The suitability of serum insulin-like growth factor 1 (IGF-1) reference ranges (RR) used locally (manufacturer-derived), were raised as a clinical concern. IGF-1 levels above the RR were reported in patients displaying no clinical signs or symptoms of acromegaly, and in whom growth hormone suppression tests were negative. No analytical issue was evident, and quality performance indicators were satisfactory.
Methods
A review of all serum IGF-1 results (Siemens IMMULITE® 2000 analyser) from July 2018-2019 was undertaken, with a total of 2162 (1151 male) patients included. Results were reviewed according to age- and gender-related RR, and assigned to one of three groups, low, normal, or high. All high IGF-1 results were reviewed alongside clinical information to determine the rate of true and false positives. Comparative stability of serum IGF-1 was also assessed at 4°C and room temperature (RT).
Results
Over the period reviewed, 8.9% of all serum IGF-1 results in adult patients (age >18) were classed as high, and 4.6% as low. For paediatric patients, there was little difference between high and low groups (11.2% and 9.6%, respectively). Further investigation into the adult 'high' group showed that the false positive rate was 2.53%, which may be expected from a Gaussian distribution where 95% of the population fit within the RR. Serum IGF-1 ($n=24$, range: 7.5-91 nmol/l) showed a mean change from day 0 to day 1 of 10.5% (SD=7.5%) for samples stored at RT, compared with a mean change of 3.5% (SD=3.0%) for samples stored at 4°C.
Conclusion
The review found no evidence that the serum IGF-1 RR in use are ineffective. However, serum IGF-1 concentrations were affected by pre-analytical storage at RT, a consequence of the introduction of a new automated track system. Changes made based on this review have improved clinicians' confidence in interpreting IGF-1 results.

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P246

A novel presentation of primary hyperparathyroidism for the Val804Met mutation

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Background
Multiple endocrine neoplasia type 2 (MEN2) is a group of pleomorphic syndromes which infer a susceptibility to several endocrine conditions. The RET Val804Met mutation is classified as a moderate-risk mutation for familial medullary thyroid cancer (MTC), without the other components of MEN2 syndromes. However, here we describe a rare case of a gentleman with RET p.V804M, presenting with primary hyperparathyroidism (PHPT) and no evidence of MTC.
Summary
A 31 year old man presented with recurrent bilateral renal stones. Investigations revealed normocalcaemic primary hyperparathyroidism (parathyroid hormone of 8.2 pmo/l and adjusted calcium of 2.60 mmol/l). Further tests indicated a low 24 hour urinary calcium-creatinine clearance ratio (0.0078). Three modalities of imaging (US, Sestamibi and 4DCT) suggested a right superior parathyroid adenoma. Genetic analysis revealed a mutation in codon 804 of the RET proto-oncogene, leading to a Valine-Methionine (Val804Met) substitution. Interestingly, thyroid function and calcitonin levels were normal and imaging showed no signs of MTC. Familial hypercalcaemic hypercalciuria (FHH) was also considered given the low 24-hour urinary calcium-creatinine clearance ratio. Genetic analysis for FHH was negative, as well as for MEN1, CDC73, GNA11 and CDKN1B. Currently, the patient remains under regular surveillance with yearly biochemistry and regular thyroid ultrasound. Familial genetic testing demonstrated that the patient's father also carries this mutation, with no evidence of MTC or PHPT, despite being >75years of age.
Conclusion
Typically, the RET Val804Met mutation has a high penetrance, with up to 80% of individuals presenting with MTC by the age of 70 years. Although there are reported associations of the Val804Met mutation with other MEN2 features, it is very rare for primary hyperparathyroidism to be the index presentation as here. We recommend investigating for other associated presentations with MEN2.

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P247

Surgical management of prolactinomas in patients with dopamine agonist-associated impulse control disorders or who are deemed at 'high risk'

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Introduction
Prolactinomas are the commonest type of secretory pituitary tumours. In current practice, dopamine agonists (DA) remain the mainstay treatment. However, treating physicians are increasingly aware of DA-associated impulse control disorders (ICD) in their patients. We describe 4 individuals with prolactinomas, who either developed ICD on DA or deemed at 'high risk', successfully managed surgically with preservation of pituitary function. All decisions for surgery were made within our Pituitary MDT (Multi-disciplinary Team).
Cases
A 56-year-old gentleman with a macroprolactinoma (prolactin 3,464 mU/l), presented with low libido. He developed symptoms of hypersexuality on cabergoline which resulted in a relationship breakdown. He therefore underwent a transsphenoidal resection (TSS), with normalisation of prolactin to 153 mU/l. A 38-year-old lady with a macroprolactinoma (prolactin 5,000 mU/l) was referred after experiencing symptoms of ICD on cabergoline (overspending, mood swings). She underwent TSS, which led to a drop in prolactin to 447 mU/l and she was able to conceive post-surgery. A 28-year-old gentleman with a macro-prolactinoma (prolactin 24,399 mU/l) presented with low libido. Notably, he has a history of major depressive episodes with suicidal intent requiring hospitalisation. TSS was offered as first-line treatment due to the risk of a mental health relapse with DA. Post-operatively, his prolactin levels normalised to 243 mU/l. A 33-year-old gentleman with a microprolactinoma (prolactin 4,544 mU/l) was referred with low libido. He struggled with emotional instability and anger management for which he required psychotherapy. TSS was suggested as first-line treatment, and he recently underwent surgery.
Conclusion
Surgical management of prolactinomas can be considered in patients with DA-induced ICD or as first-line treatment in 'high-risk' individuals. The pituitary MDT has a crucial role in identifying patients with a discrete surgical target, who are likely to benefit from surgery, without compromising pituitary function.

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P248

Vasopressin in Not a Strong Stimulus for ACTH-Cortisol Secretion In Humans

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Background
Vasopressin, secreted in equimolar amounts with copeptin, is implicated as a stimulus for ACTH secretion during dynamic tests, such as Glucagon Stimulation Test (GST) or Insulin Tolerance Test (ITT). Some individuals with intact ACTH-cortisol axis, demonstrate, however, a lack of further cortisol stimulation during GST. We have assessed whether failure of further ACTH-cortisol increase during GST may be associated with an inadequate vasopressin/copeptin release.
Subjects & Methods
We measured copeptin, ACTH, cortisol, glucose and growth hormone (GH) at 0, 60, 90, 120, 150 and 180 minutes during GST in ten individuals (nine female) age 41.4 ± 15.2 years, who had satisfactory initial cortisol concentrations (mean cortisol 20.34 ± 5.10 μg/dl), but failed to show any further cortisol increment during GST. For comparison, we measured the same parameters in two males during ITT.
Results
During GST there was a significant increase in copeptin concentrations (e.g. from 4.35 ± 2.62 pmo/l to 6.93 ± 3.80 pmo/l, 0 vs 180 min, $P = 0.02$), with an average individual increase of 98% (range 10% to 321%). There was a robust increase in GH concentrations ($P = 0.002$), and decline in cortisol ($P = 0.02$, average decline -21.8%) and a borderline non-significant fall in ACTH concentrations ($P = 0.06$). The relative increase in copeptin concentrations during ITT (176% and 52.2%) overlapped with individual increments observed during GST, but in contrast to GST, there was an increase of cortisol (20.45 → 24.26 μg/dl and 4.23 → 29.29 μg/dl, respectively).
Conclusions
Vasopressin/copeptin concentrations increase during GST despite the lack of an increment, or even a decline in ACTH-cortisol levels. This implies that vasopressin appears to be a rather weak stimulus for ACTH-cortisol secretion, at least in those with relatively high initial cortisol concentrations. An increase in cortisol concentrations during ITT cannot be explained by more robust vasopressin/copeptin response than during GST.

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P249

Acute hypoglycemia as the presenting manifestation secondary to pituitary metastasis in a patient with malignant melanoma

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Introduction
Pituitary metastasis (PM) is a rare condition and associated with a reduced life-span. The most common primary sites are breast and lung, followed by thyroid and renal cell carcinoma. Patients with PM are mostly asymptomatic and incidentally discovered during neuroimaging. Characteristic symptoms are reported in <20% and most commonly include visual involvement, diabetes insipidus, and panhypopituitarism. We here describe a case with malignant melanoma (MM) who presented with acute hypoglycemia.
Case-description
A 60-year female presented with recurrent episodes of fasting hypoglycemia up to 1.6 mmol/l, over a period of two days. She was recently diagnosed with MM of fingernails. Medications included oral estrogen and progesterone. Biochemistry revealed panhypopituitarism: morning cortisol 148 nmol/l, ACTH 2.6 mg/l, FT4 4 pmo/l, TSH 1.1 mU/l, IGF1 3.6 nmol/l, FSH 2.8 IU/l, LH 1.7 IU/l. Serum prolactin was elevated (2324 mIU/mL). She did not have polyuria, optic-chiasmal compression, or ophthalmoplegia. MRI sella revealed a bulky, and heterogenous pituitary gland and pituitary stalk was thickened. 18FDG-PET/CT demonstrated intense avid uptakes in the sellar region, right orbit, liver, adrenal and multiple bones. Thus, the pituitary lesion was regarded as possible metastasis and a biopsy was avoided. She was put on replacement doses of hydrocortisone and levothyroxine, which resulted into an improved glycemic control. She received Dabrafenib and Trametinib for management of MM. Immuno-histochemistry was positive for BRAF-mutation.
Discussion
Only few cases with MM with PM have been described in the literature until today. Our patient developed acute symptomatic hypoglycemia in the context of central adrenal insufficiency, likely related with the new diagnosis of PM. It is further uncommon for adrenal insufficiency to manifest as hypoglycemia in adults. The case highlights considering PM in elderly patients with pituitary mass and evaluation for adrenal insufficiency in patients with hypoglycemia.

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P250

A case report of Takotsubo cardiomyopathy associated with pituitary apoplexy

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Background
We present a rare diagnosis of a patient presenting with Takotsubo cardiomyopathy and pituitary apoplexy. The case highlights the difficulty in management of a cardiac event with bleeding risk in a patient with these associated diagnoses.
Case report
An 85-year-old woman was admitted to hospital with a severe frontal headache that woke her from sleep. She described chest pain associated with breathlessness later and was mildly confused. Sadly, her husband had passed away recently. She was on edoxaban. The neurological examination was normal with intact visual fields on direct confrontation. A formal visual fields could not be done due to confusion. A CT head and later MRI pituitary were performed and confirmed apoplexy with a likely adenoma just underlying the chiasm. She was started on hydrocortisone immediately. Electrocardiogram showed flutter with variable block, as well as T wave inversion in lead V6. The initial Troponin Ts were 312 and 317ng/l (<14ng/l). She was admitted to the cardiology ward and Aspirin and Clopidogrel were started for non-ST elevation myocardial infarction. Her Edoxaban was stopped prior to the MRI. Echocardiogram showed features of Takotsubo cardiomyopathy. After a discussion in the pituitary MDT, it was agreed with cardiology to continue Clopidogrel only and manage her conservatively. A pituitary MRI was requested to de done in 6 weeks for surveillance.
Discussion
There are only a few case reports of Takotsubo cardiomyopathy precipitated by a pituitary apoplexy. The challenges in managing the bleeding risk with an elevated troponin are obvious. This case showcases that a careful, individualised, multi-disciplinary approach is required to make safe treatment decisions. It is also essential to discuss the risks and benefits with the patient and family so an informed collaborative decision is made in this rare scenario.

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P251

ACTH dependent Cushing's syndrome due to a pituitary macroadenoma presenting with acute Type B aortic dissection, severe hypercortisolism and resistant hypertension

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Introduction
Cushing's syndrome is a known risk factor for aortic dissection but the association of these conditions is rare. Hypercortisolism is associated with an increased risk of cardiovascular disease and accounts for the high morbidity & mortality in untreated patients.
Case Study
A 64y old male presented with acute onset chest pain, radiating to the back. CT angiogram showed Stanford Type B dissection involving the distal aortic arch/descending aorta and bilateral adrenal hyperplasia. Past medical history included type 2 diabetes, CKD & hypertension. On examination, he had extensive skin bruising, centripetal obesity and was clinically hypogonadal. Visual field assessment showed a left upper quadrant temporal field defect. Severe hypertension in the context of the acute dissection and adrenal hyperplasia led to further investigation of secondary hypertension. Investigations showed ACTH dependent hypercortisolism with loss of diurnal variation (ACTH 340; urine free cortisol 5919). Pituitary MR showed a large macroadenoma (22 mm) causing chiasmal compression. The dissection was managed conservatively (target systolic BP 110-120 mmHg). Adrenolytic treatment with metyrapone was commenced to control severe hypertension and hypercortisolism preoperatively. Despite escalating doses of multiple antihypertensive drugs, BP control was suboptimal (systolic150-170 mmHg). This posed an ongoing risk for further dissection. In view of this and given that hypertension was driven by severe hypercortisolism, the patient underwent transsphenoidal pituitary surgery as an inpatient. Blood pressure normalised to 120-130 mmHg systolic after pituitary surgery.

Discussion
Hypercortisolism results in decreased collagen strength, synthesis, and increased capillary fragility. Only a few cases report the association of Cushing's syndrome as a likely precipitant of acute aortic dissection. This case highlights the challenges of balancing tight BP control to reduce extension of aortic dissection with the risk of potentially precipitating hypotensive pituitary apoplexy. This case exemplifies critical issues in the pharmacological management of blood pressure in a complex, high risk hypertensive patient.

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P252

Impulse Control Disorder in Patients on Dopamine Agonist

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Background
Dopamine agonists (DA) remain the first-line medical therapy for prolactinomas and idiopathic hyperprolactinemia in Endocrinology. DA can also be efficacious in a selected group of patients with acromegaly. There is increasing awareness, among endocrinologists, of Impulse Control Disorders (ICDs) as possible adverse effects of DA therapy.
Case reports
We describe ICDs in four patients (two diagnosed with prolactinoma and two diagnosed with acromegaly) treated with low-dose DA. Our patients, aged 37 to 67 years, developed a range of ICDs including hypersexuality, excessive spending, punding (repetitive performance of tasks) and obsessive thoughts with insight. Two patients reported a breakdown of established relationships or multiple failed relationships due to hypersexuality.
Discussion
ICDs are well-recognised side effects in patients with Parkinson's disease (PD) treated with higher doses of DA compared to the doses used in endocrine conditions. Emerging evidence of ICDs due to DA in Endocrinology is relatively recent, mostly documented in case reports. Other ICDs reported in the PD literature include pathologic gambling, compulsive eating and dopamine dysregulation syndrome (compulsion to seek and overuse DA). The development of ICDs can have serious consequences on patients and their families. Endocrinologists involved in the care of patients on DA therapy must be aware of this potentially devastating adverse effect and offer regular counselling regarding pertinent symptoms at initiation and during long-term follow-up, to enable early detection of ICDs. In patients who develop ICDs on DA therapy, cessation or tapering down of DA have been reported as successful management options, especially in the wider PD population. However, in Endocrinology, there are currently no published treatment guidelines for DA-induced ICDs. Due consideration should be given within a multidisciplinary approach to surgical, hormonal and non-pharmacologic (psychotherapy and cognitive behavioural therapy) treatment, depending on the initial endocrine diagnosis.

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P253

Safe Reduction in Short Synacthen Testing to Assess Hypothalamo-Pituitary Axis in patients on Corticosteroids

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Background
Short Synacthen Test (SST) is widely used to assess hypothalamic-pituitary-adrenal (HPA) axis in patients on corticosteroids. This requires significant material and human resources especially as patients often require multiple tests. We performed a retrospective cohort study, followed by the implementation of QIP methodology to reduce the number of SST in this cohort of patients.
Methodology
We reviewed 167 patients who had a SST and derived a 9am cortisol cut-off of <138 nmol/l which predicted failure of SST in 100% of patients. This value included co-efficient of biological and laboratory variability of 15.2% and 3.2% respectively. Thereafter, SST was requested only for the patients with 9am cortisol >138 nmol/l. We reviewed the data on the next 38 consecutive patients on corticosteroids referred for HPA axis assessment who had 9am cortisol and evaluated the impact on the number of SST and its cost benefits.
Results
In 23(60%) patients, 9am cortisol was >138 nmol/l and 19(50%) of these patients had SST. In 15 (39%) patients 9am cortisol was <138 nmol/l and 11(29%) patients successfully avoided SST and despite appropriate communication, 4(10%) patients had unnecessary SST (all failed) which could have been avoided with stricter implementation of the protocol. 20(53%) of these patients required further SSTs during a one-year period and 9 of these were avoided. For every 100 patients on corticosteroids referred for HPA-axis assessment, we expect to avoid 39 first and 24 repeat SSTs resulting in a saving of £3118.50 (£49.50/test) and ~94 hours of time for a doctor/specialist nurse with significant reduction in waiting time for patients.
Conclusions
The use of 9am cortisol cut-off accurately and safely predicted failure of SST and led to reduction in the number of SSTs and significant saving of cost and manpower resource. We recommend other healthcare organisations to implement a similar process.

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P254

Prevalence of cancer in a cohort of acromegaly patients

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Background
Growth hormone directly stimulates tumour growth, angiogenesis and metastasis through autocrine and paracrine effects on cancer cells, while through IGF1 inhibits apoptosis and promotes epithelial proliferation. Although disputed, some studies have shown an increased cancer incidence in acromegaly patients, especially in uncontrolled subjects, while others have not.
Aim
To assess prevalence of cancer in a cohort of patients with long term treated acromegaly.
Methods
Retrospective study by analyzing the files of 162 inpatients with acromegaly (105F/57M, mean age at diagnosis 43.7 $\pm$ 12.8 years), hospitalized in a tertiary endocrine center between 2019 and 2022. Median follow-up period was 9 years. IGF1 was measured by chemiluminescence. For cancer screening, thyroid ultrasound in palpable nodules, fine needle aspiration, cytology exam in suspected nodules and pathology exam in operated patients, colonoscopy, PAP and mammography were performed according to the guidelines. Four patients were excluded because of long distance (>5 years) between cancer and acromegaly diagnosis.
Results
96 patients (59.2%) had normal IGF1 levels at their last follow-up; 16 patients (9.9%) with cancer were identified: 7 differentiated thyroid carcinomas (DTC), 4 colorectal carcinomas, 2 cervical cancers, 1 endometrial cancer, 1 malignant melanoma, 1 non-Hodgkin lymphoma B-cell. Thyroid nodules prevalence was 66.7% ($n=108$). Fine needle aspiration biopsy was performed in 22 patients (Bethesda I:1, Bethesda II:13, Bethesda III:5, Bethesda IV, V, VI:3 patients). Colonoscopy was performed in 52 patients (32%), 27 colonoscopies were normal, 25 revealed polyps (48%); out of 25 polyps, 4 were malignant. Cancer patients showed similar acromegaly duration (median 9 years) compared to non-cancer patients (median 8.5 years, $P=$ns). 6/10 cancer patients previously underwent pituitary radiation while 50/96non-cancer patients had not ($P=0.02$, chi-square).
Conclusion
DTC and colon polyps' prevalence in our series of acromegaly patients was higher compared to non-acromegaly population, however larger prospective studies might clarify this relationship.

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P255

Pituitary mass and Pan hypopituitarism- A rare case of Langerhans Cell Histiocytosis

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Langerhans cell Histiocytosis is a rare neoplastic histiocytic disorder. It has broad spectrum of clinical presentations from single system to multi system. It mainly

affects children but can occur in adults. It can present with skin lesions, skull/jaw tumours, polyuria/polydipsia, fever, cough and dyspnea, bone pain, ataxia etc. 25% of adult cases involve Pituitary (anterior and posterior pituitary gland) and hypothalamus. *BRAF* and *MAP2K1* mutations are most commonly detected. We present a rare case with hepatic & pituitary involvement: A 46 year old female presented with headache and light-headedness for 4 weeks with an up going plantar. She underwent CT head- showing 13×11 mm suprasellar mass with optic chiasm compression and enlargement of pituitary stalk. On examination she had Right superior quadrantanopia. She had abnormal liver function tests and CT scan of liver showed multiple hyper attenuating lesions. It was discussed in MDT to arrange MRI of liver. Tumour markers and autoimmune screen was performed which was normal. She was reviewed by Endocrine team and her pituitary bloods revealed pan hypopituitarism. She was started on hydrocortisone & levothyroxine 100 mg OD. She was found to have diabetes Insipidus and was given Desmopressin. A stereotactic biopsy of suprasellar mass was performed which revealed striking infiltration of eosinophils and macrophage like cells with grooved or folded nuclei –suggestive of Langerhans cell histiocytosis (BRAF WILD TYPE). She had 4 cycles of Cladribine subcutaneous chemotherapy with good response. Repeat pituitary MRI showed unchanged hypothalamic lesion.

Conclusion

Langerhans cell Histiocytosis is a rare but important differential diagnosis in patients with pituitary mass. It affects people of all ages and has variable clinical manifestations. A careful history, examination, lab investigations, imaging and biopsy can lead to the proper diagnosis.

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P256

Two cases of acromegaly: the role of the dentist in early detection

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Introduction

Acromegaly is a rare metabolic condition in adults caused by over secretion of growth hormone from the pituitary gland. The characteristic skeletal and organ overgrowth and dental mal-occlusion issues are so insidious that they go unnoticed by the patient and family. The dentist may be the first healthcare provider to see these patients, thereby proving instrumental in early diagnosis. We report two cases of acromegaly: one case identified by a dentist and another case missed by a dentist.

Case 1

A 49-year-old man presented with a history of continued weight gain and change in appearance for over ten years. He had visited his dentist several times over many years for various dental issues. He had clinical features of acromegaly. His serum insulin-like growth factor-1 (IGF-1) level was elevated and a glucose challenge confirmed growth hormone excess. Imaging demonstrated a pituitary macroadenoma compressing the optic chiasm and invading the right cavernous sinus. He had trans-sphenoidal surgery followed by somatostatin analogue therapy for residual disease.

Case 2

A 59-year-old woman was referred by her dentist who noticed a significant increase in the size of her lower jaw. Examination revealed mandibular prognathism, large nose and large fingers. Blood tests revealed an elevated serum IGF-1 level. A glucose challenge test confirmed growth hormone excess. Imaging demonstrated a pituitary macroadenoma compressing the optic chiasm. She had trans-sphenoidal surgery and her IGF-1 levels remain in the normal range.

Conclusions

Acromegaly is a rare condition, however, early detection is required to minimise cardiovascular and metabolic risks and to reduce morbidity and mortality. The dental team should be made aware of the dental presentation of this condition as they can play a vital role in early detection and referral to the endocrinologist.

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P257

The modulatory role of curcumin and quercetin on Drosophila GSK-3: a potential therapeutic intervention in Parkinson's disease

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Aim

We explored the mechanistic interactions and potential therapeutic benefits of curcumin and quercetin co-administration with a specific focus on Glycogen synthase kinase 3 GSK-3 activity.

Methods

We hypothesize that excess GSK-3 accumulation in the substantia nigra is driven by oxidative stress and aim to test the effects of these compounds on the localization and activity of GSK-3 in the well-established model organism Drosophila melanogaster. We probed the dopaminergic neutrons characterization via Tyrosine Hydroxylase Confocal microscopy.

Results

The antioxidant properties of curcumin with quercetin mediated an anti-inflammatory response, ameliorating oxidative stress in the brain. The co-administration of both compounds as well rescue the Dopaminergic neurons in the brain of the shaggy fly.

Conclusion

The co-administration of curcumin and quercetin were able to reduce the loss of function of the nervous system typical of GSK 3 shaggy strain, by reducing the over expression of GSK 3 beta.

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P258

Unusual presentation of neurohypophysitis

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35-year lady with BMI of 43 was admitted to local hospital after acute shortness of breath. History of Right calf pain and swelling was evident which raised suspicion of VTE with high likelihood of Pulmonary Embolism. Subsequent CT Pulmonary Angiogram confirmed the same with origin of clot from her leg DVT. She had successfully thrombolysis in intensive care as per hospital protocol. Her high body mass index was thought to be risk factor for blood clots. Her periods were regular and Inpatient pregnancy test was negative. Covid swab was negative. Routine biochemistry revealed persistent high sodium level. In patient blood glucose levels were normal. She was discharged home after intravenous fluids, analgesics and advised to continue Rivaroxaban for 6 months. OP follow up sought by patient herself due to persistent nocturia and polydipsia. Her main concern was Diabetes. Detailed history revealed frequent headache episodes and disturbed sleep due to nocturia. Her serum sodium level was consistently above 160 with total urine output ranging from 8-9 liters. Fasting urine osmolality revealed her inability to concentrate urine with strong suspicion of Central Diabetes Insipidus. We started her on oral Desmopressin, the dose of which was titrated upwards on follow up visits. Rest of anterior pituitary hormonal profile was satisfactory. MRI pituitary scan was consistent with lymphocytic infundibular neurohypophysitis. We hypothesized the relative dehydration due to polyuria contributed to prothrombotic milieu which resulted in widespread thromboembolism.

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P259

Successful use of recombinant human TSH prior to radioiodine therapy in an acromegaly patient with differentiated thyroid cancer and pituitary insufficiency

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Background

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. Standard treatment includes thyroidectomy (extention depending on tumour size, pathology and lymph nodes involvement). If indicated, radioiodine therapy after TSH stimulation either by levothyroxine withdrawal or rhTSH administration is recommended. In patients with thyrotropin deficiency rhTSH administration is mandatory.

Case report

A 30-year-old woman, resident in an iodine deficient area, diagnosed with acromegaly (nadir GH in OGTT = 34.9 ng/mL, increased IGF1 = 926 ng/mL), pituitary insufficiency and DTC is presented. She underwent treatment with dopamine agonists for a long period, transsphenoidal surgery in 2008, at 52-years-old, pituitary high voltage radiotherapy (2009) and somatostatin analogue (SSA) therapy, developing pituitary gonadotropin and thyrotropin insufficiency. Thereafter, the patient was diagnosed with toxic multinodular goiter and underwent thyroid surgery. The pathology exam revealed multiple follicular variant of

papillary thyroid microcarcinoma. Due to long standing uncontrolled acromegaly, radioiodine therapy was recommended after administration of rhTSH. 100 mCi 131I was administered; stimulated thyroglobulin was increased and the scintigraphy revealed an increased uptake in her right pulmonary field. After 6 months, another 100 mCi 131I dose was administered. At last assessment acromegaly was controlled on Lanreotide therapy (mean random GH/24 hours = 0.29 ng/mL and normal IGF1 = 135.3 ng/mL) and thyroglobulin was <0.1 ng/mL, anti-TGL antibodies were negative and there is no uptake on whole body scintigraphy.
Conclusion
In acromegalic patients submitted to radiotherapy and on SSA therapy, thyrotropin deficiency should be checked before radioiodine treatment for associated thyroid carcinoma. If present, rhTSH administration is mandatory and the outcome of patient is favorable.

