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PL1

Abstract Unavailable

DOI: 10.1530/endoabs.77.PL1

Society for Endocrinology Starling Medal Lecture

PL2

Strategies to turn up the heat – investigating human brown adipose tissue function

Roland Stimson
University of Edinburgh, Edinburgh, UK

The obesity epidemic has underlined the need for new treatments to aid weight loss and prevent the associated sequelae of obesity such as type 2 diabetes, hypertension, dyslipidaemia and cardiovascular disease. The relatively recent discovery of brown adipose tissue (BAT) in adult humans has revived interest in activating this tissue to increase energy expenditure as a novel treatment for obesity and associated metabolic disease. BAT is a thermogenic organ that generates heat to maintain body temperature in a cold environment. While BAT mass and activity are reduced in obesity, BAT is a plastic organ and activity can be increased in response to certain stimuli such as repeated cold exposure. In addition, the presence of BAT in obese subjects is associated with improved metabolic health and reduced incidence of cardiovascular disease. Therefore, it is important to determine how to safely increase BAT mass and thermogenesis to determine its therapeutic potential. However, our understanding of the pathways regulating human BAT remains limited, in part due to its location and the difficulty in quantifying activity *in vivo*. While most pharmacological agents known to activate BAT or increase browning have been identified in rodents, the majority have failed to translate to humans and there are key differences in the regulation of BAT activation between the species. The recent development of novel techniques to quantify human BAT activity *in vivo* has advanced our understanding of BAT thermogenesis and identified novel genes and pathways regulating thermogenesis, some with the potential for therapeutic manipulation. In this talk I will highlight these recent developments and discuss the potential of increasing energy expenditure as a treatment for obesity-associated metabolic disease.

DOI: 10.1530/endoabs.77.PL2

Society for Endocrinology Dale Medal Lecture

PL3

Abstract Unavailable

DOI: 10.1530/endoabs.77.PL3

Society for Endocrinology Transatlantic Medal Lecture

PL4

Abstract Unavailable

DOI: 10.1530/endoabs.77.PL4

Society for Endocrinology International Medal Lecture

PL5

Activation of the gp130 receptor: a panacea for the treatment of metabolic diseases?

Mark Febbraio
Monash University, Parkville, Australia

The gp130 receptor (gp130R) cytokines interleukin-6 (IL-6) and ciliary neurotrophic factor (CNTF) can improve metabolic disease, but due to the known pro-inflammatory effects of IL-6 and the antigenic response to the clinically used form of CNTF (Axokine^{TM}), both proteins have limited therapeutic utility. Accordingly, we recently engineered a chimeric gp130R ligand, termed IC7Fc, where one gp130 binding site has been removed from IL-6 and replaced with the leukemia inhibitory factor receptor (LIFR) binding site from CNTF and then fused with the fragment crystallizable (Fc) domain of immunoglobulin G (IgG), that shows promise for treating metabolic disease[1]. Moreover, in multiple models of insulin resistance and T2D, IC7Fc either increases, or prevents the loss, of skeletal muscle mass via increased abundance and activity of the Yes-associated protein (YAP)[1]. In parallel studies, we recently demonstrated that activation of the gp130R in the intestinal epithelium activates YAP and, in doing so, prevents fructose feeding-induced gut barrier deterioration, systemic endotoxemia, non-alcoholic steatohepatitis (NASH) and NASH driven liver cancer[2]. The concept that spg130R ligands could, therefore, have therapeutic utility for the treatment of several age-related diseases will be discussed.

References
1 Findeisen, M. *et al.* Treatment of type 2 diabetes with the designer cytokine IC7Fc. *Nature* 574, 63–68, (2019).
2 Todoric, J. *et al.* Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat Metab* 2, 1034–1045, (2020).

DOI: 10.1530/endoabs.77.PL5

Society for Endocrinology European Medal Lecture

PL6

Rethinking critical illness-related corticosteroid insufficiency

Greet Van den Berghe
KU Leuven, Leuven, Belgium

Critical illnesses are characterized by increased systemic cortisol availability, a vital part of the stress response. 'Relative adrenal failure' (later termed