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P260

Cushing's Syndrome – A medical emergency and diagnostic challenge

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Background
Ectopic Cushing's syndrome (ECS) is a rare and severe condition at times presenting acutely with intense hypercortisolism. The intensity of hypercortisolism can be disproportionate to underlying tumoral condition, and associated life-threatening complications are common arising suddenly. Hypercortisolism must be controlled rapidly pending definitive treatment of tumoral source to avoid life-threatening consequences.
Case Summary
31-year-old Asian female presented with acute confusion, emotional liability, lethargy, and weight loss of 15 kgs over four months. She had moon facies, hirsutism and buffalo hump. She had one miscarriage and was diagnosed with PCOS one year ago by her GP. Initial tests showed refractory hypokalaemia (2.7 mmol/l) and raised random cortisol (4450 nmol/l). Repeated tests confirmed hypercortisolism with raised ACTH (366pg/l), normal plasma metanephrines and tumour markers. CT scan of thorax, abdomen and pelvis showed thymic mediastinal mass with bilateral adrenal hyperplasia. MRI scan of pituitary was normal. She was started on block and replace regime with metyrapone and hydrocortisone. After MDT discussion she underwent video-assisted thoracoscopic surgery to remove the thymic mass. Histopathology showed thymic large cell neuroendocrine carcinoma. PET scan post-surgery showed local active residual disease and she had failed cortisol suppression (293 nmol/l) on 48-hour low dose dexamethasone suppression test. No Ga68-DOTATOC scan avid regional nodal disease or distant metastasis identified. She underwent removal of tumour remnant followed by chemotherapy and radiotherapy. During radiotherapy, she had symptoms of cortisol excess. Biochemistry confirmed recurrence of hypercortisolism with normal CT scan of thorax, abdomen and pelvis. She was recommenced on metyrapone and hydrocortisone.
Conclusion
This case highlights the complexities in diagnosis and management of ECS presenting initially as a medical emergency necessitating immediate medical intervention to control severe hypercortisolism and associated life-threatening complications. Prompt diagnosis and rapid initiation of medical treatment for hypercortisolism is essential to reduce the burden of cortisol-induced comorbidities.

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P261

A rare case of multicentric glioblastoma causing panhypopituitarism: A case report

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Introduction
Glioblastoma, an aggressive intracranial tumour usually is a solitary lesion and not commonly located in the sella turcica. Panhypopituitarism due to multicentric glioblastoma can present with a challenging clinical picture masking or delaying the underlying diagnosis.
Case presentation
58 year old female presented with marked behavioural change, reduced appetite, nausea, polyuria & increased thirst over 4-6 weeks precipitating into an acute admission with dehydration, hypernatraemia and acute kidney injury. On a face to face review in the joint pituitary clinic, she appeared entirely disinterested in her own consultation in the presence of her husband, sister-in-law via telephone and a large multidisciplinary team, prompting the impression of her displaying signs of a frontal lobe syndrome. Full anterior pituitary biochemistry was suggestive of panhypopituitarism affecting the anterior and posterior pituitary, for which appropriate hormone replacement was administered in addition to supportive measures. MRI pituitary revealed two lesions, one in the suprasellar region and another in the left anterior cingulate gyrus. Craniotomy and biopsy at the regional neurosurgical centre confirmed multicentric WHO grade 4 glioblastoma. She had rapid disease progression precluding further treatment with the adoption of a palliative approach.
Conclusion
Multifocal glioblastoma is a rare diagnosis to encounter in the pituitary clinic. Involvement of the pituitary by a suprasellar lesion may be misleading and delay the overall diagnosis which needs prompt diagnosis and management if survival is to be improved. Good clinical history and collaborative working between endocrinology, neuroradiology, neurosurgery and acute medicine is what facilitated timely diagnosis for this patient and her very anxious family. Recognising and managing panhypopituitarism in the acute phase was important in improving physical health, although cognitive impairment was progressive until the time of her demise.

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P262

Dilated Cardiomyopathy as initial presentation of Acromegaly

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Introduction
Acromegaly is commonly associated with numerous cardiovascular manifestations such as left ventricular hypertrophy, hypertension and ischemic heart disease. However, initial presentation with dilated cardiomyopathy is relatively rare. Dilated cardiomyopathy in patients with acromegaly usually result from an extended and excessive exposure of the myocardium to growth hormone.
Case presentation
51-year-old female with background medical history of hypertension presented with altered level of consciousness and non-sustained ventricular tachycardia. After stabilization, echocardiography confirmed severe dilated Cardiomyopathy (EF 18%). She had implantable cardioverter-defibrillator inserted. Based on cardiology team high clinical suspicion of acromegaly, she was referred to endocrinology team. Investigations showed IGF-1 level of 123 nmol/l (NR 5.5-32.0). She failed oral glucose tolerance test with non-suppressed growth hormone of 37.4 ug/l. Pituitary MRI showed large pituitary macroadenoma extending into the left cavernous contacting optic chiasm without compression. Visual field showed minor superior deficit. Case was discussed at pituitary MDT with recommendation for medical therapy with somatostatin analogue (Lanreotide) with plan to proceed to endoscopic resection of the pituitary tumor. During follow-up, IGF1 improved on Lanreotide to 34.3 nmol/l and cardiac function improved EF of 51%. Repeated MRI showed no more cavernous sinus involvement. Patient is planned to undergo pituitary surgery.
Conclusion
Cardiac abnormalities are the most common cause of morbidity and mortality in patients with acromegaly. Although there is no guidelines for acromegalic cardiomyopathy, current consensus recommends trans-sphenoidal pituitary surgery as the treatment of choice for acromegalic cardiomyopathy. In cases with high risk for immediate surgical intervention, somatostatin analogue therapy with octreotide has been reported to have good clinical and echocardiographic improvement.

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P263

Pitfalls in the Biochemical Evaluation of Cushing's Syndrome: A Challenging Case and Literature Review

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A 47-year-old female presented with facial swelling, easy bruising, and concern regarding possible Cushing's syndrome. She had developed secondary amenorrhoea 3 years previously; biochemistry suggested hypogonadotrophic hypogonadism, felt to be hypothalamic secondary to low BMI and intense exercise. She was normotensive, and BMI was 17.4. There was no evidence of abdominal striae, proximal myopathy or hirsutism, but her face appeared rounder and plethoric compared with a previous photograph. Investigations revealed significantly elevated urinary free cortisol (UFC) excretion at 441 and 564 nmol/24hr (normal < 162). However, urine volumes were 4.3 and 6.7 litres respectively, indicative of polyuria, a lesser-known cause of false positive UFC. Early morning cortisol was 610 nmol/l following an overnight dexamethasone suppression test (DST), and 513 nmol/l following a 48-hour low-dose DST. ACTH was 27 ng/l. Contrast-enhanced pituitary MRI showed a 3 mm pituitary fossa lesion consistent with a microadenoma. However, subsequent investigations ultimately suggested a diagnosis of pseudo-Cushing's. Firstly, salivary cortisol measurement demonstrated intact diurnal rhythm, with appropriately low late-night concentrations. Secondly, due to the degree of non-suppression of cortisol post-dexamethasone, serum dexamethasone was quantified by liquid chromatography-mass spectrometry following a repeat ODST. Dexamethasone concentration was 1.7 nmol/l, with values > 3 nmol/l considered necessary to suppress cortisol. Finally, a dynamic contrast-enhanced pituitary MRI suggested the previously identified pituitary mass most likely represented a Rathke's cleft cyst. Furthermore, from a clinical perspective her facial swelling, plethora, and easy bruising all resolved after she was encouraged to drink to thirst only. An association between pseudo-Cushing's and false positive UFC and ODST is well established. However, where results of these investigations are significantly elevated, and above levels expected with pseudo-Cushing's, additional factors should be considered such as the impact of high fluid intake and serum dexamethasone concentration, as exemplified within this case.

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P264

Diabetes insipidus following a non-acute presentation of pituitary apoplexy – a rare presentation

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Introduction
Pituitary apoplexy (PA) is a rare endocrine emergency with less described entity being its subacute/non-acute presentation. Incidence of PA is difficult to determine, varying 2%-12% of pituitary adenoma. Hypopituitarism in PA is observed in up to 70% of cases with diabetes Insipidus (DI) observed in <5% of cases and mostly transient.
Case description
82-year old female with pituitary macroprolactinoma (1.5 cm) presented with 3-week history of occipital headaches, fatigue, polydipsia and polyuria. Cabergoline 250 mg weekly was started 3 months prior (prolactin- 4,936 mU/l). Examination revealed normal GCS, neurology and visual fields. Admission bloods revealed 9 am cortisol-60 nmol/l and prolactin-1046 mU/l. Hydrocortisone replacement initiated and Cabergoline dose increased. MRI brain showed new focus of T1 high signal on the left side of pituitary consistent with recent hemorrhage. Non-acute PA was diagnosed. Neurosurgeons opined, patient not for surgical intervention given normal neurology. During inpatient stay, the patient reported polyuria with recurrent episodes of raised urea and creatinine and mild hypernatremia. Water deprivation test showed serum osmolality of 297 mOsm/kg (285-295) with urine osmolality of 305 mOsm/Kg. Post intranasal desmopressin urine osmolality increased to 599 mOsm/kg after 150 minutes with urine output reducing from 154 ml/hr to 30 ml/hr confirming diagnosis of Cranial DI. She responded well to oral desmopressin and was discharged with prednisolone 4 mg OD, Cabergoline 250 mg twice weekly and desmopressin 50 mg OD.
Discussion
Our case illustrates non-acute PA in pituitary macroadenoma complicated by ACTH deficiency and DI thus involving both anterior and posterior pituitary axis. DI is a very rare manifestation of non-acute/sub-acute PA with 4 cases reported in literature, including one pregnant woman. Our case is interesting with respect to patient's age (the others were younger), relatively low prolactin level and lower dose of Cabergoline on presentation.

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P265

Not just a prolactinoma- Conservative management of co-secretory macroadenoma

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45 years old male of Romanian origin presented with shortness of breath and reduced exercise tolerance over 3 months with increased sweating and weight gain from 90 kgs to 118 kgs over 2 years. Also reported hands/fingers/feet size increase. He also complained that his breathlessness worse by as tongue and lips were 'large'. Denied any visual disturbance, especially peripheral vision. On examination, coarse features, prognathism and possible macroglossia noted. Photographs from 3 years ago revealed changes in facial features. No obvious visual field abnormalities on confrontation. 9AM cortisol was 158 nmol/l, TSH1.73 mIU/l (normal 0.27-4.20 mIU/l) with T4 9 pmo/l (normal 12-20 pmo/l), prolactin was 24041mIU/l (normal 86-324 mIU/l) with a raised IGF-1 111 nmol/l (normal 8.5-31 nmol/l). Macroprolactin levels were 21425 mIU/l (normal 63-245 mIU/l) MRI Pituitary revealed pituitary fossa grossly enlarged with an abnormal mass lesion arising from left side of the anterior pituitary measuring 34*26*27 mm demonstrating mild enhancement. Lesion surrounded the cavernous portion of the left internal carotid artery, involving the left cavernous sinus, extending superiorly to the left of the midline posterior to the terminal left ICA and proximal portion of the left MCA. Pituitary stalk was displaced to the right and didn't impact undersurface of the right optic chiasm. Formal perimetry - incongruous, homonymous, left upper quadrantanopia. Regional pituitary MDT opined co-secretory Prolactin/IGF-1 secreting tumour. Started on lanreotide 120 mg a month, cabergoline 500 mg thrice a day along with physiological dose hydrocort (10 mg, 5 mg, 5 mg) and levothyroxine. He is for medical management and will be followed up with serial MRI in 3 months for further surgical consideration. Co-secretion of prolactin in pituitary adenomas may buy time for medical management and conservative management may be appropriate at the outset

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P342

Variants in the neurodevelopmental gene bone morphogenetic protein/retinoic acid inducible neural-specific *2(BRINP2)* are associated with severe delayed puberty

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Gonadotropin-releasing hormone (GnRH) is the master hormone regulating the reproductive axis and its pulsatile secretion is crucial for puberty onset and fertility. Disruption in GnRH neuron development or hypothalamic function can lead to absent or delayed puberty (DP) due to GnRH deficiency, with a phenotypic spectrum from severe delayed puberty to partial or complete Hypogonadotropic Hypogonadism (HH). HH can also be present as a shared trait with other neurodevelopmental disorders (NDDs). Mutations in the gene (*BRINP2*) have been previously associated with NDDs such as autistic spectrum disorder (ASD). BRINP2 is localised to the olfactory bulb, a key site during GnRH neuron migration. The aim of our study was to identify novel genetic aetiology of severe DP by screening and identifying variants in associated genes in our cohort of patients; and ascertain the functional effects of identified variants of interest. Whole exome sequencing (WES) was performed on DNA samples from 180 probands with DP from our patient cohorts to identify potentially pathogenic novel, or rare coding variants in relevant gene pathways. Integrative analysis was performed on genomic data from human patients combined with transcriptomics analysis of rodent immortalized and primary GnRH neurons to determine novel regulators of GnRH neuronal development and function. *BRINP2* was identified as a candidate gene of interest as it was found to be significantly upregulated during GnRH neuronal development in these single cell transcriptomics analyses. WES analysis identified three variants in *BRINP2* (p.R726W, p.R649Q, p.I629V) in four unrelated probands with severely DP or partial HH, in combination with

ASD or other NDD features. These three variants are all rare or ultra-rare and are predicted to be pathogenic by in silico tools. Protein expression of the three mutants was comparable to the reference protein.

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P343

Variants in Methyl-CpG-binding protein 2 (MECP2) are associated with X-Linked Central Precocious Puberty

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Whilst several key genetic contributors to the phenotype of central precocious puberty (CPP) have been recognized, many familial cases remain without a clear genetic aetiology. Methyl-CpG-binding protein 2 (MECP2) is a chromatin-associated transcriptional regulator, which plays an essential role in neuronal maturation. It is encoded by the MECP2 gene, located at chromosome Xq28, which is highly expressed in brain tissues. Loss-of-function mutations in MECP2 are usually associated with Rett syndrome, a severe neurodevelopment disorder with female predominance characterized by developmental regression and intellectual disability. Early puberty has been demonstrated in girls with Rett syndrome. We investigated whether MECP2 defects might be associated with idiopathic CPP with or without mild neurodevelopmental abnormalities. A cohort of 331 multiethnic idiopathic CPP patients (38% familial) was investigated for MECP2 allelic variants by high-throughput sequencing. Immunohistochemistry and immunofluorescence studies were performed in pubertal female mice to determine Mecp2 expression in hypothalamic nuclei. Three rare heterozygous exonic MECP2 variants were identified in 5 girls from 4 unrelated families with CPP: a de novo p.Arg97Cys variant in monozygotic twin sisters with CPP and microcephaly; a de novo p.Ser176Arg variant in one girl with sporadic CPP, obesity and autism; and a p.Ala6_Ala8dup insertion in two unrelated girls with sporadic CPP, all predicted likely damaging by in silico proteomic tools. Patients did not manifest typical features of Rett syndrome. In female mice, experiments identified abundant Mecp2 staining in hypothalamic nuclei (arcuate, suprachiasmatic, and paraventricular) and co-localization of Mecp2 and GnRH within GnRH neurons, demonstrating Mecp2 expression in key hypothalamic nuclei responsible for GnRH regulation. We propose MECP2 as a novel candidate for CPP that may regulate pubertal timing via transcriptional modification of GnRH secretion. Further studies aim to functionally characterize *in vitro* the effect of these MECP2 variants of interest and ascertain their role in modulation of GnRH secretion.

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P344

CRN04894: an oral, nonpeptide adrenocorticotropic hormone (ACTH) receptor antagonist decreases basal and stimulated cortisol secretion in healthy volunteers

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CRN04894 is a potent, orally bioavailable nonpeptide that is a highly selective antagonist for melanocortin type 2 receptor (MC2R). This receptor is found exclusively in the adrenal cortex and is the primary mediator of adrenal activation. We report results from a randomized, double-blinded, placebo-controlled (6 active:3 placebo/cohort), multiple ascending dose (40, 60, and 80 mg) study in health volunteers evaluating safety, pharmacokinetics, and pharmacodynamics of oral, once-daily CRN04894 administered at 22:00 for 10 days. Serum cortisol was measured daily at 08:00; circadian rhythm studies were undertaken at baseline and days 1-2, 4-5, 9-10. A 1 mg ACTH (1-24) test was undertaken on day 11, 8 hours post CRN04894 last dose. The protocol defined glucocorticoid deficiency as 08:00 cortisol of <138 nmol/l which triggered the addition of oral replacement hydrocortisone to ongoing CRN04894 dosing. CRN04894 was rapidly, orally absorbed (Tmax 0.5-1.5 hour), and demonstrated a dose dependent increase in systemic exposure, with a T1/2 of ~24 hours. In the 80 mg cohort: mean 24-hour AUC for serum cortisol and androstenedione fell by 51% and 40%, respectively, at day 10 compared to baseline; median 24-hour urinary-free cortisol (UFC) decreased by 75%, while 24-hour mean ACTH AUC increased ~5-fold compared to baseline; peak cortisol in response to the day 11 ACTH stimulation test was <500 nmol/l in all subjects. These analyses include data from 2 subjects receiving replacement hydrocortisone. All adverse events (AEs) were considered mild or moderate with no serious AEs. Glucocorticoid deficiency was the most common treatment-related AE ($n=11$), although no patients had symptoms of adrenal insufficiency. In summary, CRN04894 in healthy volunteers was well tolerated and resulted in meaningful suppression of cortisol and androstenedione secretion despite exposure to persistent elevated endogenous ACTH levels. Studies are planned in patients with ACTH-dependent Cushing's syndrome and congenital adrenal hyperplasia.

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P345

Amyloid Beta Expression in the Amygdala of Aged Rhesus Macaques: Effect of Hormone Replacement Therapy

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Amyloid beta (Aβ) plaques represent one of the classic hallmarks of Alzheimer's disease (AD) pathology in the brain. In rhesus macaques, these plaques start becoming prominent when the animals are 20+ years old, although the underlying cause(s) are unclear. In the present study, our goal was to test the hypothesis that exposure to a Western-style, high-fat, high-sugar diet (WSD) and/or loss of ovarian steroids would advance the development of this histological marker of AD pathology. Specifically, we used immunohistochemistry to compare the expression of Aβ plaques in the amygdala of old female macaques, that were either maintained on a regular diet or exposed for 30 months to a WSD. Furthermore, to more closely mimic the hormonal status of post-menopausal women, all of the animals were ovariectomized (Ovx) and either received continuous estradiol hormone replacement therapy (Ovx+E) via a subcutaneous elastomer implant, or served as untreated controls. Overall, there was no obvious effect of dietary treatment on Aβ plaque deposition. However, there was a marked difference in the number of animals showing a high level of Aβ plaque deposition (i.e., $>0.1\%$ of amygdala area) between the Ovx and Ovx+E groups. Seven of the 12 (58%) Ovx controls showed this high level of Aβ plaque deposition compared to only 1 of 15 (7%) Ovx+E animals. Although it remains unclear if exposure to a WSD advances the onset of Aβ pathology, the data demonstrate that rhesus macaques, like humans, show an increased incidence of Aβ plaques during old age. Moreover, they suggest that estradiol supplementation may significantly delay or block AB plaque deposition in postmenopausal women.

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P346

Immune checkpoint inhibitor related hypothalamus pituitary adrenal axis dysfunction: A retrospective study in Derriford Hospital

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Background
Newer biological drugs such as immune checkpoint inhibitors (ICI) have recently revolutionized cancer therapy. However, hypophysitis and adrenalitis are recognized side-effects of these new therapies. Hypothalamus pituitary adrenal (HPA) axis dysfunction is associated with serious morbidity and mortality. This study aimed to monitor whether the ICI related HPA axis dysfunction recovers.
Materials and Methods
We have conducted a retrospective observational audit of patients on ICI therapy in our centre between 2013 and April 2022. We audited all the patients on ICI therapy under our oncology department, all the patients who have been referred to our endocrinology department with a suspected diagnosis of hypophysitis and all the patients who had a magnetic resonance imaging (MRI) report containing hypophysitis in the differentials. We reviewed their cortisol levels and the therapy

received. All the patients who had a low morning cortisol and/or inadequate response to short synacthen test (SST) were classified as having (HPA) axis dysfunction and they had regular follow-up with SST response monitoring.
Results
661 patients received ICI therapy during the study period, and 28 of them (an incidence of 4.23% over 9 years) developed HPA axis dysfunction. Their mean age was 65 years old and 68% were male. 24 of these 28 patients had pituitary MRI done and 6/24 had radiological features of hypophysitis. One patient was lost to follow-up and all 27 remaining patients were on glucocorticoid replacement therapy (100%), with the majority (19 patients (68%)) taking hydrocortisone. At the end of this retrospective study, 20/27 patients were still alive and there was no HPA recovery during the studied period.
Conclusion
ICI related HPA axis dysfunction is unlikely to show recovery and it will require a life long steroid replacement therapy.

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P347

Targeted Profiling of Endogenous Steroids in Mouse Plasma Using Liquid Chromatography-Mass Spectrometry Approach

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Stress is increasingly pervasive in modern society and an unavoidable stimulus to the human organism. Stressors, whether of social or physical type, activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the upregulation of glucocorticoid levels and, in some cases, its de novo biosynthesis. Aside from HPA axis regulation, corticosteroids also modulate the immune response to inflammation and affect the whole-body metabolism. Accurate quantification of endogenous steroids remains an analytical challenge. High structural similarity between steroid isomers and their active and inactive forms in various abundance levels can result in significant interferences and false positive results, especially when using immuno-assays. The present study aimed to develop a sensitive high-throughput reversed phase ultra-high performance liquid chromatography-tandem mass spectrometry (RP-UHPLC-MS/MS) method for the simultaneous determination of 40 endo- and exogenous steroids. A set of C18 estrogens, C19 androgens, C21 progestogens and corticoids, and synthetic steroids in biologically active and inactive forms was selected based on cooperation with the Laboratory of Epithelial Physiology, Czech Academy of Science, to monitor the targeted panel of analytes in mouse plasma. Overlapping of retention times and masses or fragmentation patterns of 31 of 40 steroids had to be overcome when developing the 20minute long RP-UHPLC-MS/MS method. Sample preparation methods of supported liquid extraction (SLE) and protein precipitation (PP) were developed to eliminate matrix effects and achieve the highest degree of sample purification without the loss of target analytes. Both sample preparation methods have been validated according to the EMA guideline. Finally, the PP-RP-UHPLC-MS/MS method was selected to analyse mouse plasma samples due to lower obtained LLOQs.

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P348

Use of Neurosteroids to Treat a Neuronal Antibody-mediated Seizure Model

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Background
NMDAR-Ab mediated encephalitis is a neuro-immunological disorder that presents with seizures. NMDAR-Abs cause internalisation of NMDARs while Pregnenolone sulfate (PregS) a neurosteroid upregulates NMDARs in the brain. Our previous in vitro studies have shown that PregS can reduce established ictal activity caused by NMDAR-Abs (Wright *et al*., 2021). Before proceeding with *in vivo* treatment studies, we aimed to determine baseline brain PregS levels *in vivo* and following subcutaneous PregS injections using an in-house modified LC-MS method.
Method
Rats were randomised and divided into three groups; Control, Cyclodextrin (CDX) and CDX + PregS treated. Rats were perfused after 8 hours and brain were extracted, immediately snap-freezed and stored in -80°C. PregS levels were determined from rat brain tissue (0.1 mg) spiked with internal standard (1ng of pregnenolone-17α,21,21,21-d4 sulfate) by adding 1 ml of ACN-ZnSO4 [89 g/l, 4:1 (v/v)], followed by alternate vortexing and sonication for 10min. PregS was enriched using two-step solid phase extraction (SPE) using a polymeric SPE column (HLB PRiME, Waters). A reverse phase LC method using 85% water/acetonitrile to methanol/acetonitrile gradient was systematically developed for optimal separation of PregS. Method validation was performed to establish linearity, sensitivity, recovery, and accuracy.
Results
The endogenous PregS levels were observed in control and CDX brain samples which were increased following PregS injection. On the other hand, there was no significant change in the cholesterol levels in the same brain samples. This assay has a linear dynamic range ($R^2 > 0.94$) of 0.02ng/ml-1ng/ml for PregS and the extraction recoveries were reproducible (>90% consistent).
Conclusion
Increased levels of PregS proves the used LC-MS method to be sensitive and accurate to identify endogenous brain neurosteroid levels. Further work will include *in vivo* treatment of NMDAR-Ab mediated rat models with PregS.

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P349

Co-morbidity of alzheimer-like dementia and type-2 diabetics mellitus: possible therapeutic effect of virgin coconut oil

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Alzheimer's disease is a progressive disease of the human brain characterized by memory impairment and disturbance in at least one other thinking function. Type 2 diabetes (T2D) is the kind of diabetes mellitus (DM) that occurs due to the absence or deficiency of insulin receptors and it is usually referred to as maturity-onset DM. The hippocampus, and frontal area of the brain are areas with receptors for insulin, meaning that the hippocampus structure is majorly damaged in AD due to insulin resistance and has a deficiency in the receptors for the hormone insulin implying a decline in memory and learning. Coconut oil is free from a rancid odour or taste. The active ingredients found in coconut oil is the ketone which is seen to be beneficial to those with the disease condition. This research study is primarily aimed at explaining the mechanism through which Alzheimer-like Dementia and T2DM co-exist and also studying the effect of Virgin Coconut oil (VCO) as a possible treatment of these conditions. Male rats of about 10 weeks were gotten and housed in Babcock University Animal House. The rats were split according to their weight into six groups. The high-fat diet was given to the animals for 44days coupled with Streptozotocin for 3 consecutive days to create a model of the T2DM. Neurobehavioral investigations were carried out after administration to evaluate learning and memory and also anxiety using the Barnes maze and Elevated Plus Maze respectively. The control and groups treated with VCO were compared and there was no significant difference but there was a slight decrease in the weight of the animals in the VCO treated group when compared to the control group. Results from the analysis showed the establishment of the disease conditions and the potential of VCO as a treatment for the condition.

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P350

Central diabetes insipidus associated with Covid-19 infection and vaccination – could this be a 'common' phenomenon?

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Background
Central diabetes insipidus (DI) has now been described in a handful of case reports as a symptom of Covid-19 infection - associated with acute respiratory distress syndrome (ARDS)1 - and as a possible late onset sequela secondary to Covid-19 infection. It has also once been reported following immunization with mRNA Covid-19 vaccination. Our Trust serves a population of 612,000 and we have recently observed two cases of central DI, one post Covid-19 infection and one post vaccination.
Case presentations
The first case is a 44 year old woman, normally fit and well, who presented with acute symptoms of excessive thirst (14 litres per day) and polyuria four weeks after symptomatic Covid-19 infection. The second case is a 69 year old woman, also normally well, who developed symptoms of DI three weeks following Covid-19 mRNA (Pfizer) booster vaccination.

Investigation
Both individuals were confirmed to have normal anterior pituitary function prior to undergoing modified water deprivation testing, which confirmed the diagnosis of central DI. Morning urine osmolalities were 111 and 145mOsm/kgH20, serum osmolalities 309 and 301mOsm/kgH20 respectively; urine output falling and osmolality correcting to 534 and 487 mOsm/kgH20 three hours post Desmopressin administration.
Treatment and Outcome
Desmopressin was commenced with good symptomatic benefit in both cases. MRI pituitaries are awaited. It is currently unclear whether the DI will be permanent or resolve spontaneously with time.
Discussion
Previous case reports have described DI as a rare association with Covid-19, likely secondary to pituitary hypophysitis. Our recent experience suggests this may be a more common association than previously thought. In fact, we have a third case currently under investigation for possible partial DI post Covid-19 vaccination. DI has a low population prevalence (1/25,000) and it may therefore require collaboration between centres to assess how frequently this association is being observed.

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P351

Hypophysis associated with Crohn's disease - Think DI as well as GI in dehydrated thirsty Crohn's disease patients with rising sodium!

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Introduction
Hypophysitis is a rare association of inflammatory bowel disease (IBD) with only few cases reported in the literature. It can present with isolated hormone deficiencies or panhypopituitarism. Patients may also present with symptoms secondary to inflammatory pituitary mass. Management consists of hormone replacement therapy, but high dose steroids, steroid sparing agents like Rituximab or even surgery may be required for mass effect.
Case report
A 28-year-old gentleman with 8 years history of Crohn's disease treated with 8 weekly intravenous Infliximab presented with rapid onset of unquenchable thirst, polydipsia and polyuria (300 ml/h) interfering with work and quality of life. Eight months prior to presentation, he had enrolled in a trial to switch to subcutaneous Infliximab. Despite significant polydipsia of almost 10 L/24h and number of contacts with IBD team and GP, his referral to endocrinology was delayed. At his endocrine review, he was exhausted, dehydrated, unable to work and desperate for treatment. His sodium was 144 mmol/l (133-146) despite 10L daily fluid intake, glucose and calcium were normal. There was no recent oral steroid treatment for IBD. Apart from IV to SC Infliximab delivery change, there was no other change in therapy. Anterior pituitary hormones were normal. ESR was raised at 80 mm/h despite no change in bowel symptoms. Pituitary MRI showed slightly thickened pituitary infundibulum. Due to significant symptoms, desmopressin was commenced without delay, with fantastic response.
Conclusion
This case reminds us of the association between granulomatous diseases like Crohn's disease and hypophysitis, which can also occur in context of concurrent treatment with biologic therapies such as infliximab. There were only subtle findings on MRI scan in this case and high dose oral steroids were not required. Awareness of this association in patient with IBD by non-specialists can ensure rapid access to treatment.

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P352

The heart bleeds – complex management of a patient with acromegaly, cardiomyopathy and mechanical mitral valve

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A 44 year old gentleman presented to his local hospital with a two week history of fevers and rigors. Blood cultures were positive for Streptococcus oralis, and an echocardiogram confirmed new diagnosis of hypertrophic cardiomyopathy (HCM) complicated by mitral valve infective endocarditis (IE). Unfortunately, this required a mechanical mitral valve replacement (MVR) and he started warfarin (INR target 2.5-3.5). During his admission, he reported chronic headaches. An MRI brain showed a 3.8 by 1.9 cm pituitary macroadenoma extending into the right cavernous sinus. On closer review, he had clinical features consistent with GH excess, with a significantly elevated IGF-1 (140.3nmpol/l (range 8.5-31) and unsuppressed GH during an OGTT, consistent with a diagnosis of acromegaly. He was subsequently discussed in the Pituitary MDT and started Lanreotide to attempt pre-operative tumour shrinkage. Biochemical and radiological response were limited so cabergoline treatment was added with minimal improvement in IGF-1 levels. During this period of medical therapy, multi-disciplinary discussions occurred for peri-operative anticoagulation plans, balancing the risk of pituitary haemorrhage and prosthetic valve thrombosis. Trans-sphenoidal pituitary surgery achieved a good resection and histology confirmed a sparsely granulated somatotroph pituitary adenoma (Ki67 1%), which may explain the poor response to somatostatin analogues. 3/12 post-op IGF-1 is awaited to determine remission. HCM is a known sequelae of acromegaly, contributing significantly to mortality of this disease. Successful control of GH excess is essential to improve cardiac function. Furthermore, patients with HCM are predisposed to IE and mechanical valve replacements requires appropriate anticoagulation. However, balancing the risks and benefits of peri-operative and post-operative anticoagulation in this patient with a mechanical MVR required complex and coordinated multi-disciplinary decision making. Despite best collaborative efforts, this gentleman has had a prolonged post-operative inpatient stay due to recurrent epistaxis requiring tranexamic acid and ENT procedures to achieve homeostasis with closely supervised re-warfarinisation protocol.

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P353

The burden of heatwave-related profound hyponatraemia: Is the climate change making these events more likely?

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During the warmest days reported in Wales and the United Kingdom recently, we have seen severe hyponatraemia phenomena in this part of the world. Water intoxication causes acute hyponatraemia when the sodium concentration of the blood falls too low due to prolonged sweating combined with excessive fluid consumption. Although primary polydipsia is found in a broad range of individuals including those with mental disorders, and healthy persons, as well as athletes who run marathons and long triathlons, highest hyponatremia incidence usually observed in summer months. Heatwaves or extreme weather are making these events more likely due to loss of sodium by perspiration alongside excessive hypotonic fluid intake. Interestingly, our two patients with chronic psychotic disorders had their first presentation of symptomatic dilutional hyponatremia on the same weekend when the extreme warm weather reported. Both of our patients were admitted to local emergency department after developing seizures a day after the recorded highest temperatures. They both received either 2.7% or 1.8% sodium chloride to help treat acute severe hyponatraemia, with their initial serum sodium of 106 mmol/l and 112 mmol/l respectively. Both of our patients take anti-psychotics and were relatively well prior to this event. Their family and carers reported excessive water intake a few days prior to the witnessed seizures. Both patients made excellent recovery after dyselectrolytemia correction, and they maintained the eunatremic status after recommencing their regular antipsychotics. The advice given to these patients and carers are to monitor their fluid intake, to not drink more than they are thirsting for or exceeding 2.5 litres of fluid daily, to monitor urine colour, concentration, and urinary frequency. Although a few anti-psychotics may impair thirst sensation which could disrupt homeostatic regulation of water balance and induce compulsive drinking, these strategies would be helpful to circumvent symptomatic dilutional hyponatremia as the warm weather continues.

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P354

Primary CNS lymphoma presenting with cranial diabetes insipidus – a case series

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Primary CNS lymphoma (PCNSL) accounts for 0.85% - 2.0% of primary brain tumours. PCNSL arises in periventricular regions of the corpus callosum, with hypothalamic involvement less commonly. While cases have been reported in the literature, cranial diabetes insipidus (CDI) secondary to PCNSL is a rare phenomenon. We present this case series of three patients from our institution diagnosed with CDI and panhypopituitarism in the context of PCNSL.
Cases:
1. 38-year-old female presenting with an eight-week history of increasing fatigue, reduced oral intake, polyuria and severe hypernatraemia. She was diagnosed with panhypopituitarism and CDI. MRI Brain showed multifocal enhancing mass-like lesions in the hypothalamus, lateral ventricles and medulla. Histology confirmed a high-grade B cell lymphoma. She died shortly from her disease. 2. 70-year-old man presenting following two presyncopal episodes, on a background of increasing fatigue. Subsequently, he developed progressive bulbar signs and required intubation for respiratory failure. Panhypopituitarism and CDI were diagnosed with polyuria and hypernatraemia developing following glucocorticoid replacement. CNS imaging showed hypothalamic destruction, periventricular disease and medullary involvement, which were highly suggestive of CNS lymphoma. Sadly the patient died before tissue diagnosis. 3. 42-year-old presented with progressive visual disturbance and evolving right frontal mass. Biopsy confirmed high-grade B cell follicular lymphoma. CT PET showed extensively disseminated metastases, with dural extension of frontal mass. Evolving polyuria and polydipsia were noted during an inpatient stay, and a diagnosis of CDI and panhypopituitarism was made. The patient is currently awaiting consideration for a stem cell transplant following recurrence post chemotherapy.
Discussion
While PCNSL presenting with CDI is rarely encountered in clinical practice, it is important to consider it in the differential. Our case series highlights the complexities and high mortality associated with diagnosing PCNSL and secondary endocrinopathies. More data is needed to ascertain if CDI represents an independent poor prognostic indicator in PCNSL.

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P355

An unusual case of (extremely) delayed ACTH deficiency following pituitary gamma-knife radiotherapy

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59-year-old male, with a background of treated acromegaly, presented to endocrine clinic with new onset fatigue. He was diagnosed with acromegally 18 years prior to his presentation, and had a transphenoidal hypophysectomy followed by gamma-knife radiation. Post-surgery he developed partial anterior hypopituatrism (LH and FSH). He currently takes testosterone replacement. He is still receiving medical management with Somatuline. He developed hypothyroidism 16 years following his diagnosis and started on Levothyroxine supplementation. Almost 17 years from his initial presentation, during routine Endocrine clinic follow up, he reported fatigue. His morning bloods showed a cortisol of 96 nmol/l, together with an inappropriately normal/low ACTH of 15 ng/l confirming the diagnosis of secondary adrenal insufficiency. He was commenced on hydrocortisone therapy, following which his fatigue significantly improved. He is aware of sick day rules and remains under regular endocrine follow up. Hypothalamic-pituitary-axis function progressively declines following radiation therapy. This may be secondary to pituitary atrophy due to lack of stimulation or the delayed effects of direct radiation upon a hormonal axis. The average time to new onset pituitary deficiency has been reported as 29-96 months following radiotherapy. Growth hormone is most sensitive to the effects of radiation, followed by gonadotrophins, ACTH and TSH. Interestingly, this patients' growth hormone secretion remains preserved. However, he developed ACTH deficiency after a staggering period of 17 years. Reports of late onset ACTH deficiency beyond 10 years are rare, perhaps owing to limited duration of follow up. This case demonstrates that patients who receive radiation therapy to the pituitary remain at risk of developing sequential pituitary deficiencies and endocrine follow up is essential for the rest of their lives. Endocrine deficiencies, including ACTH insufficiency, are associated with decreased quality of life and increased mortality; highlighting the importance of long term pituitary profiling and endocrine review.

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Reproductive Endocrinology and Biology

P117

Quantifying the Variability in the Outpatient Assessment of Reproductive Hormone levels

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Background
Due to practical limitations, the diagnosis of hypogonadism is predominantly based on a single measure of reproductive hormones, often with confirmation on a second occasion. Factors associated with reproductive hormone variation include: pulsatile secretion, diurnal rhythm, and food intake, which can affect the accuracy of diagnosis of reproductive disorders. There is limited data quantitatively estimating the variability of reproductive hormone levels over the day. Hormonal sampling data collected over several hours allowed quantification of how representative a single morning measure of reproductive hormones (often used for diagnosis in the clinic) is of the daily hormonal profile.
Methods
Data from 13 research studies (including 267 participants) conducted at Imperial College London were used to quantify the variability in reproductive hormones in both healthy men and women ($n=142$), and those with reproductive disorders ($n=125$). The impact on hormone levels of pulsatile secretion, diurnal variation, feeding, and overall variability (Coefficient of Variation (CV)) was quantified.
Results
The initial morning value of reproductive hormones was higher than the mean value throughout the day (percentage decrease from morning to daily mean: LH 18.5%, FSH 9.8% and Testosterone 9.6% and Oestradiol 2.7%). FSH was the least variable reproductive hormone (CV 9%), followed by sex-steroids (testosterone 12%, oestradiol 13%), whereas LH was the most variable (CV 28%). In healthy men, testosterone fell between 9am and 5pm by 14.9% (95%CI -4.20%, -25.5%), although morning levels correlated with (and could be predicted from) evening levels in the same individual ($r^2=0.53$, $P<0.0001$). Testosterone was reduced more following a mixed meal (34.3%) than after an intravenous bolus of glucose (7.4%; $P<0.0001$).
Discussion
Quantification of the variability of a single measure of reproductive hormones enables more precise estimation of the hormonal profile during the day, with relevance for the diagnosis of hypogonadism and its aetiology.

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P118

Determining the impact of FSH glycosylation variants on the pre-antral follicle transcriptome in the ageing ovary

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Ovarian ageing is a naturally occurring physiological process, marked by dynamic changes in ovarian function and hormone secretion. A key of ovarian regulator is follicle stimulating hormone (FSH). FSH is secreted as two glycosylation variants: partially glycosylated FSH (FSH21) and fully glycosylated FSH (FSH24). Analysis has shown that the ratio of FSH21:FSH24 changes with age, with FSH21 predominant during reproductive prime, and FSH24 predominant around menopause. How FSH glycoforms modulate follicle function in the ageing ovary remains unknown. This study aimed to determine the effects of FSH21 and FSH24 on follicle growth and survival in young versus ageing mice. Mouse ovarian follicles were isolated from 12-16wk-old (reproductive prime), 6-8-month (ageing) and 11+ month old (approaching ovaria senescence) C57/BL6 mice and treated -/+10ng/ml, FSH21, FSH24. Mimicking changes in ratios of FSH21:FSH24 that occur with ageing, follicles were additionally treated with 80:20 FSH21:FSH24 (mimic reproductive prime), or 20:80 FSH21:FSH24 (mimic menopause). Follicles were cultured for up to 96hrs and imaged daily to evaluate follicle morphology, with follicles snap frozen at 24hr intervals, for RNA sequencing. Morphological assessment revealed that age impacted follicle response to FSH glycoforms, with FSH21 and 80:20 FSH21:FSH24 increasing follicle growth across all time points in 12-16wk, while 80:20 FSH21:FSH24 increased 6month follicle growth, from 48-to96hrs. 20:80 FSH21:FSH24 increased 11+month follicle growth from 48hrs. Treatment of follicles with FSH24 or 20:80 FSH21:FSH24 resulted in decreased survival rates in the 12-week follicles, whereas 80:20 FSH21:FSH24 decreased survival rates in 11+month follicles. RNASeq analysis revealed both FSH glycoform and age-dependent differences in gene expression in size-matched pre-antral follicles isolated from 12-week and 11+month mice. These data suggest that FSH glycosylation distinctly modulate the follicular microenvironment to control follicle growth and survival, in an age-specific manner.

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P119

FSH glycosylation variants differentially modulate FSHR trafficking

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The Class A G protein-coupled receptor (GPCR), follicle-stimulating hormone receptor (FSHR), and its associated heterodimeric glycoprotein hormone (FSH) are essential for reproduction. As such, they're key targets of assisted conception. Post-translational modification of FSH gives rise to two predominant glycosylation variants, which are modulated with ageing: partially glycosylated FSH (FSH21/18), predominates in women's reproductive prime (20's), displays faster binding kinetics to the FSHR, and is a more potent activator of cAMP-dependent signalling. Contrasting with fully glycosylated FSH (FSH24) which is more predominant in peri-menopausal women (50's), and less bioactive. Recent studies have suggested a link between receptor trafficking and signalling, yet how FSH glycoforms modulate FSHR trafficking remains unknown. This study aimed to determine how FSH glycoforms modulate FSHR trafficking and link to signal activation. HEK293 cells transiently expressing the FSHR were pre-treated with a dynamin inhibitor, Dyngo-4a (50μM), to inhibit FSHR internalisation, before treatment with either FSH21/18 and FSH24 and cAMP analysed. When assessing live cAMP, pre-treatment with Dyngo-4a significantly attenuated both FSH21/18 and FSH24 activation, moreover, this was additionally supported by attenuation of FSH glycoform-dependent cre-luciferase activity. Confocal microscopy analysis of FSHR endosomal routing revealed temporal FSH-glycoform-dependent differences in the routing of FSHR to EEA1-positve endosomes, with FSH21/18 displaying increased FSHR-EEA1 co-localisation, contrasting to no changes observed in FSH24-treated cells in comparison to control. siRNA knockdown of the early endosomal adapter protein, APPL1, which has been linked to cAMP production supported distinct differences in FSHR endosomal routing as APPL1 knockdown had no effect on FSH21/18 dependent cAMP-signalling. However, enhanced FSH24-dependent cre-luciferase activity was observed. Together, these data suggest that differential FSH glycosylation may modulate the endosomal routing of FSHR to fine-tune cAMP production. This may have implications for altered FSH/FSHR actions in the ageing ovary, highlighting novel targeting mechanisms for enhancing assisted conception.

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P120

Female reproductive health disturbance associated with the COVID-19 pandemic persists despite improving mental health- a longitudinal observational study

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Background
The COVID-19 pandemic has adversely affected population mental health. In April 2021 we conducted an observational study which demonstrated disruption in women's reproductive and mental health during the first year of the pandemic. Our objective therefore was to perform follow up studies in this cohort of women at 6-monthly intervals, to assess the longer term enduring impact of the pandemic on reproductive and mental health.
Materials/Methods
Digital surveys were distributed in October 2021 and May 2022 via email to consenting women who had completed the study in September 2020.
Results
177 women completed all 3 surveys. Mean age of respondents was 35 years. 85% recorded their menstrual cycles. Median weight increased from 68 kg to 72 kg between the first and third surveys. 60% of women reported some change in their menstrual cycle since the beginning of the Covid 19 pandemic. 67% had contracted COVID-19 and 93% had been vaccinated against COVID-19. Cycle changes noted included worsening pre-menstrual symptoms (PMS) (72%), heavy periods (47%), painful periods (61%), missed periods (25%). Only 3% commenced or changed hormonal contraceptive. 39% of women who noted a change in their menstrual cycle in the first survey felt it had improved by the third survey, whereas changes persisted for 49% and were worse for 12%. Women who noted persistent or worsening cycle changes had higher depression (PHQ9) and anxiety (GAD7) scores and lower mental health related quality of life (HRQoL). 65% of women reported a reduced libido initially, but this had reduced to 48% by May 2022. Median anxiety and depression scores improved significantly between initial and third survey. HRQoL scores (SF12) remained unchanged over time. Sleep quality scores (PSQI) overall remained poor, but improved slightly.
Conclusions
Reproductive health disturbance related to the COVID19 pandemic persists for many women, despite improving mental health scores.

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P121

Tool development for the *in vivo* analysis of the physiological role of FSHR oligomerisation

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G protein-coupled receptors are the largest family of mammalian receptors, with key roles in controlling most physiological processes. Ovarian function is no exception, with a key ovarian GPCR, follicle stimulation hormone receptor (FSHR), and its endogenous ligand, FSH, critical for pre-antral-antral follicle growth and survival. An increasingly important way that GPCRs have been shown to regulate ligand specificity and signal amplitude is via association and formation of dimers/oligomers. Although FSHR has been demonstrated to self-associate and homomerize, the physiological regulation and significance of this remains unknown. This study therefore aimed to determine the modulation and functional consequences of FSHR oligomerisation in native ovarian granulosa cells. To do this, an N-terminally FLAG-tagged knock in FSHR mouse was generated. Phenotypic characterisation revealed that ovarian and uterine weights were the same between wild type (WT), FSHRFLAG-/+ and FSHRFLAG+/+ suggesting FSH-mediated oestrogen production was maintained. Gross morphological analysis of the reproductive tract and ovaries revealed no differences between these three genotypes. Histological analysis of ovaries showed the presence of follicles at all stages of follicular development in WT, FSHRFLAG-/+ and FSHRFLAG+/+ mice. Additionally, corpora lutea were present in all models supporting intact ovulation. Breeding strategies confirmed fertility of FSHRFLAG-/+ and FSHRFLAG+/+. Isolated of granulosa cells and super resolution analysis of FSHR monomers, dimers and oligomer populations showed ~40% of FSHR were basally associated, comparable to previously published work in HEK293 cells expressing FSHR. Additionally, analysis of the types of FSHR oligomers suggested a predominance of lower order oligomeric complexes. These data support the utilisation of this mouse model for monitoring endogenous, native FSHR oligomerisation, and provide an exciting tool to unravel the physiological roles of these receptor complexes in ovarian function and ageing.

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P122

Are elevated red blood cell parameters coincidental or correlated in patients with Turner syndrome?

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Introduction
Long-term increased morbidity and mortality in Turner Syndrome (TS) due to vascular disease is recognized, and suggested risk factors include metabolic parameters and possible change in haemostasis, however elevated red cell parameters in women with TS have not previously been noted.
Methods
Following an observation of unexplained occurrence of elevated hemoglobin, a quality improvement-project was conducted to retrospectively review full blood count (FBC) parameters of patients attending a dedicated TS clinic.
Results
The cohort included 120 patients; median age 34(27-49)years, median age at diagnosis of TS 13(7-17)years and median body-mass-index (BMI) 26.9(22.9-31.7) Kgm^2. 45,X was the commonest karyotype [46(34.1%)] and most were on HRT(57.8%); majority being on topical(83.1%), estrogen and progesterone combination(84.6%) with 65.2% on medroxyprogesterone. Twenty-five percent

had primary hypothyroidism (PH) and 19.3% had non-alcoholic fatty liver disease (NAFLD). Of the total, 6 patients had anemia (3/6 confirmed iron deficiency), 25(47.2%) patients had at least a single abnormally elevated RBC parameter in consecutive FBCs whilst 7(5.8%) had ≥ 2 abnormally elevated parameters (out of hemoglobin, hematocrit, RBC count). Of these 7 patients (median age 37.5[31,47] years and median BMI 30.7[22,36.6] Kgm^2), none had a history of thrombosis, smoking or evidence of obstructive sleep apnea. All except one were on combined HRT with monthly withdrawal bleeding, 4/7 had congenital non-cyanotic structural heart disease, 3/7 had PH, 3/7 had NAFLD and 1/7 had coeliac disease. Median of RBC parameters among these patients; hemoglobin 156[154,160]g/l, hematocrit 0.46[0.44,0.47]L/l, RBC count 5.08[5.01,5.24] x10^12/l. Specialized hematological evaluation awaited.

Conclusions

Consistently abnormally elevated RBC-parameters occurred in 5.8% of women with TS without any clinically obvious explanation. Larger cohort studies are needed to explore this observation, it's possible pathogenesis and any long-term influence on morbidity.

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P123

Androgen receptor splice-variants in granulosa-lutein cells of women with polycystic ovary syndrome (PCOS)

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Defects in any of the four functional domains of the androgen receptor (AR) (resulting from loss-of-function or gain-of-function mutations), may affect androgen action. Specific *AR* splice variants have been reported in women with PCOS (Wang *et al*, *PNAS* 2015 112 4743). In this study we sought to identify *AR* splice variants in granulosa-lutein (GL) cells of women with and without PCOS and to assess their functional significance. GL cells were harvested from women undergoing IVF (6 with PCOS, 9 controls). AR gene expression by qPCR was performed, using primers directed against full-length *AR* (*AR-fl*) and well-recognised AR variants (*AR-567es, AR-v7, AR-exon1*) as well as those that appear to be exclusively expressed in PCOS GL cells – with an insertion (*AR-ins*) or deletion (*AR-del*) between exons 2 and 3. *AR-fl* expression was greater in women with PCOS than those without. *AR-v7* was undetectable in all samples. Variants *AR-del, AR-567es* and *AR-exon1* were expressed in GL cells but showed no differences between controls and PCOS. There was, however, a 3-fold increase ($P<0.05$) in expression of *AR-ins* in cells from women with PCOS compared with controls. *AR-flor* or *AR-ins* was transfected into HEK293 cells and exposed to dihydrotestosterone (DHT) in culture. Using immunohistochemistry, we observed that *AR-fl* was, as expected, translocated to the nucleus upon DHT treatment; by contrast *AR-ins* remained cytoplasmic. Preliminary studies of non-genomic *AR* signalling in HEK293 cells show that both *AR-fl* and *AR-ins* respond within 30 mins to DHT exposure, by activation of both PI3K and MAPK pathways. In summary, *AR* splice variants were detected in GL cells of women with and without PCOS, with greater expression of *AR-ins* found in cells from PCOS. We suggest that non-genomic signalling of *AR-fl* and *AR-ins* observed in HEK293 cells results in aberrant function in PCOS GL cells, in which both *AR-fl* and *AR-ins* are overexpressed.

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P124

Divergent G-protein signal control at the very early endosome (VEE) from the dually coupled luteinizing hormone receptor (LHR)

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Membrane trafficking of G-protein coupled receptors (GPCRs) is a critical mechanism by which cells mediate complex signaling pathways. Endosomes are increasingly recognized as platforms for GPCR signaling. The VEE was first identified using the LHR, a GPCR that is key in reproduction. We have shown that recycling of the LHR is driven by receptor mediated Gαs cAMP signaling from the VEE and PKA-dependent phosphorylation of the adaptor protein, APPL1, while APPL1 negatively regulates LH-activated VEE signaling in a PKA-independent manner. In the ovary, LHR also activates Gαq-signaling during the LH surge, a signal that is important in ovulation. The role of the VEE and APPL1 on the Gαq-pathway are unknown. Here we investigate if LHR-mediated Gαq-signaling is spatially regulated via APPL1 and how LHR-Gαs/Gαq spatially directed signaling may be integrated. Pre-treatment with Dyngo-4a in HEK293s expressing LHR reduced LH-dependent IP1 levels, indicating the Gαq-pathway requires receptor internalization. Depletion of APPL1 had no effect on IP1-levels, suggesting APPL1 doesn't impact Gαq-signaling despite its ability to negatively regulate Gαs-signaling. Potential G-protein crosstalk was investigated in HEK293 GΔs and GΔq CRISPR-Cas9 knockouts. GΔs resulted in a complete loss of Gαs-cAMP while, GΔq resulted in increased cAMP compared to WT. However, pre-treatment with a Gαq chemical inhibitor in WT HEK293 showed no change in cAMP-levels. Depletion of APPL1 in GΔq resulted in loss of sensitivity to APPL1 via Gαs-cAMP in contrast to the negative regulatory effects that were previously observed. Depletion of APPL1 in GΔs cells resulted in a decrease of Gαq-IP1. These data combined indicate regulatory roles for the G-proteins where their physical presence mediate responses within a signaling-complex of proteins in which APPL1 also plays a regulatory role, thereby having a synergistic effect in propagating LHR signaling to modulate activity at the level of the VEE and APPL1.

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P125

Simulation via Instant Messaging - Birmingham Advance helps to narrow the gap of knowledge and expectations between clinicians and women with polycystic ovary syndrome: A SIMBA-PCOS mixed-method study

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Introduction

Educational interventions for healthcare professionals (HCPs) in diabetes and endocrinology often limits patient and public involvement (PPI). We studied the effectiveness of Simulation via Instant Messaging-Birmingham Advance (SIMBA) as a tool to improve knowledge about polycystic ovary syndrome (PCOS) in HCP and women with PCOS. Additionally, we aimed to identify and reduce gaps in knowledge and expectations between HCP and women living with PCOS.

Methods

HCP and women with PCOS underwent simulation-based and workshop-based learning respectively on four PCOS case scenarios. These were followed by a debriefing session chaired by experts in PCOS, where women with PCOS also shared their experiences of PCOS. Data on confidence and expectations regarding PCOS were collected pre-and post-SIMBA. Wilcoxon Signed-Rank test was used to compare changes in confidence pre-and post-simulation. Thematic induction was used to identify areas of gaps between expectation and care from questionnaires and discussion session involving HCP and women with PCOS.

Results

25 HCP and 15 women with PCOS completed our questionnaires. HCPs reported increased confidence to manage PCOS cases (simulated: +41.0%, $P<0.001$; non-simulated: +40.0%, $P<0.001$). 90% and 100% HCPs agreed SIMBA-PCOS benefits women with PCOS to understand better their condition and understand each other's perspectives on PCOS respectively. There was a 6.25% ($P=0.0141$) and 17.7% ($P=0.0002$) increase in PPI participants' confidence in HCPs to diagnose and manage PCOS-related issues respectively. Thematic analysis revealed four areas of gaps between expectation and care—delays in diagnosis, lack of information provided regarding further symptoms development and long-term complications, symptom-focused care instead of a holistic approach, and lack of information provided for the treatment they receive.

Conclusion

SIMBA-PCOS is an effective tool for both women with PCOS and HCPs to enhance their confidence and understand each other's perspectives. It also helped reduce gaps in knowledge and expectations between women with PCOS and HCPs.

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P126

Experience of Prescribing Testosterone Gel to Menopausal Women at a Single UK Centre: The Biochemistry and The Patent Experience

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Introduction
It has been suggested that sexual dysfunction affects as many as 43% of women in the population. In relation to this, symptoms of hypoactive sexual desire disorder (HSDD) can be alleviated with testosterone replacement.
Aim
To determine what is the pre- and 24-hour post dose circulating level of testosterone in women applying Testogel 16.2 mg/g.
Methods
In a group of 10 menopausal women applying Testogel 16.2 mg/g at the dose of 20.25 mg every 3-4 days as part of their usual care together with oestrogen +/- progestogen HRT, we measured serum testosterone/free androgen index (FAI) pre-application of Testogel and 24 hours after its application. Testosterone was measured by mass spectrometry. The Female Sexual functioning Index (FSFI) was completed by the women.
Results
Mean pre-Testogel administration testosterone level (corresponding to a trough level) was 0.7: 0.65-1.5 nmol/l (median: 25-75% interquartile range) rising at 24 hours post Testogel to 3.2: 2.7-5.3) nmol/l. Free Androgen Index (testosterone/SHBGx100) pre-Testogel was 1.5:0.6-3.7) (ref range 4.5 or less) rising to 5.7: 3.4-7.2) at 24 hours post Testogel. The rise in serum testosterone was not associated with any untoward effects in terms of hirsutism/acne. Range of duration of treatment with Testogel was 6 months-12 years. All women reported an improvement in sexual function with Testogel. FSFI median score was 24.5/36(25-75% interquartile range 18-28 with highest domain scores for sexual satisfaction and arousal (4.2/6) and moderate scores for orgasm and desire (3.6/6) with lowest domain score for lubrication (2.4/6) and no reported issues re pain on intercourse.
Conclusions
The increase in serum testosterone level after application of Testogel was not associated with untoward reported/manifest consequences, likely because the elevation is short-lived. FSFI score indicated reasonable sexual function in this group of women treated with Testogel for HSDD. Next step will be a 24hour day-curve pharmacokinetic profile.

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P127

Interleukin-6 increases at the onset of lactation and promotes mammary glycolysis: insights from clinical and cellular studies

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The onset of lactation occurs during postpartum days 1-4 and is associated with altered mammary metabolism leading to increased milk component synthesis. We hypothesised that increases in metabolic hormones or cytokines after childbirth may support these processes. To investigate this, we recruited $n=12$ pregnant women following informed consent and measured: prolactin; thyroid-stimulating hormone; insulin; cortisol; insulin-like growth factor-1; and interleukin-6 (IL-6) in serial blood samples obtained in pregnancy (36 weeks' gestation) and during postpartum days 1-4. Of these circulating factors, only IL-6 showed a significant increase after childbirth (plasma IL-6 $=61\pm34$pg/mL on postpartum day 1 vs. 1.1 ± 0.4pg/mL at 36 weeks' gestation, $P<0.01$) with levels normalising by postpartum day 4. We assessed the metabolic effects of IL-6 in human mammary cells (HMECs). IL-6 administered as a 100ng/mL dose caused a >90-fold increase ($P<0.0001$, $n=4$) in the phosphorylation of signal transducer and activator of transcription-3 (STAT3), which is the major IL-6 signalling protein. Phosphorylated STAT3 influences oxidative phosphorylation and glycolysis, and we assessed these processes by measuring extracellular O_2 and pH, respectively. HMECs treated with 100ng/mL of IL-6 for $\leq$48hrs showed no alterations in extracellular O_2 compared to control cells. However, IL-6-treated HMECs showed a significant increase in the extracellular acidification rate (0.44 ± 0.004 vs. 0.37 ± 0.007mpH/min/10^6 cells for control HMECs, $P<0.001$, $n=4$), consistent with increased glycolysis. IL-6 also influences mitochondrial function, and we evaluated this by incubating HMECs with tetramethylrhodamine methyl ester (TMRM), a fluorescent dye sequestered in active mitochondria. HMECs treated with 100ng/mL IL-6 for $\leq$8hrs showed a >20% decrease in TMRM fluorescence ($P<0.01$, $n=4$) consistent with reduced mitochondrial activity. In summary, these findings demonstrate that circulating concentrations of the IL-6 metabolic cytokine transiently increase at the onset of lactation. Moreover, IL-6 may promote mammary glycolysis, which is a pathway generating substrates for milk synthesis.

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P128

Therapeutic Mechanism of Aqueous Extract of Momordica Against Monosodium Glutamate Induced Ovarian Toxicity

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Background
Monosodium glutamate (MSG) use for food addictive have become quite alarming taken together with the huge reports of its toxic effects in the different organ of the body. Thus, this study demonstrates the therapeutic potentials of Mc on MSG-induced ovarian toxicity in female Wistar rats.
Methods
A total of 28 female rats (weight $=165\pm3$g) were randomly assigned into 4 groups (A – D, $n=7$) and treated orally as follows: A – PBS (1 ml daily for 21 days); B – Mc (200 mg/kg daily for 14 days); C – MSG (4 g/kg daily for 21 days); D – MSG then Mc (4 g/kg MSG daily for 21 days followed by 200 mg/kg Mc daily for subsequent 14 days).
Results
Mc was effective in reversing the toxic effects of MSG as evidence of improved cellular morphology of the ovary which shows a wide cortex with numerous primary, secondary and Graafian follicles, as well as newly formed and degenerated corpora lutea. Mc also improved the body weight changes as well as modulated ovarian oxidative redox activities by improving the antioxidative system (SOD, GPx) and inhibiting lipid peroxidation following MSG intake. Furthermore, Mc effectively modulates hormonal activities following MSG perturbation thereby restoring proper ovarian functions.
Conclusion
This study, thus concludes that Mc has therapeutic potential in modulating various cellular mechanisms by which MSG induces ovarian toxicity and subsequent infertility in Wistar rats

Keywords: Monosodium glutamate, ovary, infertility, Momordica charantia
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P129

Adipocytes-Derived Extracellular Vesicle-miR-26b Induces the process of Polycystic Ovary Syndrome

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Background
Adipocyte cells could produce numerous extracellular vesicles and orchestrate the balance of endocrinological system. Polycystic ovary syndrome (PCOS) is a refractory reproductive disease and also a kind of endocrine and metabolic disease. The aim of the study was to explore the effects of adipocyte-derived extracellular vesicles-miR-26b on cumulus cells (CCs) and development of PCOS.
Methods
The crosstalk mediated by extracellular vesicle-miR-26b between adipocytes and CCs was determined in CC cells co-cultured with mature adipocytes or incubated with extracellular vesicle isolated from mature adipocytes. CCK-8 assay and flow cytometry were conducted in CCs treated with or without extracellular vesicles; microRNA (miRNA) sequencing was conducted for clarifying the key molecular. Hormone levels and ovary ovulation ability were conducted with animal experiment.
Results
The results indicated that mature adipocytes derived extracellular vesicles highly expressed miRNA-26b. Adipocyte-derived extracellular vesicles inhibited viability and promoted apoptosis in CCs via targeting JAG1. Furthermore,

extracellular vesicles derived from mature adipocyte disrupted the ovary ovulation and impaired the hormone levels.
Conclusions
These results identify a novel signaling pathway that adipocytes-derived extracellular vesicles-miR-26b promotes cell apoptosis in CCs and disrupted the ovary ovulation in the development of PCOS. The study indicates that adipose tissue-derived extracellular vesicles-miR-26b may play a key role in the PCOS and also provides insight into developing new therapeutic strategies for PCOS.

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P130

Turner Syndrome - a case report illustrating the importance of early gynaecology input for women who are unable to tolerate progestins

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A 41-year-old woman with primary ovarian failure secondary to Turner syndrome presented in December 2020 with heavy vaginal bleeding. She had not attended appointments during the Covid-19 epidemic because of concerns around contracting the virus. She was anaemic with haemoglobin 47g/dl. Ultrasound showed grossly thickened and heterogenous endometrium (60 mm). Cross sectional imaging and hysteroscopy confirmed locally advanced endometrial carcinoma (Stage 3). She proceeded to hysterectomy in June 2021. She did not wish to have chemotherapy and a palliative approach was taken. She sadly died in February 2022. Our patient had been on unopposed oestrogen, a known risk factor for endometrial hyperplasia and dysplasia. She had taken premarin from age 16 to 38 years and had not wanted to change her HRT regimen having experienced progestin side effects. An ultrasound scan 2 years earlier was reported as reassuring. A request to change her to a combined oestrogen-progestin patch had been made but she had not presented to her GP to collect the prescription. This young woman had firm beliefs about her hormone replacement regimen, but at the time of her presentation said that the risks of unopposed oestrogen had not been explained to her in a way which she understood. At a serious untoward incident meeting we felt that although the risks had been discussed, earlier discussion with a gynaecologist would have been helpful. Because it is unusual for endocrinologists to manage women who are not taking a progestin, there was less experience of the significance of her bleeding pattern. Hence, we are particularly keen to share the details of this tragic case to raise awareness amongst our colleagues and trainees. Contributory factors to our patient's outcome were the Covid-19 epidemic, and an historical difficulty knowing what medications were being prescribed in primary care.

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P266

Identification of a transcription factor that modulates ERα-Dependent Hypothalamic Estrogen Sensing

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Coupling the release of pituitary hormones to the developmental stage of the oocyte is essential for female fertility. It is thought to require estrogen to have simultaneous positive and negative feedback effects on two spatially-distinct regions of the hypothalamus, the arcuate nucleus and 'AVPV' nucleus. However, the mechanistic basis for this differential effect is not known. Therefore, we mapped the genomic binding of the estrogen receptor alpha (ERα) in both locations under estrogen stimulation. We found differences that were consistent with the hypothesis that region-specific transcription factors modulate ERα activity. Indeed, we went on to find that a specific transcription factor is present exclusively in the arcuate hypothalamic nucleus and serves as a ligand-dependent repressor of the Kiss1-gene, which is essential for fertility. We generated mice lacking this transcription factor in Kisspeptin-neurons and show that these fail to appropriately modulate hormone secretion. Concordantly, these mice fail to cycle normally, and have impaired fertility. Together, these findings have implications for our understanding of how hypothalamic estrogen signalling translates to appropriate gonadotropin release and the maintenance of fertility.

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P267

Spatial and ligand-directed control of Prostaglandin EP2 signalling

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Prostaglandin E2 acts via 4 GPCRs, EP1-4. EP2 regulates inflammation and has important roles in cardiovascular function, reproduction, and malignancy. GPCR signalling and trafficking are highly integrated as signals from the endomembrane can exhibit distinct profiles from the plasma membrane. Whether EP2 activity is spatially regulated and if this is modified by ligand bias is currently unknown. In HEK 293 cells, three selective EP2 ligands, butaprost, AH13205, and PGN9856i, elicited potent cAMP responses, with EC50s of 415 nM, 436 nM and 2.59 nM, respectively. In both HEK 293 cells and primary myometrial cells from term pregnancies only AH13205 and butaprost were able to increase intracellular Ca2+ levels or PGE2 secretion, and AH13205 increased PGE2 secretion ~40 fold more than butaprost. In HEK 293 cells whilst EP2 exhibited minimal ligand-induced internalisation with all ligands, there was significant constitutive internalisation, which was dynamin-dependent. The dynamin inhibitor Dyngo-4a also reduced cAMP signalling by 70% and the maximal Ca2+ response by 50%. Neither butaprost nor AH13205-dependent PGE2 release was dynamin-dependent, demonstrating a differential spatial requirement for EP2 signalling. Overall, EP2 is constitutively internalised and undergoes minimal ligand-induced internalisation. However, there is a differential spatial requirement for cAMP, Ca2+ and PGE2 signalling in HEK 293 cells demonstrating the physiological importance of constitutive EP2 trafficking. Furthermore, there is distinct ligand bias as different ligands exhibit either extreme inflammatory bias via the Gαq-Ca2+-PGE2 pathway or bias to the Gαs-cAMP pathway. These ligands provide novel tools for probing EP2 function and may provide a novel therapeutic strategy for maintenance of pregnancy where it is beneficial to promote the Gas-cAMP pathway without promoting inflammation.

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P268

Cluster analysis with routine hormonal parameters identifies two distinct subsets of polycystic ovary syndrome (PCOS)

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Introduction
Women with PCOS have a higher risk of metabolic syndrome and cardiovascular complications. We aimed to understand if routinely measured hormonal parameters can identify women with PCOS with a higher risk of metabolic syndrome (MetS).
Methods
The data for the study consisted of a discovery cohort (PCOS clinic database) and a replication cohort (Hull PCOS Biobank.) We used eight routinely measured hormonal parameters in our clinics (free androgen index (FAI), sex hormone-binding globulin SHBG), dehydroepiandrosterone sulphate (DHEAS), androstenedione, luteinizing hormone (LH), follicular stimulating hormone (FSH), antimullerian hormone and 17 hydroxy-progesterone) to perform a K-means clustering and an unsupervised machine learning algorithm. We used NbClust Package in R to determine the best number of clusters. The MetS score (siMS) was calculated by using the formula: 2*waist-circumference/Height + (Baseline glucose/5.6) + (Triglycerides/1.7) + (systolic blood pressure/130) - (HDL/1.28)
Results
The study consisted of 199 women with PCOS in the discovery cohort and 111 in the replication cohort. The cluster analysis showed a smaller cluster with statistically significantly higher LH, FAI, and androstenedione levels in both the discovery (31% of women with PCOS and replication cohort (33% of women with PCOS). The mean MetS score was higher in the smaller cluster (2.85 vs 3.01); however, this was not statistically significant. In the regression analysis, androstenedione (Beta = 0.03, $P = 0.03$) and FAI (Beta = 0.04, $P = 0.01$) were independently and statistically significantly associated with MetS.
Conclusions
We identified a subset of women with PCOS with significantly higher levels of LH, FAI and androstenedione; In addition, androstenedione was independently associated with a higher MetS score and can be a useful marker for metabolic syndrome in women with PCOS.

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P269

Metformin Exposure *In-Utero* Influences Placental Pathways Associated with Mitochondrial Activity

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Metformin is a first-line therapy for type-2 diabetes mellitus and gestational diabetes mellitus (GDM) which shows significant benefits for maternal health. However, offspring exposed to metformin *in-utero* have an increased risk of being born small for gestational age and developing cardiometabolic complications in adulthood. The mechanisms responsible are unknown. As fetal growth is dependent on optimal placental function, we assessed whether metformin exposure alters fetal growth by impacting placental development and function. Publicly available microarray data (ArrayExpress: E-MTAB-6418) from term placentae of obese women with GDM, treated with metformin ($n=12$) or placebo ($n=8$) from 12 16 weeks' gestation, was used to assess the impact of *in-utero*¬ metformin exposure on birthweight and the placental transcriptome. Offspring exposed to metformin were born 375g lighter ($P=0.35$) and 46 significant DEGs ($P<0.01$; $-0.58 \geq \text{Log}_2\text{FoldChange} \geq 0.58$; FDR <0.05) were identified in placentae of metformin treated women. Functional enrichment and Ingenuity Pathway analyses were performed to predict functional impact of differentially expressed genes (DEGs). DEGs were enriched in pathways associated with placental metabolism, development, nutrient transport and mitochondrial dysfunction. To investigate if these functional effects were a direct consequence of metformin, term human placental villous explants from uncomplicated pregnancies ($n=5$) were exposed to metformin (40μM-1 mm) for up to 72 hours. Total and activated (phosphorylated; p) AMPK levels were assessed by western blotting. Metformin (100μM-1 mm) induced pAMPK expression in explants after 24 hours. QPCR analysis revealed metformin did not directly affect genes associated with placental development or nutrient transport. However, following 72 hour treatment, metformin (100μM) altered the expression of genes associated with mitochondrial activity (*PINK1, PARKIN, LC3, BCL2*). These results demonstrate *in-utero* metformin exposure alters genes associated with placental development, metabolism, nutrient transport and mitochondrial activity. However, data from *ex-vivo* placental tissue treated with metformin suggests metformin may have both direct and indirect actions on the placenta.

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P270

How do endocrinologists and GPs perceive contemporary transgender care?: results from a qualitative study of UK doctors

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Background
A growing number of people in the United Kingdom are seeking medical treatment to align their sexual characteristics with their gender identity. With waiting lists for specialist clinics currently lasting over four years, endocrinologists are increasingly called upon to manage transgender care as part of their general duties. While surveys and qualitative studies from North America have investigated doctors' ideas and experiences of transgender care, little is known about endocrinologists' experiences in the UK.
Method
UK endocrinologists and general practitioners ($n=16$) with past or current experience of caring for transgender patients were recruited through societies representing both specialties, and through snowballing. The doctors' experiences of transgender medicine were explored through in-depth semi-structured online interviews. Data was coded using NVivo for Mac and analysed according to Braun's and Clarke's guidelines for reflexive thematic analysis, wherein themes were iteratively refined as interviews progressed.
Results
Seven themes were identified: 1) the desire for more comprehensive training, 2) concerns with current prescribing practices, 3) problems emerging from lack of access to specialist clinics, 4) the etiology of transgender identity, 5) the special challenges of treating non-binary patients, 6) the place of patient choice in transgender care, 7) uncertainties surrounding each medical specialty's role in the process. This report focuses on clinicians' thoughts on their training needs, their conceptions of the current barriers to treatment—including the divide between primary and secondary care—and their ideas for improving transgender care.
Conclusion
Transgender care is likely to remain a part of a general endocrinologists' duties. Further training is necessary to support clinicians to develop their competence and increase their confidence in this area.

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P271

Relationships between adipocyte fatty acid-binding protein with parameters of obesity in women with polycystic ovary syndrome

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Introduction
Adipocyte fatty acid binding protein (A-FABP) is mainly expressed in adipocytes, and circulating A-FABP has been associated with markers of obesity. Women with PCOS are at increased risk of developing abdominal obesity what could be related to serum concentration of A-FABP.
Aim
The aim of the present study was to investigate the relationships between serum concentration of A-FABP and parameters of obesity e.g. waist to hip ratio (WHR) and the amount of adipose tissue assessed during bioelectrical impedance in women with PCOS.
Materials and Methods
We examined 133 patients: 66 women diagnosed with PCOS by the Rotterdam criteria and 67 healthy controls, matched by the body mass index. Serum concentrations of A-FABP, total testosterone were measured and free androgen index (FAI) was calculated. Body composition analysis was conducted using bioelectrical impedance analysis.
Results
In the PCOS group, the serum concentrations of A-FABP, total testosterone and FAI were significantly higher in comparison to the control group (all $P<0.05$; respectively). We found association between FABP-A and WHR ($r=0.26$, $P=0.04$) and percentage of adipose tissue ($r=0.33$, $P=0.01$) assessed by bioelectrical impedance in women with PCOS, whereas this relationship have not been found in the control group (($r=-0.06$, $P=0.64$), ($r=0.16$, $P=0.22$); respectively).
Conclusion
Our results indicate that A-FABP is an adipokine that may be connected with abdominal obesity in PCOS patients.

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P272

***Vernonia amydalina* leaf extract ameliorates hyperandrogenism and oxidative stress in polycystic ovarian syndrome-induced Sprague-Dawley rats**

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Polycystic ovarian syndrome (PCOS) is a common endocrine and gynaecological disorder, occurring in 5% to 20% women of reproductive age. It is characterized by hyperandogenism, ovulatory dysfunction and polycystic ovaries. Impaired hypothalamic-pituitary-ovarian axis, insulin resistance and oxidative stress are identified causal mechanisms of PCOS. *Vernonia amydalina*(VA) leaf is a medicinal plant containing bioactive phytochemicals known to improve insulin sensitivity. Its potential use as a plant-based treatment option for PCOS is therefore explored due to the side effects of currently available drugs for treating PCOS. The study aim to investigate the effect of oral VA leaf extract administration on serum testosterone levels, oxidative stress parameters and ovarian weight in letrozole-induced PCOS rats. Fifteen cyclic female Sprague-Dawley rats weighing between 160g to 180g were orally administered letrozole once daily for 28 days at 1 mg/kg body weight. Successful induction of PCOS was confirmed by increased ovarian weight, polycystic ovaries and increased serum testosterone levels. The rats were randomly divided into two groups, namely VA-treatment group administered once daily with 400 mg/kg body weight of VA orally for 28 days and positive control rats which received a placebo. Serum levels of testosterone, oxidative stress parameters (malondialdehyde, superoxide dismutase and catalase) and ovarian weight were assessed in both groups after treatment. Serum testosterone (7.9 ± 1.15ng/ml vs. 16.03 ± 1.09ng/ml), malondialdehyde levels (1.9 ± 0.17U/mol vs. 5.98 ± 0.39U/mol) and ovarian weight (0.28 ± 0.04g vs. 0.49 ± 0.05g) were significantly lower in VA-treated PCOS rats compared to the untreated rats. Catalase and superoxide dismutase levels were not significantly different (1.64 ± 0.04U/mol vs. 1.61 ± 0.06U/mol; 1.71 ± 0.06U/mol vs. 1.59 ± 0.03U/mol respectively) in both groups. These results show that oral administration of VA leaf extract ameliorates PCOS through reduction in oxidative stress and androgen production in rat model.

Keywords: PCOS, polycystic ovaries, *Vernonia amydalina*, medicinal plants
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P273

Interleukin-15, a pleiotropic cytokine, is increased in the mammary gland during lactation

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Lactation promotes infant development and confers long-term health benefits to mothers and infants. However, the endocrine and paracrine mechanisms mediating milk synthesis remain to be fully elucidated. Hormones such as prolactin and progesterone trigger the onset of lactation, whereas local mammary factors are considered to play a greater role in the maintenance of milk synthesis. We hypothesised that mammary epithelial cytokines are required for established lactation, and utilised *in silico* and *ex vivo* approaches to identify candidate paracrine factors. *In silico* expression analysis was performed using a publicly available mammary epithelial cell RNA-seq dataset obtained from age-matched virgin, pregnant, and lactating mice ($n=2$ mice per group). An analysis of >250 genes encoding paracrine factors demonstrated that 6 genes (*Il15*, *Apln*, *Cxcl3, Egf*, *Pdgfd*, and *Nrg1*) had a greater than 2-fold increase in expression in mammary epithelial cells from lactating mice compared to cells from pregnant or virgin mice. Of these genes, *Il15* which encodes interleukin-15, showed the greatest increase in expression (>8-fold increase) during lactation. Moreover, interleukin-15, a cytokine with immune and metabolic roles, is reported to signal via the signal transducer and activator of transcription 5 (STAT5) protein, which is the major intracellular mediator of milk synthesis. We therefore validated expression of interleukin-15 ex vivo by quantitative reverse transcriptase-PCR (qRT-PCR) using mammary glands obtained from $n=5$ virgin mice, $n=5$ mice in early lactation (lactation day 1), and $n=5$ mice in established lactation (lactation day 7). This showed that mammary gland interleukin-15 expression was not significantly increased during early lactation, but markedly increased, by around 40-fold in mice during established lactation compared to virgin mice ($P<0.001$). In summary, these findings highlight a potential role for mammary-expressed interleukin-15 during lactation. Further studies are warranted to determine whether this cytokine promotes milk synthesis.

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P274

Investigating hormones triggering the onset of sustained lactation (INSIGHT) pilot study

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The onset of human lactation is characterised by increased breast fullness and the start of copious milk secretion. The process, which typically occurs 1-4 days postpartum, is triggered by a decrease in serum progesterone and high prolactin concentrations, although the exact levels are ill-defined. We aim to establish reference intervals for hormones triggering the onset of sustained lactation and understand how breastfeeding influences hormone secretion, so as to improve the clinical management of lactation insufficiency, which affects 5-15% of breastfeeding women. We therefore conducted a 3-month single centre pilot study to evaluate ease of recruitment and blood sampling during and after pregnancy. Women aged $^{3}18$ years with a singleton pregnancy were recruited with informed consent. Blood samples were obtained at 36 weeks' gestation, and then before and after a breastfeed at a single home visit during days 3-5 postpartum. Lactation onset was ascertained using a validated breast fullness scale. Twenty-nine (94%) out of the 31 women recruited (age range 24-41 years) completed the study. All gave birth at term (37-42 weeks' gestation) and reported lactation onset by day 4 postpartum. The mean $\pm$ SEM serum progesterone concentration fell significantly from 491 ± 25 pmo/l at 36 weeks' gestation to 3.0 ± 0.3 pmo/l ($P<0.0001$) on days 3-5 postpartum. The mean $\pm$ SEM serum prolactin concentration did not significantly change between the same time-points (3535 ± 209 versus 4080 ± 300 mIU/l); however, prolactin levels rose significantly 45 min after breastfeeding started (4080 ± 300 to 5229 ± 283 mIU/l, $P<0.01$). In summary, we have demonstrated the feasibility of recruiting women for hormone measurements before and soon after childbirth to establish lactation hormone reference intervals.

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P275

Follicle Sizes That are Most Likely to Yield Oocytes During In Vitro Fertilisation (IVF) Treatment

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Background
Infertility affects 1 in 6 couples causing devastating psychological impact. In vitro fertilisation (IVF) treatment can aid couples to conceive, but personalisation of treatment is needed to optimise patient outcomes. Machine learning can aid in the analysis of large complex datasets such as those encountered during IVF treatment. One example is in determining the optimal follicle size on the day of trigger to maximise the number of oocytes collected. Both follicles that are too small and those that are too large are less likely to yield oocytes. Therefore, determining the optimal follicle size range for oocyte yield provides valuable information for the clinician during cycle management.
Method
Retrospective cohort study analysing follicle sizes on the day of trigger compared to the number of oocytes retrieved from 8,030 IVF cycles conducted at the Hammersmith IVF unit in women aged under 35 years. Random forest ensemble machine learning technique was used to identify the follicle sizes that most contributed to the number of oocytes retrieved.
Results
Follicles of 11-19 mm on the day of trigger were most likely to yield oocytes, and mature oocytes, following both human chorionic gonadotrophin or gonadotrophin releasing hormone agonist. The number of follicles in the 11-19 mm range was more closely associated with the number of oocytes retrieved ($r^2=0.58$) than follicles smaller or larger than this range ($r^2=0.051$). The most predictive follicles sizes on the day prior to trigger (Day -1) were 10-18 mm, and the day prior to that (Day -2) were 6-17 mm, consistent with the median follicle growth rate of 1-2 mm per day.
Conclusion
Follicles of size 11-19 mm on the day of trigger are most likely to yield oocytes, providing vital information for clinicians managing ovarian stimulation to optimise patient outcomes.

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P276

Is there a consensus for Management of Hormone Replacement for Males and Females with Hypogonadism in the UK? SfE national survey

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Background
Optimization of sex hormone replacement therapy (SHRT) is essential in long-term management of patients with hypogonadism. However, approaches to formulations of therapy, dose change (if any), monitoring of adequacy of therapy and safety are not standardised.
Objectives
The survey aimed to establish the approach to management of SHRT for male and female hypogonadism.
Methods
Online survey, live for 4 weeks (1/11/2021) disseminated through SfE website and social media platforms to members.
Results
40 responses; 27/40 (68%) consultants, 12/40 (30%) speciality trainees and 1 endocrine nurse specialist. For hypogonadal men, 25/40 (63%) respondents preferred transdermal testosterone (T) as first line replacement, 15/40 (38%) who preferred intramuscular T. 60% preferred trough T levels to assess adequacy of replacement while 25% (10/40) preferred measurement of T level after gel application;4 (10%) chose monitoring using calculated free T. While T safety was monitored with measurement of haematocrit 47% (39/40) and Prostate specific antigen (PSA) in 37/40 (45%), only 2 % (2/40) chose digital rectal examination.

For women with hypogonadism, the preferred method of hormone replacement was transdermal HRT in 35%, oral combined HRT in 33% and conventional 4 weekly cycle of cOCP in 23% with only half of respondents rely on serum oestradiol to assess biochemical adequacy. In men, the adequacy of monitoring was performed clinically by assessing sexual function 38/40, energy levels 34/40, psychological status 27/40, muscle strength 17/40 and bone density in 2/40. In women, while sexual function (30/40), energy levels (29/40), psychological status (27/40), and bone density in 24/40 are used to assess clincial adequacy. The majority never used T preparation but 28% (11/40) use T for hypogonadal women.

Conclusion

A clear variation in clinical practice does exist when it comes to hormone replacement therapy in men and women highlighting the need for a national consensus for treatment standardisation

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P277

Comparative analysis of the fertility-enhancing potentials of graded doses of Newbouldia laevis and Zinc in male Wistar rats

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Infertility has become a real public health problem because of its increasing prevalence, widespread distribution, and the difficulties inherent in its management. Male factor infertility is thought to be the cause of up to 50% of all infertilities across the world. In some parts of Africa and from time immemorial, a wide variety of plants are of great medicinal importance. Many plant extracts have been used as fertility agents in folklore and traditional medicines to enhance fertility, producing results similar to that of Zinc. According to research. Newbouldia laevis (NL) extract could act as an adjunct that can inhibit or promote hormonal imbalances in males at certain dosages as exemplified in the experimental animal models. The research aimed at determining the comparative effect of Zinc and graded doses of NL on male fertility. The thirty-six male Wistar rats weighing between 55 - 125g were used for the research. The rats were randomly assigned into 6 groups of 5 rats each and treated with normal saline, Zinc, N. Laevis low dose for a short-term (LS), high dose short-term (HS), low dose long-term (LL), and high dose long-term (HL). Results revealed that at high doses NL impacted negatively on the semen parameters specifically the motility and count of sperm cells irrespective of the duration of treatment, however, the germinal epithelial cell population was unaffected. The testosterone levels were initially impacted but the gonads recovered with long-term treatments. The FSH levels were reduced in all groups treated with NL. This was further appreciated in the number of pubs from each group. Mating with the long-term NL yielded more pubs. The research concludes that moderate use of NL extract for a longer period may have possible beneficial effects on the male fertility potential.

Keywords: Newbouldia laevis, testes, Zinc, Fertility potential, reproductive hormones

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P278

Severe Virilization due to ovarian hyperthecosis

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Approximately 10% of the female present with features of hyperandrogenism in their life. It is common in adolescent and childbearing age and less common in menopausal age. A 56-year-old female with a history of type 2 diabetes mellitus, hypertension presented with progressively worsening features of virilization for 1 year. Patient had severe hirsutism, androgenic alopecia and clitoromegaly. She had no loss of weight, loss of appetite suggestive of underlying malignancy. However, there was no clinical evidence of Cushing's syndrome, no evidence of worsening hypertension or paroxysms suggestive of pheochromocytoma. She had no clinical evidence of increased pigmentation, postural dizziness suggestive of late onset congenital adrenal hyperplasia. She is a mother of one and she had no history of oligomenorrhoea or subfertility suggestive of poly cystic ovary syndrome. She became menopausal at the age of 45 and not on hormonal supplements. Investigations found to have high serum total testosterone levels (23.5 nmol/l), free androgen index was 95, and other adrenal hormones were within the normal range. Her contrast enhanced computer tomography (CECT) abdomen did not reveal any abnormality of the adrenals or ovaries. She was offered bilateral adrenal and ovarian venous sampling. It revealed excess testosterone secretion from her left ovary. She underwent laparoscopic bilateral salphingoophorectomy and hysterectomy. Histology found to have stromal cell hyperplasia without evidence of malignancy. She recovered clinically and biochemically following surgery. However severe hyperandrogenism causing virilisation is rare. In post-menopausal women, some of these clinical manifestations could be physiological. However careful evaluation and treatment needed in these patients as these symptoms could be pointing towards neoplastic or functional disease.

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P279

Growth hormone therapy in the management of short stature due to turner syndrome in Nigeria: a case report

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Introduction

Turner Syndrome (TS) is the most common chromosomal abnormality affecting phenotypic females. Short stature (SS) is one of the most consistent clinical features of TS, with consequent poor psychosocial outcomes. Management involves early diagnosis and administration of recombinant human growth hormone (rhGH). The cost of therapy however hampers treatment in resource-challenged regions. The objective of this presentation is to report the outcome and challenges of rhGH therapy in maximizing the height of patients with SS, in Nigeria, a resource-challenged setting.

Case presentation

An 18-year-old schoolgirl presented to the endocrine clinic on account of short stature and failure to attain menarche. Childhood developmental milestones and academic performance were normal. Past medical and surgical history was unremarkable. She withdrew from high school as a result of stigmatization from her peers. General examination revealed scanty axillary and pubic hairs. Her height was 1.37m, Weight: 33 kg, BMI: 17.6 kg/m^2, and arm span: 1.35m. Breast development was Tanner stage 1 with widely spaced nipples. Radiograph of left wrist showed bone age 11 years. Abdominopelvic ultrasound showed a hypoplastic uterus. Her blood tests showed elevated Follicle stimulating and Luteinizing hormone levels with reduced Serum oestradiol. Her karyotype was 45XO. A diagnosis of short stature secondary to Turner syndrome with hypergonadotropic hypogonadism was made. She was commenced on SC Growth hormone 1.62 mg four times weekly and also oestradiol therapy. Treatment was intermittently affected by financial constraints and poor supply chain due to Covid-19 pandemic. Her current height after 2 years of follow-up was 1.50m. She was then able to resume her academic pursuits.

Conclusion

Early initiation of HGH in short stature improvesgrowth and allows appreciable progression to adult height, leading to enhanced quality of life. The high cost of rhGH (about £560 monthly) impairs effective management in resource-challenged regions like Nigeria where minimum wage is £58 monthly.

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P356

The impact of body mass index and lifestyle factors on serum concentrations of reproductive and thyroid hormones in premenopausal women

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The impact of BMI, exercise, smoking, drug and alcohol use on reproductive and thyroid hormones has little or conflicting evidence. We therefore aimed to investigate the association between these factors and serum hormone concentrations. Capillary blood samples were taken from 932 eumenorrheic Hertility Health users on menstrual cycle day 3 between Sept 2020 and June 2022. Serum concentrations of Anti-Müllerian hormone, Estradiol (E2), Luteinising

Hormone (LH), Follicle-Stimulating Hormone, free Thyroxine, Thyroid-Stimulating Hormone (TSH) and Prolactin (Prl) were measured via chemiluminescence immunoassay. Women self-reported their height, weight, exercise frequency, weekly alcohol consumption, recreational drug use and smoking status. Women with PCOS or premature ovarian insufficiency were excluded from analysis. Following stratification into two age groups (18-30 and 31-40), data was log-transformed and the Pearson correlation coefficient (r) between pairs of variables was calculated; P values <0.05 were considered statistically significant. In 18-30 year olds, BMI negatively correlated with E2 ($r=$-0.13, $P=0.02$, $n=308$) and LH ($r=$-0.24, $P<0.01$, $n=306$) and positively correlated with TSH ($r=0.12$, $P=0.04$, $n=292$). Exercise frequency positively correlated with LH ($r=0.16$, $P=0.02$, $n=201$) and drug use negatively correlated with Prl ($r=$-0.2, $P=0.02$, $n=151$). In 31-40 year olds, BMI negatively correlated with E2 ($r=$-0.11, $P<0.01$, $n=548$), LH ($r=$-0.20, $P<0.01$, $n=545$) and Prl ($r=$-0.12, $P=0.03$, $n=352$). These data suggest BMI has a weak but significant negative association with reproductive hormones and a weak positive association with TSH. Exercise frequency and drug use have a small positive association with reproductive hormones, whilst alcohol consumption and smoking status did not appear to have a significant impact. Further investigation into these associations is necessary.

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P357

The rapeutic potentials of *Vernonia amygdalina* in letrozole and high-fat diet induced polycystic ovary syndrome in female wistar rats

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Polycystic ovary syndrome (PCOS) is an endocrine disorder that is common among women in their reproductive ages. This condition is associated with insulin resistance, oxidative stress, hormonal imbalance, and inflammation. Various drugs are used in treating this disorder but with side effects, hence the need for an alternative treatment with minimal side effects. This study was aimed at investigating the effect of methanol extract of *Vernonia amygdalina* on the reproductive hormones and insulin levels, inflammation markers and oxidative stress in PCOS rats. In this study, 25 female Wistar rats were divided into 5 groups ($n=5$): control, PCOS control, treated groups (200 and 400 mg/kgbw methanol extract of *Vernonia amygdalina*), standard group (metformin and clomiphene citrate). PCOS was induced by oral administration of 1 mg/kgbw letrozole dissolved in 0.5% carboxymethylcellulose (CMC) and high fat diet for 28 days. The treatment groups were treated with the extract for 2 weeks and thereafter, the ovaries were removed, weighed, and subjected to histopathological studies. Serum reproductive hormone levels, antioxidant activities, lipid profile, anti-inflammatory and insulin levels were evaluated. Extract of *Vernonia amygdalina* significantly reduced LH ($P=0.0001$), increased FSH ($P=0.0001$), and progesterone levels and had no significant change in estradiol and testosterone levels in comparison with the PCOS control group. Treatment with *Vernonia amygdalina* reduced IL-6, CRP and TNF-α levels. There was a significant decrease ($P=0.009$) in MDA level but no significant difference in CAT and SOD levels after treatment with Vernonia amygdalina compared with the PCOS control group. Groups treated with *Vernonia amygdalina* had significant reductions ($P=0.0001$) in triglycerides, LDL-C ($P=0.0001$), insulin levels ($P=0.0009$) and significant increase ($P=0.009$) in HDL-C level. The ovarian weight and cysts were significantly reduced after treatment. Extract of *Vernonia amygdalina* could be used in the management of some conditions associated with PCOS.

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P358

The reproductive years: the experience of women attending routine diabetes care

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Reproductive morbidity is increased in women with diabetes, including a higher prevalence of polycystic ovary syndrome, hypothalamic amenorrhoea and premature ovarian failure. Routine discussion of reproductive and menstrual dysfunction for women with diabetes remains a peripheral feature of clinical consultations. Here we aimed to determine women's own reproductive care experience. We surveyed women of all ages attending routine diabetes care using a detailed clinical questionnaire. Participant experience of discussion of menstrual history, contraceptive use and preconception advice in routine clinical consultations was determined. 54 women completed the survey. The median age was 37.5 years (IQR 23-51) with a median BMI 27.4 kg/m^2 (IQR 22.5-31.2). 44 (82%) and 10 (18%) had type 1 (T1DM) and type 2 diabetes (T2DM), respectively. Median HbA1c was 58 (IQR 53-70) mmol/mol. Patients were living with diabetes for a median of 13.2 ± 14.0 years. 38% had Type 1 diabetes (T1DM) prior to menarche. There was no significant difference in age of menarche in those diagnosed with T1DM before menarche compared to those diagnosed after menarche ($P=0.64$). 65% of respondents were premenopausal ($n=34$). 47% of this group recalled discussing their menstrual cycle during consultation, while just 41% reported awareness of preconception advice ($n=14$). Oral contraceptives had been used by 68.5%. 33.2% had previously utilized contraceptive implant or injection, while an intrauterine device had been used by 23%. 16.7% of total respondents had experienced miscarriage. Overall, 77% of women reported regular menstrual cycles. Participants with T1DM reported a high prevalence of both hirsutism and acne at 38.6% and 31.8%, respectively. Consensus statements recommend greater awareness and recognition of reproductive issues facing women with type 1 diabetes. This survey highlights the need to reinforce preconception counselling. The high prevalence of hirsutism and acne in this cohort should prompt consideration for biochemical evaluation for androgen excess in this population.

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P359

A rare case of male infertility; *XX male syndrome*…

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Introduction
The XX male syndrome occurs in 1 in 20,000 births. This syndrome results from crossover between the X and Y chromosomes, which transfers the sex-determining region of the Y chromosome to the X chromosome. They lack the azoospermia factor region of the Y chromosome, which is essential for spermatogenesis; thus causing infertility.
Case Description
34-year-old gentleman was referred to endocrinology clinic for infertility and semen analysis showing azoospermia. He had symptoms of hypogonadism and examination showed normal male phenotype with small testes. Investigations showed hypergonadotropic hypogonadism, hence Klinefelter's syndrome was suspected and karyotyping requested. Karyotype analysis revealed a 46,XX karyotype. Further testing by (QF)-PCR was consistent with the presence of two X chromosomes but also indicated the presence of material from the distal region of the Y chromosome short arm. This included the SRY (sex-determining region Y) gene locus and FISH studies for the X chromosome centromere and SRY confirmed a picture of two X chromosomes, one of which contained SRY. A review of the karyotype showed a consistent dark band at the distal end of the short arm of one X chromosome, representing band Yp11.3 from the Y chromosome which contains the SRY gene locus. Therefore, one copy of the X chromosome in this patient's karyotype is actually a derivative X chromosome resulting from a translocation between the short arms of an X chromosome and a Y chromosome. Diagnosis and prognosis of infertility was explained to the patient with genetic counselling. He was then started on testosterone replacement.
Discussion
XX males are phenotypically similar to Klinefelter's males. They have small testes, azoospermia, infertility, and seminiferous tubule hyalinization. They both present with hypergonadotropic hypogonadism. However, men with this disorder have below average height and do not have intellectual impairment unlike Klinefelter's males.

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P360

Reduced accuracy of gold top blood collection tubes for reproductive hormone profiling in capillary blood samples

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While evidence of concordance between reproductive hormone measurements in venipuncture and capillary serum exists, variation between blood collection tubes has not been investigated. We compared the performance of two capillary and venipuncture blood collection tubes (red and gold top) and assessed variation between two leading tube manufacturers. To compare tube types, venipuncture and finger prick capillary samples were concurrently collected from 11 premenopausal women in red and gold top tubes. In all four sample types, serum concentrations of Anti-Müllerian Hormone (AMH), Estradiol (E2), Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH) were measured via chemiluminescence immunoassay. To compare capillary tube manufacturers, the same hormones were measured in a second cohort of 8 premenopausal women using Greiner and Becton Dickinson (BD) red top tubes. Data was log-transformed prior to statistical analysis via paired t test and subsequent Cohen's d (d) to calculate effect size; P values = <0.05 were considered significant. Gold top capillary tubes produced higher AMH ($P<0.001$, d = 0.12), FSH ($P<0.001$, d = 0.30) and LH ($P<0.001$, d = 0.29) measurements compared to gold top venipuncture tubes. Measurements of AMH ($P<0.001$, d = 0.22), FSH ($P<0.001$, d = 0.29) and LH ($P=0.008$, d = 0.13) were higher and E2 measurements were lower ($P=0.012$, d = 0.34) in gold top compared to red top capillary tubes. No significant differences were found between red top capillary tubes and venipuncture tubes. Greiner red top tubes produced moderately lower E2 measurements than BD ($P=0.046$, d = 0.04), however no other significant differences were found. This suggests that gold top, but not red top, capillary blood collection tubes yield significantly different measurements than venipuncture tubes and measurements are not manufacturer-dependent. Further investigation into gold top tubes is required.

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P361

Genomic imprinting and maternal adaptations to pregnancy

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In late pregnancy the mother must mobilise considerable energy stores to support fetal growth. Failure to appropriately nourish the fetus has significant obstetric consequences – gestational diabetes and fetal growth restriction (FGR). Despite this, relatively little is known about how metabolic responses are stimulated in the mother, and how they may go wrong. We previously found that high levels of the product of an imprinted gene, *Delta-like homologue-1* (*Dlk1*), circulate in maternal blood in late gestation, and that the fetus is the source of this protein. By manipulating maternal DLK1 levels in mice we demonstrated that DLK1 is a fetal signal that mediates the maternal response to starvation by activation of the ketogenic pathway. We hypothesised that low DLK1 might be a clinically relevant marker to predict restricted growth in human pregnancy, and indeed found that low DLK1 is associated with FGR. Our first case-control study finding has since been replicated by others, and in our larger population-based study. We are currently exploring how the *cis*-regulatory landscape influences *Dlk1* expression in both normal development and disease, and investigating the molecular physiology of DLK1 signalling. We will present data that indicates that DLK1 has a direct impact on placental hormone production and that as a consequence, alteration of Dlk1 gene dosage impacts maternal adipose storage and mobilisation - key processes that ensure adequate nutrient provision to the growing fetus.

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P362

Clinical utility of GnRH analogues in female androgen excess: diagnostic and therapeutic implications

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Rare causes of severe androgen excess (AE) can present a diagnostic challenge to endocrinologists. Imaging may not identify occult ovarian pathology, and the detection of adrenal nodular disease may be indicative of incidental pathology. GnRH analogues can be used both as a medical treatment and as a diagnostic utility to confirm ovarian source, particularly in women with a preferential elevation of serum testosterone (T). In this case series, we present three cases highlighting the dual clinical applications of GnRH analogues. Case 1: Diagnostic Utility of GnRH Analogues 68-year-old female presenting with a four-year history of symptoms suggestive of severe AE with virilisation and T of 50 nmol/l (0-1.7). Following GnRH administration, T was completely suppressed, indicating a benign ovarian process. She was referred for surgery based on ultrasound findings of an ovarian mass. Histology confirmed a benign ovarian steroid cell tumour. Case 2: Therapeutic Application of GnRH Analogue 25-year-old female with severe insulin resistance syndrome due to acquired partial lipodystrophy presented clinically and biochemically with severe AE. After administration of triptorelin 3 mg, androgens were completely suppressed with significant clinical improvement in symptoms. She continues on maintenance GnRH therapy with add-back oestrogen and progesterone. Case 3: Combining Diagnostic & Therapeutic Application of GnRH Analogue 67-year-old presenting with a 15-year history of symptoms of postmenopausal AE without virilisation. A non-contrast adrenal CT showed a nodule. However, a GnRH suppression test confirmed ovarian aetiology. The patient wished to avoid surgery and proceeded with a therapeutic trial of GnRH and subsequent long-term use. This resulted in a significant improvement in symptoms. GnRH analogues desensitise and downregulate the gonadotrophs in the pituitary gland, inhibiting oestrogen and androgen secretion. GnRH analogue suppression is an important clinical tool that improves diagnostic accuracy as well as symptom burden for women with severe AE due to ovarian disease.

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P363

Turner Syndrome with 45X gene presenting with Menorrhagia: A diagnostic dilemma

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Turner syndrome (TS) is the most common chromosomal anomaly in females and its occurrence is about 1:4000 live births. This is the only monomer disease that humans can survive (1). It is characterized by the presence of one X chromosome and a partial or complete loss of the second X chromosome. Clinical features of TS can vary, mainly classified into Growth failure, gonadal insufficiency, cardiovascular diseases, or learning disabilities. Short stature is the only phenotypic abnormality that presents in virtually all patients with turner syndrome (2). Patients with incidental findings of turner syndrome have had significantly fewer phenotypic features and cardiac defects (3). Here we present Ms. C, a 16-year-old girl, who presented with menorrhagia, diagnosed with Turner syndrome during a routine evaluation for an incidental finding of short stature. She was noted to be shorter than her peers since childhood and did not seek medical advice. She attained normal menarche at the age of 13 and has been having frequent heavy cycles since then which required repeated blood transfusions. Her height was 119 cm (Mid parental height was 143 cm). She had a webbed neck and a wide carrying angle, otherwise, the examination was nil significant. Karyotyping examination resulted in a 45X chromosomal pattern with a negative SRY gene. About 15-20% of patients with TS go through spontaneous puberty and only half of them complete it with menarche which usually ends up in secondary amenorrhea (4). A small number of patients have regular menstrual cycles and ovarian function (5) and interestingly there are very few reported cases of menorrhagia, thus implying it is exceedingly rare (5). This is a good learning point, that any female with short stature, irrespective of other features, should be evaluated for TS.

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Thyroid

P131

Therapeutic database of anti-thyroid medication over 10 years in northern ireland (NI) 2010-2019: trends, demographics and deprivation

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Anonymised therapeutic data has been available for all patients in NI across 364 general practices since 2008. The database records age, gender, trusts and postcodes, which allows for spatial deprivation analyses. Patients were categorised in deciles (1-most deprived, 10-least) according to published criteria. We examined carbimazole (CBZ) and propylthiouracil (PTU) prescriptions over 10 years (2010 to 2019). Patients treated definitively with surgery/radioiodine are invariably pre-treated with anti-thyroid medication in NI and so are captured in this database. The median age of the population in NI in mid-2019 was 38.9 years (vs 43.7y for European Union). The number of patients in NI prescribed CBZ/PTU was ~4000 patients/year or ~0.2% population (3,760 in 2010 with population of 1.80million; 4,025 in 2019 with pop of 1.89million). This is lower than published prevalence estimates (including subclinical disease) of ~0.8-1%. There was a modest reduction (4%) over 10 years from what would have been expected, when controlled for change in demographic structure. In 2019, females accounted for 80% of patients. The standardised incidence ratio was maximal in 35-44 year group. Patients aged 0-24 years accounted for 32% of the general pop vs 3% (113) of patients on treatment. CBZ and PTU represented 93% and 7% of prescription items, respectively. Of those prescribed PTU, 89% were female. The proportion of patients on anti-thyroid medications was modestly but persistently higher in the more deprived cohort deciles (Z testing $P<0.05$). This is in keeping with a previous report from Birmingham describing deprivation as an independent risk for thyroid dysfunction among 20 general practices. The reason(s) for changing medical treatment rates and deprivation differences require exploration (eg definitive treatment rates, environmental factors). This database offers a caveated resource for following overt and treated hyperthyroidism rates, generating hypotheses and commissioning services such as transition clinics.

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P132

Reconsidering the role of thyroidectomy in thyroid eye disease (TED) patients

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Purpose
Graves' disease is an autoimmune condition that can cause hyperthyroidism and thyroid eye disease (TED). Definitive treatment is required in approximately 50% patients. Thyroidectomy remains the least chosen primary treatment (2%-18%) despite it having the highest cure rate (>95%). Our aim was to determine the current relationship between patients' TED and thyroidectomy in a multidisciplinary specialist eye clinic at a tertiary referral centre.
Methods
A retrospective review of medical records was performed for patients who underwent total surgical thyroidectomy at Oxford University Hospitals and/or were diagnosed with TED by the Oxford TED clinic between Jan 2011 – Nov 2019. Patients were divided into 3 groups for the purpose of data analysis: (1) all patients who underwent total thyroidectomy for non-malignant thyroid pathology, (2) all patients diagnosed with TED and (3) patients diagnosed with TED who underwent thyroidectomy. Patient demographics, smoking status, age at diagnosis, TED severity and medical therapy were recorded. Exclusion criteria included patients younger than18 years, incomplete data, thyroidectomy for neoplasia and no MDT-confirmed diagnosis of TED.
Results
Overall, 248 patients were included: 129 underwent thyroidectomy (Group 1), 168 were diagnosed with TED (Group 2), and 49 patients diagnosed with TED underwent thyroidectomy (Group 3). 29% of TED patients underwent a thyroidectomy. 38% of thyroidectomy patients had documented TED. Of all patients who underwent thyroidectomy, those with TED were significantly older (47 vs. 37 years, $P<0.01$) and more likely to smoke (47% vs. 28%, $P<0.01$).
Conclusions
This study demonstrates a paradigm shift in use of thyroidectomy in TED patients with double the proportion of TED patients undergoing thyroidectomy compared with similar studies pre-2015. Possible reasons include increasing use of an MDT TED approach, improved surgical thyroidectomy technique and access to thyroidectomy and reduced use of radioiodine in TED.

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P133

Comparison of supervised rapid thyroxine absorption test in refractory and well-controlled primary hypothyroid patients in a tertiary care center in Sri Lanka and formulation of a prediction model to predict the expected FT4 rise during the test

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Introduction
Refractory hypothyroidism is associated with significantly increased morbidity and healthcare costs. During the evaluation of refractory disease, a thyroxine absorption test is frequently performed using different protocols. We assessed the usefulness of the supervised rapid thyroxine absorption test in a low-resource setting and formulated a useful model to determine the expected FT4 rise in hypothyroid patients without known malabsorption.
Methods
A cross-sectional study was performed comparing 24 cases of refractory hypothyroidism (TSH > 4 mIU/l on thyroxine >2 micrograms/kg/day) without known malabsorption and 25 controls (normal TSH on thyroxine <1.6 micrograms/kg/day). Data on baseline characteristics and medication history were collected. A supervised rapid thyroxine absorption test was performed in both groups giving oral levothyroxine 1000 micrograms after 10 hours fast. Serum TSH at baseline (0 hours) and FT4 at 0,1,2,3,4,5 hours following thyroxine ingestion were analyzed.
Results
There was no statistically significant difference in FT4 levels during absorption test in both groups. Males had a higher thyroxine absorption rate than females ($P=$ value $= 0.0136$). Higher baseline TSH was associated with reduced absorption rate. (P value $-=0.0002$). After pooling all absorption tests of both groups, it showed a gradual FT4 rise until 4 hours and plateaued thereafter.
Mean FT4 rise from the baseline (95% CI):
Conclusion
There was no statistically significant difference in thyroxine absorption in refractory and well-controlled hypothyroid patients in this cohort. The new model would be useful in a low-resource setting where, measurement of FT4 only at 0 and 4 hours and calculating the percentage rise of FT4, can be used to exclude pseudo-malabsorption in refractory hypothyroidism.
Table 1

Hours after thyroxine ingestion	Mean percentage rise from the baseline (0 hours)	95% CI
1	52.1%	40.2% - 64%
2	104.3%	88.0% - 121%
3	149.4%	128.4% - 170.5%
4	152.7%	136.7% - 177.7%
5	156.9%	133.8% - 180.0%

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P134

High TRAB at the Time of Radio-iodine therapy (RAIT) Predicts Persistent Hyperthyroidism

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Background and Aim
RAIT has a high success rate in achieving cure of hyperthyroidism but there is unpredictability of thyroid status during the initial post-RAI period, making it

difficult to counsel patients or plan medical therapy. We assessed the role of updated TRAB level at the time of RAIT in predicting persistent post-RAI hyperthyroidism.
Patients and Methods
We measured TRAB at the time of RAIT (fixed 550MBq dose) in 26 patients with Graves' disease. Patients were followed-up at 6, 12, 24 weeks and as required. Post-RAI antithyroid agents were started only if required. We recorded demographic data, thyroid function and antithyroid agent use at each visit. Thyroid status was correlated to age, gender, T4 at diagnosis and TRAB at RAIT.
Results
20% males, mean age 49 years; T4 and TRAB at diagnosis and at RAIT were 33 pmo/l, 15 pmo/l, 10 IU/l and 9.4IU/l respectively. Patients with persistent post-RAIT hyperthyroidism had a significantly higher mean TRAB at RAIT as compared to those who were not hyperthyroid at 6 and 12 weeks (23.4 v 4.3 IU/l and 17.1 v 7.1IU/l; $P<0.05$, respectively) and patients with TRAB >6IU/l were more likely to be hyperthyroidism at this stage (chi square; $P<0.05$). Patients who were hyperthyroid at 24 weeks requiring a second dose also had a higher mean TRAB (12.7 v 8.6IU/l), but this was not statistically significant.
Conclusions
TRAB of >6IU/l at the time of RAIT allows us to predict persistent hyperthyroidism until 4 months post-RAI and may prompt clinicians to start proactive antithyroid therapy. We also believe that with the inclusion of higher number of patients we would be able to predict hyperthyroidism at 6 months and early consideration of second dose of RAIT. Untreated T4 level at diagnosis is also predictive but is often not available at the time of RAIT

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P135

Thyroid function testing in people treated with Lithium: We are doing more thyroid tests than is necessary

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Introduction
Lithium is a common pharmacological intervention for the treatment of bipolar affective disorder and is advocated by clinical practice guidelines (NICE 2021). Blood test monitoring is essential for management of lithium treatment and UK NICE guidance recommends 6-monthly serum testing of thyroid function. We here examine conformity to guidance and the consequences of monitoring outside these intervals.
Methods
We extracted serum lithium/thyroid hormone results at one centre Jan 2009-Dec 2020. We identified 266 patients who started lithium during this period with no history of thyroid abnormality within the previous 2 years and were at risk of developing thyroid abnormalities. We determined interval between tests, time between onset of lithium testing and first TSH outside laboratory reference range and assessed the impact of testing outside recommended 6-monthly intervals.
Results
The most common testing frequency was 3-monthly ($\pm$1month), accounting for 37.3% of test intervals. Kaplan-Meier analysis showed that most thyroid dysfunction manifests within 3 years (proportion with abnormal TSH at 3 years = 91.4%, 19.9% of total patients). In the first 3 months from commencing lithium therapy, 8 patients developed subclinical hypothyroidism and had clinical follow-up data available. Of these, half spontaneously normalised without clinical intervention. In the remaining patients, thyroxine replacement was only initiated after multiple episodes of subclinical hypothyroidism (median2 years after initiating lithium, range 6 months-3 years).
Conclusions
Our data suggest that thyroid function tests are typically requested too frequently in patients on lithium, potentially resulting in over-diagnosis of thyroid abnormalities. 90.4% of TSH tests were outside the recommended 6-monthly ($\pm$1 month) interval. There was no evidence that early detection of abnormal thyroid results leads to earlier treatment. The initial thyroid dysfunction spontaneously resolved in half of cases without intervention. Importantly more than 90% of patients who developed thyroid dysfunction did so within three years of commencing lithium.

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P136

Evaluation of Prevalence and Causes of Thyroid dysfunction in Hospitalized Patients

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Aim
To evaluate thyroid dysfunction in all patients admitted to hospitals in Aneurin Bevan University Health Board (ABUHB) from October 2019 to September 2021.
Method
This report is based on a retrospective observational study of the thyroid tests and case notes of 95 patients admitted to all the hospitals under ABUHB for acute concerns (other than thyroid dysfunction) over 2 years.
Results
In-Patient scanned notes and pathology results were reviewed to identify all patients having TSH <0.01. A total of 95 patients were identified, out of which 26 were found to have sub-clinical hyperthyroidism, and 69 were overtly hyperthyroid. Of the sub-clinical group, 12 of the 26 patients were found to have thyroid antibodies – 6 TRab/TSI, 2 TPO, and 4 positive for both TRab and TPO, but a total of 15 of the 26 patients were known to have thyroid dysfunction previously. Causes of previous thyroid illness included – Graves' disease, Multi-nodular Goitre, Hypopituitarism, Thyroiditis and Thyroid cancer. Mortality was significantly higher (30.7%) in the sub-clinical group, as compared to 13.04% in the hyperthyroid group. History of thyroid dysfunction and gestational thyroid dysfunction was noted to be similar in both groups.
Conclusion
Thyroid dysfunction is common in patients admitted to hospital in acute settings, with most of them having Graves' disease. This study also highlights significant mortality in these patients. Further studies are needed to ascertain the extent and nature of this correlation and its implications.
Analysis of the 2 groups revealed

	Sub-clinical hyperthyroid group 26 of 95(27.4%)	Hyperthyroid Group 69 of 95 (72.6%)
Gestational	1 (3.8%)	3 (4.3%)
	15 (57%)	42 (60.8%)
History of thyroid illness previously		
• Graves	10	36
• MNG	1	2
• H ypopituitarism	1	0
• Thyroid Cancer	3	0
• Thyroiditis	0	4
Mortality		
• Within one month	8 (30.7%)	9 (13.04%)
of this admission	3 (37.5%)	5 (55.5%)

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P137

Treatment-refractory hypothyroidism probably secondary to concurrent phenytoin administration

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Introduction
Persistent symptoms of hypothyroidism or raised levels of thyroid stimulating hormone (TSH) despite adequate levothyroxine replacement (>1.6 µg/kg body weight) suggest treatment-refractory hypothyroidism. Adherence to treatment and conditions that might impair absorption or increase demand for levothyroxine should be explored.
Case
A 51-year-old man presented with raised TSH levels despite being on 425 mg daily of levothyroxine. He had total thyroidectomy performed for follicular thyroid cancer 14 months prior. He took his levothyroxine regularly before breakfast. Other medical history included epilepsy and hypertension, for which he took phenytoin 400 mg daily and ramipril 10 mg daily. He had been seizure-free since childhood. He weighed 114 kg.
Investigations and management
His serum TSH level was 17.1 mU/l (normal range: 0.3-4.1), free thyroxine of 16.7 pmo/l (12-22), and free triiodothyronine of 3.4 pmo/l (3.1-6.8): similar

results for the past year. Other blood results, including malabsorption screening were normal. There was no assay interference. A supervised levothyroxine administration test did not demonstrate any improvement. The timing of levothyroxine administration was changed to bedtime but did not make any difference. The patient would not consider an alternative anti-epileptic because he feared a seizure relapse and losing his driving license. While on 600 mg daily of levothyroxine, his TSH was 18.4 mU/l. The patient decided to change the timing of levothyroxine administration to 02:00 in the morning and keep his phenytoin to 07:00. His TSH level improved to 4.91 mU/l at three months and to 0.29 mU/l a year later.

Discussion

The elimination half-life of phenytoin is about 22 hours. Phenytoin is a potent inducer of hepatic cytochrome P450 enzymes responsible for thyroid hormone metabolism. Phenytoin may also displace thyroid hormones from the binding globulins. Patients need advice concerning timing of levothyroxine administration when co-administered with phenytoin.

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P138

Antithyroid Arthritis syndrome: A rare side effect

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Carbimazole is one of the most commonly prescribed endocrine medications. There are a wide range of side effects associated including bone marrow disorders, severe cutaneous reactions, agranulocytosis and vasculitis. There have been few reports of anti-thyroid associated arthritis, described as migratory arthritis with prompt resolution following medication discontinuation. Side effects reported in British national Formulary and Electronic Medicine Compendium include myopathy but not inflammatory arthritis. We present a case of 56-year-old lady found to have Graves' thyrotoxicosis with background of eosinophilic asthma, primary biliary cirrhosis and Sjogren's syndrome. After starting 20 mg carbimazole she complained of swollen and painful joints spreading between different locations, muscle aches and dark urine with worsening mobility. Investigations demonstrated ESR 119, CRP 126, TSH receptor antibody 4.2, TSH <0.01, T4 30.9 pmo/l, T3 12.4 pmo/l, ANA/ANCA/ENA negative. Carbimazole was stopped by the patient with rapid resolution of symptoms. Inflammatory markers subsequently normalized. She was given low dose of propylthiouracil which was tolerated well and opted for early radioactive iodine treatment in view of underlying liver disease and concern about side effects.

Conclusion

It is important to recognize migratory arthritis as a potential side effect and differentiate from vasculitis which can manifest similarly. This case demonstrates the investigations required in differential diagnosis of these symptoms and highlights the improvement seen with drug withdrawal. Patients with thyroid disease often experience a multitude of symptoms and it is important for physicians to be able to recognize those that may relate to therapy rather than underlying disease.

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P139

A rare case of Hashimoto's encephalopathy

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Introduction

In rare but severe cases, Hashimoto's thyroiditis can present with neurological manifestations including stroke-like episodes, cognitive decline, neuropsychiatric symptoms, and coma. This is referred to as Hashimoto's encephalopathy which is characterized by high titers of antithyroid peroxidase antibodies and is responsive to steroids. Herein, we present a case of a patient with acute onset aphasia, altered mental status with progression to respiratory distress and intubation who was promptly identified to have Hashimoto's encephalopathy and treated with steroids.

Case description

A 59-year-old female with a history of ESRD presented with acute onset aphasia, confusion and involuntary body shaking. Due to lab abnormalities meningoencephalopathy initially considered however patient was unresponsive to antimicrobial therapy. Further lab studies, LPx2, MRIx2 did not support infectious etiology. Patient became increasingly agitated and hypertensive requiring precedex, nicardipine drip and transfer to ICU where she was subsequently intubated for airway protection. Labs noted elevated TSH at 10.5 with normal free T4 at 1.2, and elevated TPO-Ab at 2100. In absence of alternate etiology Hashimoto's encephalopathy was considered and she was started on three-day course of 1g Solumedrol. She was successfully extubated on the third day and her mental status returned to baseline with resolution of all symptoms. Patient was eventually discharged home on steroid taper.

Discussion

Hashimoto's encephalopathy remains a diagnosis of exclusion. Although a strong association with autoimmune thyroid disease exists, the etiology of Hashimoto's encephalopathy still remains unclear. More than 60% of the cases in literature are noted to either clinically euthyroid or subclinically hypothyroid. Taking this into account, the value of high antithyroid antibodies may less likely be pathogenic and may be better utilized as a marker of treatment response instead. Further research regarding this disease process is therefore required in pursuit of clear guidelines for diagnosis and treatment.

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P140

Review of Nottingham University Hospital Antenatal Thyroid Service for Patients with Autoimmune Hyperthyroidism

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Background

Nottingham University Hospitals (NUH) has a joint endocrine/antenatal clinic to manage autoimmune hyperthyroidism in pregnancy, with the aim of close monitoring and management.

Aim

To review service according to NUH standards (Pregnant Women with Thyroid Dysfunction):

1. At 20 weeks if thyrotoxic/on antithyroid drugs (ATD)/post radio-iodine or surgery, check thyrotropin receptor autoantibodies (TSHRAb).
1. If >3x upper limit of normal (ULN), arrange foetal monitoring
2. At 30 weeks repeat TSHRAb if previously >3xULN and continue foetal monitoring
2. Check thyroid function test (TFT) every 4 weeks when on ATD, using lowest dose to maintain TFT normal/borderline high.
3. Inform neonatologists if TSHRAb ≥ 1.0 IU/l.
4. Check TFT at 6 weeks.

Results

Between April 2019-March 2021, 33 patients were seen in endocrine/antenatal clinic with a diagnosis of autoimmune hyperthyroidism.

1. All patients (33/33 100%) had TSHRAb antibodies measured in 2nd trimester.
1. 6 patients had raised TSHRAb antibodies (>3xULN). 100% of these had foetal monitoring.
2. All patients with raised TSHRAb antibodies continued to have foetal monitoring in 3rd trimester. 3/6 patients had TSHRAb antibodies remeasured in 3rd trimester (1 premature birth).
2. 17/33 patients were on ATD in their pregnancy. 11/17 continued on ATD throughout pregnancy. 100% of these patients had TFT checked roughly every 4 weeks and were on lowest dose to maintain TFTs normal/borderline high.
3. All babies born to patients with raised TSHRAb antibodies (6) had TFTs checked in neonatal period as neonatologists were informed. 1/6 of these babies had neonatal thyrotoxicosis.
4. 25/32 had 6 week TFT check (1 patient OOA). Of the 7 not checked, 5 were documented in clinic letters for GP to do so.

Conclusion

The standards laid out in the clinical guideline are followed in clinical practice in the joint antenatal/endocrine thyroid clinic.

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P141

Are we following NICE guidelines in classifying hyperthyroid patients presenting to endocrinology clinic in a DGH?

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Background

Nice guideline recommends using TSH receptor antibody as a tool for classification of hyperthyroid patients; and considering technetium scanning of the thyroid gland if

TRAbs are negative. Early diagnosis of TED is also essential for treatment to be effective. The most common way to assess the severity of TED is to use the Clinical Activity Score (CAS) 7-point scale.
Objectives
We aimed to evaluate if hyperthyroid patients are classified correctly and timely as per NICE guidelines. Also, to check if CAS score was done to assess severity of TED and referring to ophthalmologist was considered.
Methodology
Retrospective electronic case notes review of 33 patients who were seen for the first time in the endocrinology clinic and diagnosed with hyperthyroidism between 31/08/2020 to 31/08/2021. These patients had been transferred from consultant clinic to endocrine pharmacist's thyroid clinic after their first appointment.
Results
$n=33$ (thyrotoxic patients reviewed in endocrinology clinic), TRAb was recorded for total 30 patients, among them 15 had TRAb done prior coming to the clinic. It was checked within 2 months for 13 patients and within 4 months for 2 patients. CAS score was done in total of 12 patients. Referral to ophthalmology was done for 3 patients. 29 patients were started on Carbimazole. 2 patients on Propylthiouracil, 2 patients were not started on any medication. 23 patients which is almost 70% had a review in thyroid clinic within 3 months of first clinic appointment.
Discussions
1. While 90% had a TRAb test within 120 days since presentation, but there is room for improvement to make it as close as possible to 100% as recommended by NICE.
2. We should focus on calculation of CAS score as it helps in identifying thyroid eye disease patients. As missing the TED can have serious consequences on patient safety.

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P142

Thyroid storm triggered by RSV pneumonia

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A 42-year-old lady, with a diagnosis of Graves' disease presented with a day's history of fever, cough, coryzal symptoms and diarrhoea. Being diagnosed with Graves' disease in 2015, she had been poorly compliant with ATDs. Prior to this presentation, her last FT4 was 31.4 pmo/l with a suppressed TSH. She was intermittently taking propylthiouracil (was intolerant of carbimazole). She had refused RAI and preferred surgery, but hadn't been keeping up with her ENT appointments. On assessment, she was a bit agitated, pyrexial, tachycardic with crackles being auscultated over the left base. Chest X-ray confirmed a left basal consolidation, her FT4 was 62.1 pmo/l, FT3 was 7.7 pmo/l with a suppressed TSH, and the Burch-Wartofsky score was 55, thus suggestive of thyroid storm. Basic investigations for the aetiology of the pneumonia were sent off. She was started on antibiotics along with intravenous fluids, high doses of propylthiouracil, hydrocortisone, propranolol and potassium iodide. After 48 hours her FT4 had reduced to 49.3 pmo/l, which then normalised by Day 6 of presentation. Simultaneously, her clinical parameters started improving. The result of the viral throat swab was positive for RSV A and B. Since this usually requires symptomatic treatment in immunocompetent individuals, the antibiotics were stopped. The steroids, potassium iodide and beta blockers were omitted once she was clinically and biochemically euthyroid and the propylthiouracil was reduced to her usual maintenance doses. Periodic monitoring of her FT4 showed that she continued to be euthyroid biochemically. Thyroid storm is a rare but potentially fatal condition. Although it can develop in patients with longstanding untreated/irregularly treated hyperthyroidism, it is often precipitated by an acute event such as thyroid or nonthyroidal surgery, infection or an acute iodine load. We believe the RSV infection, coupled with the poorly treated Graves' led to thyroid storm.

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P143

A delayed diagnosis of Graves' disease in a patent with severe hyperthyroidism-associated hypercalcaemia

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Introduction
Mild hypercalcaemia can occur in patients with Graves' disease. Postulated mechanisms include increased bone resorption and mobilisation of calcium from the bones in response to increased interleukin-6 and catecholamine levels. The coexistence of primary hyperparathyroidism and Graves' disease is rare. Hypercalcaemia with suppressed or unsuppressed parathyroid hormone levels should prompt a search for non-parathyroid or parathyroid causes, respectively.
Case
A 71-year-old man presented with a history of vomiting and confusion for ten days, and weight loss of 24 kg over ten months. His medical history included ischaemic heart disease and type 2 diabetes. His usual medications included metformin, aspirin, alogliptin, ramipril, simvastatin and lansoprazole. He was a non-smoker. Examination revealed dehydration and mild confusion.
Investigations and management
His serum calcium was 3.19 mmol/l with an unsuppressed (normal) parathyroid hormone level of 4.1 pmo/l. Full blood count, serum electrophoresis, phosphate, renal and kidney function were normal. Urinalysis ruled out hypocalciuric hypercalcaemia. Chest x-ray and electrocardiogram were normal. Total body imaging ruled out underlying neoplasia. After rehydration, the patient was discharged from hospital. Parathyroid imaging (ultrasound, sestamibi, 4D-CT) and bone density scan were normal. However, he was readmitted three weeks later with a serum calcium of 3.16 mmol/l. Subsequent tests revealed a serum thyroid stimulating hormone of 0.01 mU/l, free thyroxine of 35.7 pmo/l, free triiodothyronine of 11.3 pmo/l, and raised thyroid receptor antibodies (TRAb), indicating Graves' disease. He was started on Carbimazole 20 mg daily for the hyperthyroidism. His calcium levels returned to normal once his thyroid function was under control.
Conclusions
This patient had hyperthyroidism-associated hypercalcaemia. The diagnosis of Graves' disease was delayed during the search for other causes of severe hypercalcaemia. This case emphasises the importance of thorough history taking and remembering hyperthyroidism as a cause of hypercalcaemia.

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P144

Human chorionic gonadotropin (hCG) mediated thyrotoxicosis secondary to metastatic choriocarcinoma

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This female patient presented acutely with headache and neck pain associated with vomiting. Neurological examination was normal. Urine pregnancy test prior to imaging was unexpectedly positive. CT head demonstrated a 2.5x1.5 cm hyperattenuating lesion at the left frontoparietal region. Thyroid function tests were in keeping with thyrotoxicosis (TSH <0.01 mU/l, free T4 37.2 pmo/l, free T3 >30.7 pmo/l). Antithyroid medication was commenced and TSH receptor antibody requested. Serum human chorionic gonadotrophin (hCG) was markedly elevated. Ultrasound abdomen identified no evidence of pregnancy, raising the suspicion of an hCG-secreting tumour. CT thorax, abdomen and pelvis identified a right lower lobe subpleural lung mass with bilateral lung nodules and low attenuation lesions of the liver, kidneys and spleen, highly suspicious for metastases. MRI head identified multiple intra-axial enhancing lesions. Liver biopsy histology identified metastatic choriocarcinoma. Unfortunately, the patient deteriorated developing anaemia and haemoptysis. They were rapidly transferred to the specialist quaternary centre and commenced on chemotherapy. Subsequently, they developed multiple sites of haemorrhage (hepatic, renal and pulmonary) and required support with multiple blood product transfusions and critical care admission due to respiratory and haemodynamic compromise. Biochemically, hCG improved dramatically with chemotherapy from a level over 8,000,000 IU/l to 300,000 IU/l. In this context, there was rapid improvement in thyroid function with free T4 levels normalising. HCG-mediated hyperthyroidism is a rare cause of thyrotoxicosis. HCG is a glycoprotein hormone that has intrinsic thyroid-stimulating activity due to structural homology between thyroid stimulating hormone (TSH) and hCG. Anti-thyroid medication can be used to control hyperthyroidism associated with very high levels of hCG. Reducing or normalising hCG levels can quickly induce a euthyroid state. Paraneoplastic hCG secretion is managed with treatment of the underlying malignancy and antithyroid medication. Chemotherapy can lead to a transient elevation in hCG levels and patients should be monitored for thyrotoxicosis or thyroid storm.

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P145

Iodine-based contrast media-induced hyperthyroidism in a patient with underlying subclinical hyperthyroidism and multinodular goitre

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Background
The prevalence of iodine-based contrast media-induced (ICM-induced) thyroid dysfunction varies (1-15%). Contrast-induced hyperthyroidism is predominantly found in iodine-deficient regions and in patients with underlying nodular goitre or latent Graves' disease. Beta-blockers are first-line therapy, but anti-thyroid medication are used for severe symptomatic cases.
Case Report
A 79-year-old man presented with a 4-day history of bilious vomiting, diarrhoea and weight loss. He had a subtotal colectomy for ulcerative colitis a year before, and since then had multiple admissions with gastrointestinal and stoma-related issues. Additional history included subclinical hyperthyroidism, ischaemic heart disease, atrial fibrillation, diabetes, asthma and depression. Regular medication included metformin, digoxin, aspirin, rivaroxaban, bisoprolol, omeprazole, venlafaxime, atorvastatin and loperamide.
Investigation and management
Initial blood results were consistent with dehydration. Inflammatory markers were normal. Abdominal x-ray demonstrated no evidence of bowel obstruction. Gastroscopy demonstrated external compression of the esophagus. A computerized tomography scan demonstrated a large multinodular goitre compressing the trachea. An ultrasound confirmed the same plus reduced vascularity. Subsequent tests revealed a serum TSH of 0.02 mU/l (normal range: 0.3-4.1), free thyroxine: 26.9 pmo/l (12-22), free triiodothyronine: 3.9 pmo/l (3.1-6.8): indicating overt hyperthyroidism. Thyroid uptake scan indicated poor uptake. Thyroid receptor antibodies and thyroid peroxidase antibodies were negative. Further history revealed the patient had undergone radiological imaging involving the use of iodine-based contrast media, on three separate occasions, within the prior three months. A diagnosis of ICM-induced hyperthyroidism was made and carbimazole was prescribed. Biochemical monitoring and tapering the carbimazole dose was performed monthly. Results returned to the usual subclinical levels after three months.
Conclusions
This patient had risk factors for ICM-induced hyperthyroidism. Although most cases of ICM-induced hyperthyroidism are mild and transient, there is a small risk of severe thyrotoxicosis with serious cardiovascular complications. Therefore, clinicians need to be aware of this adverse effect.

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P146

Three times unlucky or a unifying endocrine diagnosis?

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Introduction
Graves' disease (GD) has a well-known association with thymic hyperplasia caused by TSHR expression in thymus and regresses by approximately 33-90% with treatment. Splenomegaly due to lymphoid hyperplasia has also been linked with GD in about 10% patients. Cerebral venous sinus thrombosis (CVST) linked with GD is documented in literature but is more common occurrence in solid cancers.
Case presentation
We report a case of 32-year man admitted under neurology with severe headaches, photophobia and weight loss. His MRI venogram confirmed thrombus within the great cerebral vein of Galen, straight sinus and proximal right transverse sinus. CT TAP showed 2.7 cm unilateral renal mass, 15.5 cm splenomegaly and 2 cm liver lesion confirmed as focal nodular hyperplasia on MRI liver. His TFT showed TSH $<$ 0.01 mU/l, FT3 8.0 pmo/l (4.3-6.8) and FT4 21.5 pmo/l (7.7-15.1), Anti-TPO 170 iu/ml ($n<10$), TSI 0.30 iu/l ($n<0.1$). Connective tissue and antiphospholipid screen were negative. JAK-2 mutation was low level positive at 0.8, 0.9 and 1.2%. He underwent laparoscopic nephrectomy for G3, pT1a, R0 tumour. Histopathology confirmed renal cell carcinoma. His TFTs normalised with carbimazole and his repeat imaging 1 year later showed reduction in size of thymic tissue to 2.6 x 1.8 cm from initial 4.7 x 2.1 cm with normalization of splenomegaly on ultrasound.
Conclusions
Thymic hyperplasia, splenomegaly and cavernous sinus thrombosis in individual patients is an extremely rare occurrence and could possibly be due to GD in this case, which is supported by reduction in thymic size and resolution of splenomegaly with carbimazole. Moreover, small non-metastatic RCC is less likely to be a cause of his CVST. Haematology felt, that 1% JAK2 clone, which has not expanded in the past year, is unlikely to indicate myeloproliferative neoplasm and insufficient to offer an explanation of his CSVT.

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P147

An Unusual Presentation of An Autoimmune thyroid Disease

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40years old lady with 12 months history of hyperthyroidism. Treated with ATD. Referred by her treating physician for RAI therapy due to intolerance to ATD and high dose requirement after 12 months. Patient being treated as Classical Graves' Hyperthyroidism. She had symptoms of hyperthyroidism at time of presentation but none at time of assessment in our hospital. Main current issue was painful neck swelling: developed slowly over preceding two months. No problems with swallowing. No change in voice. Also intermittent itching: started when first started ATD, improved when given different tablet but remains troublesome. No eye symptoms. Examination revealed moderate, hard, diffuse, painful, non-vascular goiter. Thyroid uptake scan showed low uptake Tc99 uptake 1.5 % and ultrasound showed diffuse low echogenicity with reduced vascularity. Blood tests revealed extremely high Tg and TPO Abs Titers and low titer TRAb and very high Serum IgG4 level. Our patient converted to hypothyroidism shortly after a course of steroids. FNA cytology consistent with Hashimoto's and IgG4 level improved with treatment. Our patient has hyperthyroidism caused by Hashimoto's presenting with unusually prolonged Hashitoxicosis phase (12 months), Longest reported case in the literature is 5 months. Thyroid functional Conversion appears to be induced by steroids: Possibly affecting the dominating thyroid Ab type i.e Conversion from Stimulating to Blocking TSHRAbs. IgG4 Thyroiditis appears to responsive to steroids, may need further/ longer courses of GCs or may need Thyroidectomy.

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P280

Novel targets determination among patients with angioinvasive differentiated thyroid cancer

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The most effective conventional treatment for differentiated thyroid cancer (DTC) still remains total thyroidectomy with subsequent adjuvant therapy with radioiodine ablation (RAI). In case of unsuccessful RAI treatment, an alternative method is the tyrosine kinase inhibitor therapy. However, its usage is related to many side effects and is not well tolerated by patients. Despite the great progress in the clinical management of patients with DTC, the lack of alternative therapies is remarkable. Since oxidative stress has been implicated as DTC risk factor, the determination of oxidative stress-related proteins may be useful in DTC clinical management, especially in angioinvasion diagnosis. The oxidative stress-related pathways profiling in DTC development analysis will enable a better understanding of the DTC progression simultaneously enabling new medical targets discovery. In this case, we analyzed the level of oxidative stress-related proteins, such as total oxidative stress capacity (TOC), total antioxidant capacity (TAC), sirtuin 1 (SIRT1), sirtuin 3 (SIRT3) and DNA oxidative stress damage products to determine their role in DTC angioinvasion processes and designate potential properties as targeted therapy. For this study 80 patients diagnosed with different stages of DTC after total thyroidectomy were enrolled. All patients were diagnosed as having papillary DTC based on laboratory tests and ultrasound imaging, and confirmed by fine needle aspiration biopsy, followed by histopathological examination. The study group consisted of DTC patients with angioinvasion and for the reference group DTC patients without angioinvasion were enrolled. Considering the received results, TAC, DNA oxidative stress damage products, SIRT1 and SIRT3 measurements have been implicated to DTC angioinvasion ($P=0.04$; $P<0.001$; $P<0.05$; $P=0.01$). Moreover, our study revealed that SIRT1 and DNA/RNA oxidative stress damage products are useful in detection of DTC angioinvasion, and thus could be considered as a marker supporting additional indication for RAI therapy (AUC$=0.7$; AUC$=0.71$; all $P<0.05$ respectively).

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P281

The potential interaction between medical treatment and radioiodine treatment success: a systematic review

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Introduction
Radioactive iodine (RAI) therapy is a critical component in the post-surgical management of thyroid cancer patients, as well as being a central therapeutic option in the treatment of hyperthyroidism. Previous work suggests that antithyroid drugs hinder the efficacy of RAI therapy in patients. However, the effects of other background medications on RAI treatment efficacy have not been evaluated. Therefore, we performed a systematic review and metanalysis investigating the potential off-target effects of medication on RAI therapy in patients with thyroid cancer and hyperthyroidism.
Methods
Systematic review and meta-analysis according to the 2020 PRISMA guidelines. Databases searched: MEDLINE, EMBASE and Cochrane Library for studies published between 2001 and 2021.
Results
Sixty-nine unique studies were identified. After screening, 17 studies with 3313 participants were included. One study investigated thyroid cancer, with the rest targeted to hyperthyroidism. The majority of studies evaluated the effects of antithyroid drugs; the other drugs studied included lithium, prednisone and glycididazole sodium. Antithyroid drugs were associated with negative impacts on post-RAI outcomes ($n=5$ studies, RR$=0.81$, $P=0.02$). However, meta-analysis found moderate heterogeneity between studies ($I2 = 51\ \%$, $\tau2 = 0.0199$, $P=0.08$). Interestingly, lithium ($n=3$ studies), prednisone ($n=$study) and glycididazole ($n=1$ study) appeared to have positive impacts on post-RAI outcomes upon qualitative analysis.
Conclusion
Our review reinforces previous work regarding the effects of antithyroid drugs on RAI outcomes. However, the lack of standardisation between studies supports further randomised control trials with uniform standards.

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P282

The future of TSH receptor antibody (TRAb) testing at university hospitals birmingham (UHB)

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Background
Graves' disease (GD) is an autoimmune condition accounting for up to 80% of thyrotoxicosis cases.1 90% of these patients have TSH receptor antibodies (TRAbs).2 Current NICE guidance recommends testing for TRAbs in adults with confirmed thyrotoxicosis to differentiate between thyrotoxicosis with hyperthyroidism (e.g GD and toxic multinodular goitre) and thyrotoxicosis without hyperthyroidism (e.g thyroiditis).2
Objective
To evaluate the necessity of the TRAb blood test to confirm a diagnosis of Graves' disease in patients presenting with a clinical diagnosis of thyrotoxicosis.
Methodology
We chronologically selected the first 102 patients with TRAb tests performed between January 2020 and September 2021 at UHB. Patients pregnant at the time of testing were excluded. We recorded group demographics, initial diagnosis at clinical assessment, TRAb result and post-TRAb diagnosis.
Results
Of our 102 patients, 57 (56%) had a pre-TRAb diagnosis of GD. Of this group, 49 (86%) of the patients with an initial diagnosis of GD did not have their diagnosis altered post-TRAb. For those without an initial diagnosis of GD ($n=45$), 28 (63%) did not have their diagnosis altered post-TRAb. In the group as a whole, 77 (75%) did not have their diagnosis altered once TRAb results were available.
Conclusions
Our audit suggests that for patients with a clinical diagnosis of GD, from an endocrinologist, TRAb testing added little benefit as it did not alter diagnosis in the majority of cases. In those without an initial diagnosis of GD, the TRAb was more useful.
Recommendations
Our audit supports the British Thyroid Association's recommendation that TRAb testing is 'not essential where there is a strong clinical picture of GD.3 Clinical diagnosis appears highly reliable and due to similar initial management of GD and toxic nodular goitre, not confirming a diagnosis of GD poses minimal risk to the patient.

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P283

Abnormalities of thyroid function tests in patients receiving Immune Checkpoint Inhibitor Treatment for Cancer; importance of a wide-angled lens

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Introduction
In cancer patients treated with immune checkpoint-inhibitors (ICI) that target CTLA-4, PD-1 and/or PD-L-1, thyroid dysfunction represents the commonest associated endocrinopathy (1). Patients receiving ICI should be monitored for thyroid dysfunction. A case of PD-1 inhibitor-induced thyroid function test (TFT) interference has been reported (2) and having noted discordant results, we undertook a preliminary assessment of the extent of such ICI-related TFT interference in a cohort of our patients.
Methods
A quality improvement-project was conducted in a dedicated endocrine-immunotherapy clinic to investigate discordant TFT in patients receiving ICI. Discordant TFT results obtained locally by the Abbott Architect assays were reassessed by Beckman Coulter assays and Perkin-Elmer AutoDELFIA assays.
Results
Over an 8-month period, 3 male and 5 female patients were observed to have clinically discordant TFTs. The median age was 64 (IQR 55.5-82.5) years, and half (50%) of them had metastatic melanoma. All received PD-1 or PD-L-1 inhibitor therapy $\pm$ CTLA-4 inhibitors, with median treatment duration of 7 (IQR 4-30) months. All the patients had normal TFTs preceding ICI, with one patient being on levothyroxine replacement (LT4) for autoimmune primary hypothyroidism. Subsequently, 4 (50%) developed immunotherapy induced thyroiditis followed by hypothyroidism needing LT4, and 6 (75%) had other immunotherapy-related adverse reactions (rash, hypoadrenalism, hepatitis, colitis and polyarthritis). Upon routine TFT assessment using Abbott Architect assays, all had spuriously high free thyroid hormone (FT4) levels that were found to be normal when reanalyzed with Beckman Coulter assays or Perkin-Elmer AutoDELFIA assays, that were compatible with clinical thyroid status of all the patients except for one who had unexplained intermittent palpitations and heat intolerance.
Conclusions
Potential ICI therapy-induced interference in TFTs performed on some assay platforms is important. Clinicians should exercise caution when interpreting TFTs in patients receiving ICI, and should raise concerns with the laboratory in cases with discordant results.

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P284

The Barnet Thyrotoxicosis Pathway – A Quality Improvement Project

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Background
Thyrotoxicosis is a common endocrine disorder in the UK, with a prevalence of 2% in females and 0.2% in men. Endocrine services at Barnet / Chase Farm Hospitals receive ~250 new referrals per year, equating to a local incidence of 50 per 100,000. There is often a significant delay between GP referral and Endocrine clinic review, resulting in delays to commencing anti-thyroid treatment. These delays have been exacerbated by the Covid crisis. A need was identified for a standardized treatment pathway to more efficiently assess and treat newly diagnosed patients with thyrotoxicosis.

Methods
A treatment pathway was developed for use in both the Emergency Department (ED) and Ambulatory Care (AEC) to provide a standardized approach to investigating and treating patients with confirmed thyrotoxicosis (suppressed TSH and elevated T4 or T3), identified either in the ED or by GP and referred to secondary care.
Results
Data were collected over a 7-month period in 2021. 44 eligible patients were treated using the pathway during this time. 75% were new diagnoses of Graves' disease, 16% thyroiditis and 9% toxic goitre. The average time from initial identification of abnormal TFTs to initiation of anti-thyroid treatment (if appropriate) for these patients was 4 days. The average time to follow-up in Endocrine clinic was 6 weeks, greatly improving clinical effectiveness.
Conclusions
Feedback for the pathway was overwhelmingly positive from a wide range of sources – ED consultants, ED / AEC junior doctors, GPs made aware of the project and, most importantly, from patients. Both time to treatment and time to Endocrine clinic follow-up have been improved. Moving forward, plans include greater Primary Care involvement to streamline referrals and greater use of IT resources to aid pathway adherence.

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P285

Preoperative Rapid Optimisation in poorly controlled Graves' disease: An outpatient experience during the COVID-19 pandemic

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Background
Traditional method in Sheffield involved preoperative admission and use of an intensive regimen. The pandemic led to the development and implementation of an outpatient-based protocol (SPROG - 'Sheffield Peri-operative Rapid Optimisation in Graves' disease (GD)') for patients' intolerant to thionamides and/or with uncontrolled disease requiring thyroidectomy. Control was achieved using sequential addition and dose-escalation of drugs such as Lugol's iodine, cholestyramine, beta blockers and steroids (with or without thionamides) with close monitoring 10-14 days pre-surgery.
Aims
To evaluate the safety and efficacy of the SPROG protocol followed by thyroidectomy.
Methods
Patients underwent thyroidectomy for poorly controlled GD between November 2020 and January 2022 were identified. Demographics, clinical and biochemical data as well as outcomes including incidence of peri-operative thyroid storm, post-surgical hypoparathyroidism (PoSH) and recurrent laryngeal nerve palsy were recorded.
Results
7 females and 1 male with a median age of 43 years (range:15-47) were included. Indications using SPROG protocol were thyroid eye disease (5/8; 62%)), neutropenia (2/8; 25%)) and relapse with uncontrolled thyrotoxicosis (1/8; 13%). Pre-protocol median (range) free T4 (fT4) and T3 (fT3) were 70.5 pmo/l (23.2–100) and 27.6 pmo/l (7.7-50), respectively. Following treatment, levels of free hormones were significantly reduced ($P = 0.012$) with median (range) fT4 of 21.2 [10.5–37.9] pmo/l and fT3 of 6.9 [4.4–11.1] pmo/l. None developed perioperative thyroid storm or PoSH. Recurrent laryngeal palsy persisted in 1 patient whilst another developed steroid-induced adrenal insufficiency.
Conclusion
SPROG protocol was safe, efficient, and cost-effective during the pandemic. A close collaboration between medical and surgical teams was key to optimise thyroid function pre-surgery.

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P286

Graves' thyrotoxicosis and spontaneous coronary artery dissection: Is there a link?

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Background
Spontaneous coronary artery dissection (SCAD) is a rare condition, which is sometimes underdiagnosed in patients with chest pain and presumably normal coronaries. There have been a few case reports of patients with thyroid dysfunction and arterial dissections.
Case
We present a 20 year old female with recent diagnosis of Graves' thyrotoxicosis managed with methimazole. She initially presented in South Korea with shortness of breath on exertion and was diagnosed with hyperthyroidism. She then presented to A&E with thyrotoxicosis, constant central chest pain radiating down her left arm, worsening shortness of breath and reduced exercise tolerance. Past medical history includes iron deficiency anaemia, polycystic ovarian syndrome and atrial septal defect repair. Investigations revealed suppressed TSH (<0.01 mU/l), raised thyroid hormones (free T4 31.2 pmo/l, free T3 14.1 pmo/l), and initial troponin 2,452ng/l and D dimer 907ng/mL. ECG showed sinus rhythm and inferior T wave inversion. TSH receptor and TPO antibodies were positive. She also had detectable IgG and IgM for Parvovirus B19. A preliminary diagnosis of myocarditis was made, secondary to viral illness, and felt unlikely to be associated with mild thyrotoxicosis. Urgent echocardiogram showed dilated left ventricle with severely impaired systolic function and ejection fraction of 41%. She was urgently transferred to the cardiac centre for angiography, which showed SCAD affecting mid to distal LAD. She was then transferred to the cardiothoracic unit for specialist monitoring.
Conclusion
Cardiac sounding chest pain should not be dismissed in young individuals, especially those with autoimmune thyroid disease. Studies have concluded that there is a high prevalence of autoimmune thyroid dysfunction in patients with SCAD. These patients are more frequently women, more frequently have distal dissections like our patient, and are managed with a conservative medical strategy.

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P287

Primary MALT lymphoma of thyroid with hypothyroidism and absence of Hashimoto's disease

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Primary thyroid lymphoma accounts for $<5\%$ of thyroid malignancies. The most common (up to 70%) and clinically aggressive sub-type is non-Hodgkin's B-cell lymphoma. Mucosa-associated lymphoid tissue (MALT) lymphoma is less common (up to 30%) and clinically more indolent. Females are more frequently affected than males (4-8:1) with onset in 6th and 7th decades. A strong association with Hashimoto's disease ($>90\%$) is recognised. A 66 year old male presented with an 18 month history of a painless, increasing in size anterior neck mass. He had also experienced hoarsening of voice for 10 months. Systemic symptoms were absent. Primary hypothyroidism had been diagnosed two years earlier and CT imaging of thorax, abdomen and pelvis (following minor trauma) coincidentally demonstrated the presence of an asymmetrical goitre, left lobe larger than the right, with tracheal deviation and retrosternal extension. Ten years earlier a CT pulmonary angiogram confirming pulmonary embolism coincidentally demonstrated normal appearance of thyroid. Treatment: thyroxine 75 mg od, bisoprolol 5 mg od and warfarin variable dose. Examination confirmed the presence of an asymmetric smooth goitre with left lobe larger than right. Investigations: fT4 12.5 pmo/l, fT3 4.6 pmo/l, TSH 3.86 mU/l, anti-TPO antibodies negative at 4.8 U/ml and lactate dehydrogenase slightly elevated at 398 U/l. CT imaging confirmed increased goitre size, minimal tracheal compression and suspicious left-sided cervical lymphadenopathy. The relatively rapid increase in size of the goitre, progressive hypothyroidism and negative anti-TPO antibodies led to suspicion of thyroid lymphoma. Ultrasound guided thyroid biopsy and lymph node FNA confirmed stage 2E MALT lymphoma. This case confirms the need for vigilance in cases of rapidly enlarging goitre and the diagnostic utility of biopsy. The negative serology suggests infiltration of thyroid tissue as possible aetiology of the hypothyroidism. Treatment of primary MALT lymphoma of thyroid remains controversial.

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P288

Arterial Thrombus in a Graves thyrotoxicosis - Hyper-coagulable state and Hyperthyroidism

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Hyperthyroidism is not a well-known cause of venous thromboembolism. Hyper-coagulable and hypofibrinolytic states are described in hyperthyroidism. A meta-analysis of 51 studies evaluating the consequence (exogenous and endogenous effect on coagulation, raised thyroid levels were associated with a rise in clotting factor VIII, IX, Von Willebrand factor and fibrinogen. The procoagulant effect noticed in hyperthyroidism facilitated by thyroid hormone receptor beta gene. 40-year-old HGV driver presents with hot sweats, weight loss over 10 months, tremor. Examination revealed mild tremor, Heart rate 80 per minute. No sympathetic signs of thyrotoxicosis and thyroid eye disease. Blood test showed TSH < 0.01mIU/l FT4-76.3 pmo/l, normal white cell count, high TRAB antibody titres. A diagnosis of Graves' disease was made and was commenced on carbimazole 20 mg bd and propranolol 20 mg tds. He was rendered neutropenic and carbimazole was stopped. Following this he was started on dexamethasone 1 mg BD and cholestyramine 4g TDS. Given the severe symptoms and high antibody titres he was offered surgery. Lugol's iodine, propranolol, cholestyramine, dexamethasone was used to achieve the pre-operative objective of thyroid function of FT4 < 30 pmo/l and FT3- < 10 pmo/l. Three days prior to surgery, he presented back to hospital with acute painful right lower limb. He has been having intermittent claudication since past 2 weeks. An MRA revealed embolus or thrombus in the right common to external iliac artery obstructing the flow into the right internal iliac artery. He then underwent right femoral tibial embolectomy, on table angiogram and thrombolysis and fasciotomies. Unfortunately, the limb could not be salvaged, and he was planned for a below knee amputation. Total thyroidectomy and Guillotine amputation were performed, at this stage the thyroid function normalised. This case emphasise the significance of hyperthyroidism in hyper coagulable states. There is a paucity of large scale prospective multi-centre studies in establishing hyperthyroidism as a risk factor for VTE.

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P289

Graves' disease with benign ethnic neutropenia-a grave combination

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Benign Ethnic Neutropenia (BEN) is a common form of neutropenia defined as an absolute blood neutrophil count (ANC) of < 1.5 x 10^9/l, usually observed in Afro-Caribbeans. These patients are not at increased risk of infection despite their neutropenia, unless they are on medications which can cause neutropenia. Amongst these drugs antithyroid medications are known to cause agranulocytosis defined as ANC of <500/μl. We report a case of 24 years old male with sickle cell disease who presented to clinic with a new diagnosis of Graves' disease 2 months ago. His neutrophil count was 0.89 x10^9/l when he was started on carbimazole 20 mg once a day. Whilst on it, counts dropped to 0.53 x10^9/l after 1 month, hence carbimazole was held. Workup for neutropenia (viral infection & haematinic) was negative, concluding a diagnosis of BEN. Neutropenia improved with a count of 1.0 x 10^9/l with persistent thyrotoxic picture on bloods, carbimazole was resumed at 40 mg with advice to do weekly blood counts and stop carbimazole when counts drop to less than 0.8 x 10^9/l, with administration of granulocyte-colony stimulating factor (Filgrastim 30 million units) after discussion with Haematology team. Signs of neutropenic sepsis and urgency to attend emergency department were explained. His neutrophil count remained above 1.0 x 10^9/l with stable thyroid function, hence carbimazole was reduced to 20 mg OD. Alternative treatment options of radioiodine ablation versus thyroidectomy were discussed. Patient was a prison inmate hence radioiodine ablation was not a favourable option due to being in proximity with others. He preferred to continue carbimazole, with a plan of referring for surgical intervention in the future. This case emphasizes the challenges faced while treating such cases of Graves' disease, where recognition of risk of agranulocytosis, patient education, considering alternative options of treatment and discussion with Multidisciplinary Team are imperative

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P290

Late relapse of thyroid eye disease (TED)

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Generally, after an initial active phase TED rarely reactivates. However, epidemiological evidence is scant. The following cases highlight the propensity for Graves' orbitopathy to reactivate many years later.

Case 1

A 69-year-old woman had Graves' disease aged 29, and was reviewed in the TED clinic (ophthalmology, rheumatology and endocrinology), with reactivation of orbitopathy 40 years after initial disease. She was an ex-smoker, had hypertension and previous TIA. Her aunt and daughter had autoimmune thyroid disease. She underwent radioiodine therapy (RAI) at age 34 and her TED symptoms had settled without intervention. Currently, she reported six months of progressive proptosis, diplopia and retrobulbar ache. There was conjunctival injection, eyelid oedema and restriction. The patient was clinically and biochemically euthyroid on levothyroxine. Her TSH receptor antibody (TSHRAB) titre was >30 IU/l (NR <0.4). CT imaging identified tendon sparing extraocular myopathy. Left sided visual acuity and colour perception were reduced. Ocular motility was restricted. IV methylprednisolone was commenced with oral rituximab and mycophenolate. Orbital decompressive surgery was planned if there was no adequate clinical improvement.

Case 2

An 89-year-old woman was seen during her third relapse of TED. Orbitopathy occurred at age 58 and 77. At age 77 she had optic neuropathy and was treated with IV glucocorticoid and bilateral orbital decompression. Most recently she presented with vision loss in the right eye, reduced ocular motility and proptosis. She was clinically and biochemically euthyroid on levothyroxine. TSHRABs were 8.5 U/l. MRI imaging showed tendon sparing extraocular myopathy. She was managed with intravenous glucocorticoid, methotrexate, ciclosporin and rituximab. Reporting worsening of vision between doses of glucocorticoid, she underwent repeat bilateral orbital decompression with subsequent radiotherapy. Her vision improved, with ongoing horizontal diplopia.

Conclusion

This highlights the potential for late recurrence of TED; further epidemiological data is needed.

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P291

Clinical case of Alemtuzumab induced thyroid storm requiring urgent inpatient thyroidectomy

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38 year old woman presented with palpitations, chest tightness, dizziness and light headedness. There was no evidence of infection clinically or biochemically. She had a background of Alemtuzumab induced Graves' thyrotoxicosis, relapsing remitting Multiple Sclerosis. Her regular medications included Carbimazole 20 mg three times a day, Amitriptyline 120 mg daily, Propranolol 40 mg four times a day, Tizanidine 2 mg daily (up to 18 mg), Tramadol 50 mg as required, Senna 7.5 mg daily, Chlorphenamine 4 mg daily, Fexofenadine 180 mg daily and Ibuprofen 5% gel as required. On admission, her biochemistry revealed a free T4 of 57 pmo/l and TSH of <0.01 mU/l. She also had a raised troponin of 71ng/l. ECG showed sinus tachycardia with no ST-T changes. Her Carbimazole dose was increased to 30 mg three times a day. Blood tests were done 2 days after increasing the dose of carbimazole and she remained in thyrotoxicosis with her free T4 > 100 and TSH <0.01. She was therefore started on lugol's Iodine 0.2ml three times a day, titrated up to 0.3ml three times a day. Due to her resistant thyroid storm, she was additionally treated with steroids. She had an echocardiogram which was normal. Throughout her admission, she remained in persistent sinus tachycardia at around 105 beats per minute to 130 beats per minute despite use of propranolol. The lady underwent a total thyroidectomy 20 days after she first presented. She was euthyroid (T4 = 22, TSH = <0.01) at the time of surgery. She recovered well post operatively and having stable calcium levels. Both the carbimazole and propranolol tablets were discontinued after surgery. She was commenced on levothyroxine 100 micrograms once daily. The histology confirmed Graves' Disease and there was an incidental finding of a papillary thyroid cancer on histology and this was reviewed by our regional thyroid cancer MDT and they recommended conservative management in view of the incidental finding.

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P292

Thyroid Storm presenting without fever

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Thyroid storm is rare and life threatening manifestation of thyroid hormone excess. It has high mortality rate with delayed treatment. As early intervention is associated with improved patient outcome, prompt diagnosis based on clinical grounds is of paramount importance. We present a case of thyroid storm which was different in terms of absence of fever on presentation, presence of thrombocytopenia and deranged cholestatic LFTs which resolved after treatment of thyroid storm. 55 year female with background of Graves' disease (Treatment stopped in 2016), presented with 4 days history of breathlessness. A week ago she had cough which settled after course of oral antibiotics. She also had history of weight loss and night sweats for last 3 months. On presentation, She was in fast Atrial fibrillation with rate of 240bpm and few beats of Broad complex tachycardia with blood pressure of 90/60 mmhg. She was apyrexial and was in heart failure with bibasal crackles, bilateral pitting oedema, CXR showing bilateral pleural effusion and upper lobe diversion. She appeared cachectic with exophthalmos and proximal myopathy. She had small painless palpable goitre. Burch-Wartofsky Point Scale for diagnosis of thyroid Storm was 60 which prompted treatment in lines of thyroid storm. Later on her thyroid function tests showed raised T3 and T4 with supressed TSH and TBII was raised. After advice from Endocrinologist, she was treated with systemic steroids, beta blockers, high doses of PTU, cholestyramine and diuretics for heart failure. Lugol's iodine was withheld as she started to improve clinically. She also had raised Transaminases and thrombocytopenia which resolved once the thyroid hormone levels improved. She was planned for inpatient thyroidectomy. She remained apyrexial throughout while fever is thought to be universal in thyroid storm which highlights the fact that storm should be considered even in the absence of fever.

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P293

Pfizer vaccine induced subacute thyroiditis

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31 years old lady with no past medical history or family history of thyroid disease had her first dose of Pfizer vaccine and few days later she presented unwell, Febrile with painful swelling in the neck. She was thought to have Covid because of fever. Examination revealed tender thyroid enlargement with positive bruit and Tachycardia. Investigations showed florid thyrotoxicosis with TSH: < 0.02, fT4: 60.0, CRP: 60, rest of investigation: normal, TRab and TPO AB: pending, Covid PCR: negative repeatedly. Thyroid USS: inflamed thyroid with increased vascularity. She was diagnosed as subacute thyroiditis and started on steroids with follow up in clinic. TRab and TPO ab were negative further confirming the diagnosis. The patient improve on prednisolone both clinically and biochemically. TFT started to normalize. She was reviewed in clinic 2 months later in good conditions with no symptoms. She was successfully weaned off steroid. Discussion: Subacute thyroiditis is a common condition that can occur for many reasons like post viral upper respiratory tract infection, postpartum and autoimmune (Hashimoto's). It is common among females. It has been documented to happen after administration of inactivated vaccine or live attenuated vaccine like influenzas vaccine and Hepatitis B vaccine. There are 2 cases of subacute thyroiditis which have been reported post SARS-CoV-2 vaccination with Spikevax (Moderna Biotech, Spain) and Vaxzevria (AstraZeneca; Sweden) respectively and one case of Pfizer-biontech vaccine induced thyroiditis. It was thought to be a less likely possibility to happen with Pfizer as it is an mRNA vaccine. Learning: Consider Subacute thyroiditis in patient after SARS-CoV-2 vaccination. The disease tends to run a benign course with rapid recovery. It is steroid responsive. Patients might end up in hypothyroid status. More studies should be carried to insure less occurrence of this side effects. The vaccine should still be used given the fact of how can covid pneumonia be serious in comparison to the potential side effect that will happen in few patients.

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P294

A Challenging Case of Oscillating Hashimoto's thyroiditis and Hyperthyroidism

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Introduction
Hashitoxicosis is the rare case of autoimmune thyroid disease. While transforming from Graves' disease to spontaneous hypothyroid is well known, development of hyperthyroidism following hypothyroidism is a rare phenomenon which can pose a challenge in management. We report here a case of Hashitoxicosis managed with "Block and Replace Therapy" to maintain her euthyroid while waiting for definitive therapy.
Case Report
A 30-year-old lady with background history of hypothyroidism and migraines was referred to endocrine service with persistent symptomatic hypothyroidism; lethargy, menorrhagia and dry eyes despite treated with Levothyroxine. Her weight was 66.4 kg. Clinically, there was a large soft goiter, large right palpebral fissure without suggestive features of minor thyroid eye disease. Biochemically consistence with hypothyroidism; TSH 10.21 mU/l (0.35-5.50) and T4 10.9 pmo/l (10.0-20.0). Her family history included autoimmune hyperthyroidism, hypothyroidism, vitiligo and vitamin B12 deficiency. She became clinically thyrotoxicosis after 3 months with fine tremors and palpitation with heart rate of 200 bpm and biochemically with TSH 0.01, T4 47.6 and T3 10.5. The levothyroxine dose was reduced. Thereafter, her TSH went up to 26.12, T4 9.4 and TPO Antibodies >1300. Her thyroid function test was closely monitored due to labile state. The patient declined the definitive management (Radioactive iodine and thyroidectomy) initially as she was looking after two young children and cosmetics reasons. Therefore, ' Block and Replace therapy' was commenced in consideration of labile thyroid status and stopped once the euthyroid state was maintained (TSH 1.43, T4 12.4) over 16 months. Afterwards, the TSH went up to 29.7 and T4 12.4. She was started on Levothyroxine and referred to surgeons for thyroidectomy after discussion in endocrine MDT.
Conclusion
It was a challenging management of fluctuating thyroid status which also highlighted that the clinicians should be aware of potential transformation from blocking to stimulating antibodies.

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P295

Radioactive Iodine treatment (RAI) for benign thyroid disease: ESHT outcomes

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Introduction
Following a National training programme for Endocrinologists to provide RAI treatment for benign thyroid disease, the ESHT NHS Trust started Radioactive iodine (RAI) treatment for benign thyroid disease a couple of years ago. Previously ESHT trust patients were referred to neighbouring trusts for RAI treatment.
Data/Results
The data was collected over a 12-18 month period. A total of 34 patients received RAI treatment during this period; 28 Females (82%): 6 Males (18%). 62% (21 patients) of patients had relapsing autoimmune thyrotoxicosis, 32% (11 patients) of patients had Toxic multinodular goitre and 2 patients (6%) had single toxic adenoma. 32 patients have 6 months follow up data and 17 patients have completed twelve months follow up after the RAI. 2 out of the 34 patients have not yet completed 6 months follow up. Out of 32 patients who have completed 6 months follow up after RAI, 88% have been treated (65% patient hypothyroid, 23% euthyroid) and 2 patients (6%) remained hyperthyroid (One patient is on carbimazole and thyroid tests are normal, second patient has suppressed TSH with normal FT4 without any treatment, both are under regular follow up). Out of the 17 patients who have completed 12 months follow up after the RAI treatment all (100%) have been treated (80% of patients now hypothyroid, 20% euthyroid).
Conclusion
All the Patients who has completed 12 months follow up, after single dose of RAI treatment, has responded well to the treatment. None of our patients had any side effects or complications. Some of the patients did not have the appropriate follow up appointments as recommended. Our management pathway will be reviewed to avoid this in the future.

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P296

Euthyroidism: following a course of radio iodine therapy for Graves' disease

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Introduction
Graves' disease is the commonest cause of thyrotoxicosis; and is usually responsive to radio-iodine therapy. In Nigeria, radio-iodine therapy is becoming a common and cost effective option for treatment of thyrotoxicosis; with the less likelihood of most of the complications associated with thyroidectomy.
Case presentation
A 49-year-old Nigerian lady, presented to the endocrinology clinic, at LAUTECH Teaching Hospital, Ogbomoso, 8 years ago with a 10 year history of an anterior neck swelling, which only increased in size during pregnancies. She noticed hand tremors and palpitations. Physical examination, revealed tachycardia, mild hypertension and a WHO grade 1 goitre. There were no features suggestive of an accompanying thyroid eye disease. Past medical history was significant for hypertension and was on antihypertensives, on and off. A thyroid function tests ordered showed a fully suppressed TSH- 0.02 mUI/l (reference limits, 0.37-3.5 mIU/l) and a raised free T4- 20.4 pmo/l (reference limits, 7.2-16.4 pmo/l). An ECG revealed a sinus tachycardia. Her features were suggestive of thyrotoxicosis secondary to Graves' disease. She was commenced on tablets carbimazole 30 mg daily and propanolol 40 mg twice daily. Carbimazole, was continued at a reduced dose of 5 mg daily, after she achieved resolution of symptoms and biochemical euthyroidism. Definitive treatment options including: radio-iodine therapy and thyroidectomy, were discussed with the patient. She opted for radio-iodine therapy and she was referred to the nuclear medicine department, University College Hospital, Ibadan, Nigeria, 2 years, after the initial diagnosis. She was treated with a single dose, 30 mCi of Iodine 131. She developed transient hypothyroidism and was treated with 25 mg daily of levothyroxine; which was discontinued after few months.
Conclusions
Our patient did not need to recommence levothyroxine; and the thyroid function tests have remained within reference limits in last 6 years.

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P297

A rare case of agranulocytosis secondary to carbimazole medication complicated by a prolonged COVID-19 infection

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A 55 year-old Nepalese lady, previously fit and well, presented to her GP 2 months ago with palpitations and weight loss. She was diagnosed with Graves thyrotoxicosis based on her clinical history and biochemistry, and was started on carbimazole 40 mg daily. She suffered from COVID19 infection a month later and started self-isolating. She continued to feel unwell for three weeks but did not seek urgent medical attention due to the perceived general recommended isolation guidelines. When she presented to the hospital, she was acutely unwell with pyrexia, hypotension and tachycardia. Blood tests revealed severe neutropenia with raised CRP. COVID lateral flow and PCR remained positive. She was treated for unresolved COVID19 infection and agranulocytosis secondary to carbimazole. She was started on filgrastim, intravenous fluids and antibiotics. Carbimazole was stopped and steroids were not indicated as she was saturating well on air and her thyroid blood tests at that time was euthyroid. Definitive thyroid treatment was discussed and thyroidectomy was planned urgently. She was started on high dose beta-blocker when clinically better. Unfortunately, she became severely thyrotoxic again within two weeks and was therefore optimised with Lugol iodine, steroids and high dose beta-blocker prior to total thyroidectomy. This case described an unwell patient with slow recovery from COVID19 infection due to presence of agranulocytosis. It also highlighted the importance of going through the rare agranulocytosis side effect of carbimazole with patient and with the ongoing COVID19 pandemic, patient should be reminded of the importance of seeking urgent medical attention and blood test if unwell or suffering from COVID19 infection, despite the recommended isolation guidelines. The latter is particularly crucial if the COVID19 symptoms persist for a prolonged period. Carbimazole counselling should therefore include the context of COVID19 infection and patients on this medication should be given the drug alert card.

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P364

Evaluating the progression to hypothyroidism in preconception euthyroid thyroid-peroxidase antibody positive women

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Background and aims
Thyroid peroxidase antibody (TPOAb) positivity is prevalent in women of reproductive age and pre-disposes to thyroid dysfunction, namely hypothyroidism, which has adverse effects on pregnancy. The aim of this study was to report the rate of development of abnormal thyroid function among initially euthyroid TPOAb positive women recruited into TABLET trial. To also identify factors associated with the development of hypothyroidism and to compare outcomes between euthyroid and treated hypothyroid individuals.
Methods
This was an observational cohort study across 49 UK hospitals between 2011-2016. Participants were euthyroid TPOAb-positive women aged 16-40years with a history of miscarriage or subfertility planning pregnancy, randomized to levothyroxine 50 mg daily or placebo. The main outcome measures were abnormal thyroid function, conception rate and live birth (LBR) $\geq$34weeks.
Results
A total of 70/940 (7.4%) TPOAb-positive women developed subclinical (SCH) or overt (OH) hypothyroidism: 27/470 taking levothyroxine and 43/470 on placebo (relative risk (RR) 0.63; 95%CI 0.39-1.00;$P=0.05$); 83% of cases emerging pre-pregnancy. Baseline mean serum TSH concentrations were higher in those who developed hypothyroidism compared to those who did not (TSH 2.66mIU/l vs 2.05mIU/l;$P<0.001$). Treated SCH/OH demonstrated a higher failure-to-conceive rate compared to euthyroid women (adjusted RR 2.02 [1.56-2.62]; $P<0.001$). The LBR $\geq$34weeks was similar in the treated SCH/OH and euthyroid groups (adjusted RR 1.09 [0.77-1.55];$P=0.6$).
Conclusions
Approximately 7% of euthyroid TPOAb-positive women will develop hypothyroidism within 1year preconception, or in pregnancy. Conception rates are lower in women with treated SCH/OH compared to euthyroid women, but live birth rates are comparable. Thyroid function in TPOAb-positive women should be monitored regularly, when trying to conceive, to ensure prompt diagnosis and appropriate treatment initiation.

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P365

A rise in the incidence of Graves' disease in North West Wales during the COVID-19 pandemic: an effect of the SARS-CoV-2 virus or vaccine?

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Graves' disease (GD) is the most common cause of hyperthyroidism with incidence rates of 20-50 cases per 100,000. Genetic predisposition and environmental factors are known to play a role in its pathogenesis. After perceiving an increase in the number of cases presenting to our thyroid clinic we confirmed a rise in the incidence of GD in North West Wales since the start of the COVID-19 pandemic. The annual incidence of GD was calculated using the number of positive thyroid stimulating immunoglobulins (TSI) results with associated thyrotoxicosis. 40 new cases of GD were diagnosed in 2019, 48 in 2020 and 64 in 2021 i.e. a 60% increase in 2021 from the pre-pandemic level in 2019. The number of relapses of known cases was similar with 17 in 2019, 19 in 2020 and 20 in 2021. There was no significant difference in mean TSI levels (8.6 IU/l in 2019, 11.7 IU/l in 2020 and 12.1 IU/l in 2021) or severity of the thyrotoxicosis (mean fT4 levels 37.1 pmo/l in 2019, 42.2 pmo/l in 2020 and 39.6 pmo/l in 2021). Figures for the first 6 months of 2022 suggest a decrease in the incidence rate with 22 new cases (representing a 50% decrease compared to the same period in 2021) and 15 relapses of GD. Cases of GD post-COVID infection and vaccination have been reported in the literature. Initial analysis of our data suggests the possibility of a COVID vaccination effect in the increase. The incidence of GD for the first half of 2022 suggests a return to the pre-pandemic rate.

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P366

Use of Burch-Wartofsky score when assessing the severity of hyperthyroidism, a retrospective study

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Introduction
Thyroid storm, a life-threatening endocrine emergency, requires prompt intervention and treatment to improve outcomes. The diagnosis is made clinically, based on symptoms including hyperpyrexia, tachycardia, nausea, diarrhoea and altered cognition. The Burch-Wartofsky (BW) score is a symptom-based score recommended to determine the likelihood of thyroid storm. This retrospective study aims to determine use of the BW scale and its effect on management.
Data collection
The CHI numbers of inpatients with significantly elevated fT4 (>25 pmo/l) at the QEUH labs between Jan-21 and Nov-21 were obtained via Laboratory Information System (LIMS) search. Patients in the maternity, oncology unit, on levothyroxine or with detectable TSH were excluded. Information included: descriptive characteristics, TSH, antibody status and acute diagnosis/treatment. BW score and outcome, was retrospectively calculated using patient notes.
Results
BW score was used clinically in 1/51 patients included. Most patients were diagnosed clinically with "acute thyrotoxicosis," however, the opinion of an endocrinologist was not always sought. Of 29 patients with a BW score indicating 'storm unlikely' none were clinically identified at risk of deterioration. Of 15 patients with a BW score suggesting 'impending storm', 1 was identified clinically as impending storm. Of 7 patients with a BW score indicating 'thyroid storm', 2 were clinically diagnosed with thyroid storm. BW score never suggested a less severe diagnosis, in 6 instances the BW score suggested a more severe diagnosis than the clinical decision. A weak positive correlation between BW score and fT4 was noted (spearman co-efficient: 0.28, $P<0.05$).
Conclusions
The use of the BW score in clinical practice would standardise classification of patients; subsequently, identifying patients at higher risk of clinical deterioration, requiring prompt treatment. As a result of this first audit cycle, we are discussing with clinical biochemistry issuing reports to recommend endocrinology review and encourage use of BW scale where appropriate.

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P367

L-T3 Prescribing & Deprescribing - Single Centre Experience

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Introduction
90-95% of patients with primary hypothyroidism respond well to levothyroxine (L-T4) therapy. A minority remain symptomatic despite optimised L-T4 therapy. There is limited evidence supporting the role of liothyronine (L-T3) in this subgroup of patients. By looking at 3- and 6-month trials, we aim to review our practice of L-T4/l-T3 therapy.
Method
We reviewed medical and pharmacy records of all patients receiving L-T4/l-T3 therapy from January-2019 to July-2022. Data were collected and tabulated from clinic letters, pharmacy and ICE software.
Result
15 patients were identified – 12 (80%) females, mean age 51.3 years (29-63). Baseline mean TSH was 1.12 mU/l (range $<$0.01-5.68) but only 6 (40%) within reference, with 7 (46.7%) low TSH indicating overtreatment. Pre-trial, the mean L-T4 dose was 118.6 mg (75-187.5 mg od). The modal L-T3 starting dose (8 patients) was 10 mg bd (range 5 mg od–10 mg tds), and all had a concomitant reduction in L-T4 dose. At 3 months, patients' subjective symptom reports yielded that 9 (60%) felt an improvement in symptoms, 4 (26.7%) felt no improvement, and 2 (13.3%) experienced side effects. TSH level as a guide to thyroid status showed 5 (33.3%) within, 2 (13.3%) above and 8 (53.3%) below the reference range. Accounting for one outlier (TSH 23.85), the mean TSH was 1.08 mU/l (0.01-5.79). 6 patients required follow up to 6 months, 2 with normal TSH, 2 low, and 2 awaited. Mean TSH was 0.77 (0.04-1.43). After trial completion, 8 (53.3%) patients continued combination therapy in primary care, 5 (33.3%) changed back to L-T4 monotherapy. 2 patients are awaiting review.
Discussion
A majority of patients had marked improvement in symptoms after L-T3/l-T4 combination therapy & able to maintain euthyroid status, demonstrating that careful use of combination therapy may benefit a select group of cases. However, further large studies are required to fully explore this potential.

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P368

Falsely elevated serum TSH in a mother and her four children

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Background
Elevated TSH concentration should be assessed and treated with caution because of the possibility of transient thyroid dysfunction, or, in rare cases, measurement interference. We describe a case with a rare cause of elevated TSH level in a 39-year-old mother and her four children.
Case Summary
A 39-year-old lady was referred with a long history of high serum TSH ranging between 18.9 to 38.7 (reference interval 0.4-4.0 mU/l) with FT4 concentration ranging between 12.0-15.6 but within reference interval 12.0-22.0 pmo/l using Roche Elecsys thyroid assays. There were no associated significant hypothyroid symptoms or signs and no family history of thyroid disorder. Serum TSH concentration was also elevated using assays from Abbott and Perkin Elmer DELFIA. Despite this, she never required levothyroxine therapy. Mutations associated with thyroid hormone resistance were not detected by *THRβ* gene sequencing. She has four male children aged 10, 8, 3 years, and 8 months. All had elevated TSH concentration noted at birth, and all were commenced on levothyroxine replacement. However, the older three children were successfully weaned off levothyroxine by age of 30 months. Recovery of TSH immunoreactivity following polyethylene-glycol precipitation (PEG) was low at 17 (27-70) % suggesting immunoglobulin-based TSH assay interference. Gel filtration chromatography confirmed the presence of high molecular mass TSH immunoreactivity in the samples of the mother and PEG recovery was also abnormal at 21 (27-20) % in her youngest child.
Discussion
Increased immunoreactive TSH, in this case, is likely to be due to Macro-TSH, an immunoglobulin TSH complex. This can accumulate in circulation, simulating a laboratory picture of subclinical hypothyroidism. Multiple TSH assays can be affected. Macro-TSH can be detected by immunosubtration and dilution studies and confirmed by gel filtration chromatography. As transplacental transmission of Macro-TSH can occur. Maternal TSH should be checked following all positive Guthrie tests to prevent inappropriate diagnosis and treatment.

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P369

A rare case of profound refractory hypothyroidism: Compliance or Formulation issue?

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We report a case of a 57-year-old woman with profound uncontrolled hypothyroidism diagnosed in 1999. At her first Endocrine clinic visit in 2015, her TSH level was 93.4 mU/l with FT4 level of 4.8 pmo/l. Despite increasing her Levothyroxine dose, her TSH level remained persistently above 80 mU/l with a low FT4. She had a gastroscopy and coeliac screening which were non-significant. Triiodothyronine 10 mg was added to Levothyroxine 100 mg once daily in October 2015. However, she remained unwell clinically with fatigue and under-replaced with her TSH remaining elevated at 83 mU/l with a low T4 (3.5 pmo/l) and T3 (2.7 pmo/l). Thyroid absorption test showed no variation of TSH levels, highlighting no active absorption of Levothyroxine tablets despite having tried various tablet formulations. She declined to take natural thyroid extract. In December 2019, a fresh endocrine re-assessment following re-referral by her GP identified a likely allergic reaction to Levothyroxine tablet formulations as she reported facial swelling within 20 minutes after taking her tablets. She was initiated on liquid form of Levothyroxine 100 mg with Liothyronine 10 mg tablets. The patient reported disappearance of her previous allergic reaction on liquid Levothyroxine. Unfortunately, her prescription was not renewed by her GP due to the higher cost. Following re-issue via hospital prescription, her TSH level gradually improved to 0.72 mU/l with her latest FT4 at 24.6 pmo/l. In assessing uncontrolled hypothyroidism, a careful history is

extremely important as well as a good understanding of the pharmacology of different Levothyroxine formulations. This patient not only had an allergy to different Levothyroxine tablet excipients, but also a resulting absorption issue. One should think about the option of alternative Levothyroxine liquid formulation which has a faster rate of absorption and time to peak concentration over tablets.

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Nursing Practice

P148

Incidence of COVID-19 in People with Primary Adrenal Insufficiency in the UK and Reported Self-Management - A prospective study

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Background
People with Primary adrenal insufficiency (PAI) were identified as a vulnerable group by the UK government during the COVID-19 pandemic. Hence our aim was to evaluate the incidence of COVID-19, and associated adrenal crisis (AC) in people with PAI in the UK.
Methods
A prospective observational study of patients with PAI was performed between January-June 2022. Participants were recruited via the Addison's Disease Self Help Group. Diagnosis of PAI was self-reported, but required fludrocortisone to be prescribed. Participants were contacted using weekly SMS messages. The messages contained a link where respondents affirmed their consent and answered four questions (if they had been unwell, increased their steroids, developed AC or sought support). COVID-19 diagnosis was self-reported based on a lateral flow or PCR. AC was defined as per Hahner et. al (2015) criteria.
Results
82 patients were recruited and 75 responded to the weekly messages. 63 (84%) were women. 66 (88%) with Addison's disease, 7 (9.3%) had Bilateral adrenalectomy/haemorrhage and 2 (2.7%) with congenital adrenal hyperplasia. 29/75 (38.7%) developed COVID-19. Of these 8/29 (27.6%) increased their steroid medication to the COVID recommended regimen of 20 mg/6hrly. In addition, 10 (34.5%) participants doubled their dose, 6 (20.7%) more than their doubled dose, but this did not equate to the same as the 6hrly regimen. However, 4 (13.8%) participants less than doubled, and one reported taking extra but no dose stated. One participant was admitted to hospital with an AC, having only increased their hydrocortisone dose by 10 mg and did not administer emergency hydrocortisone injection.
Conclusion
During the pandemic COVID-19 infections were common in people with PAI, but AC was rare. Most patients adjusted their glucocorticoid dose appropriately, which probably contributed to the low risk of AC. Hence, appropriate education can possibly prevent the occurrence of AC during the pandemic.

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P149

Our Grampian experience of establishing an endocrine nurse specialist service within the Gender identity clinic

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Background
People wanting to access gender affirming hormone therapy (GAHT) as part of gender affirming treatments are increasing in number and often face long waiting lists. Nationally there is often limited and inconsistent endocrine support for this group. As a result people often feel unsupported and confused in their treatment journey. (In 2019 we set up a dedicated endocrine clinic within the Grampian GIC (gender identity clinic), with the specific remit to see all people wanting GAHT. It became clear that after initial establishment of this service that an endocrine nurse specialist role would be of fundamental benefit to provide an ongoing supportive framework for person centred care. What we did We have almost 400 people within the service requiring ongoing follow up for GAHT. A new nurse led clinic was developed to cover review of hormone therapy (e.g. blood test monitoring, titration of hormonal regime, review of effects of hormones) and overall health (e.g. assessment of cardiovascular risk, healthy lifestyle advice and relevant gender appropriate screening guidance). This framework of care has been developed and is ever evolving to provide a supportive care journey for the person within the GIC. The nurse specialist attends local and national GIC MDTs and has been involved in redevelopment of national guidelines. Progress to date Within the endocrine service waiting lists are up to date. All people on long term GAHT who wish specialist endocrine follow-up can access this service. People on GAHT now have an assessable, timely and knowledgeable point of contact via the endocrine nurse specialist.
Discussion
We hope by sharing the work undertaken by Grampian endocrine-GIC to highlight a useable framework that can be mirrored by other services when developing support for people on GAHT.

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P150

Use of Health Literacy Tools to Improve Written Information for Patients with or at Risk of Adrenal Insufficiency

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Background
The National Patient Safety Alert (2020) and introduction of the NHS Steroid Emergency Card has led to the development of guidelines, publications and patient information, aiming to improve safety and management of adrenal insufficiency and prevention of adrenal crisis. Health Education England (HEE), 'Plain English' and NHS England guidance recommends patient information is accessible and clear to a broad range of people, to ensure patients are fully aware of their condition and management.
Aim
We aimed to produce a clear, understandable, patient information leaflet (PIS) for people with or at risk of adrenal insufficiency, following a recommended process of development.
Methods
The PIS was developed using an iterative process; from creating content to the first evaluation of the leaflet by health care professionals. Content was co-authored by three adrenal endocrine specialist nurses. The leaflet was assessed for readability using the Flesch Reading Ease/Flesch Kincaid Grade Level available via Microsoft Word and the online readability assessment tool, Hemmingway Editor. A group of 50 endocrine specialist nurses assessed how understandable and clear the content of the PIS was based on HEE's 'health literacy-how to guide' and four step user testing. Specifically they were asked to find 15 key points from the PIS.
Results
The leaflet required several iterations to meet an acceptable readability score (Flesch Reading Ease-60.0, Flesch Kincaid Grade level-8.2, Hemmingway Editor, Grade 6-Good). Feedback from the group of endocrine specialist nurses was that the PIS target group was not clear, however key information was easily found.
Conclusion
This process has highlighted the importance of collaborating with key stakeholders, utilising available guidelines and readability tools in the development and evaluation of PIS. The leaflet requires further iteration and review, by both clinicians and people with or at risk of adrenal insufficiency, before being implemented in practice.

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P151

Transforming 'Late Effects' care post Covid-19

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Childhood cancer survivors are a growing population. Lifelong endocrine follow up is essential for brain tumour and bone marrow transplant survivors who received radiotherapy. Patients attending the 'late effects' clinic have investigations coordinated with an annual appointment including endocrine bloods, urine protein:creatinine ratio, blood pressure and weight. The Covid-19 pandemic necessitated appointments to be telephone. Patients were asked to arrange their annual investigations via the GP surgery in conjunction with their

appointment. In 2020, 24 patients received a telephone appointment, with 9 face to face prior to lockdown. 55% of patients had bloods taken in conjunction with the consultation. In 2021, 47 patients received a telephone appointment and 55% of patients had bloods taken in conjunction with the consultation. In 2019 prior to the pandemic, 33 patients were seen for a face to face appointment and 97% of them had bloods taken in conjunction with the consultation. Patients who attended face to face in 2019 had their urine protein;creatinine ratio taken at their appointment. In 2020 60% of patients had their urine checked remotely, and in 2021 it was 50%. In 2019 prior to the pandemic, 13% of appointments were not attended, which reduced to 4% in 2021 when appointments were telephone. Telephone appointments increased patient attendance but remote investigations were less successful in spite of communication with the GP surgery and patient. The NHS England Outpatient Recovery and Transformation Programme aims to offer appointments by telephone or video call and the 'late effects' service would benefit from this approach to improve attendance. However, more work is needed to implement the NHS long term plan and further service improvement to streamline this for childhood cancer survivors being seen in the 'late effects' service.

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Author Index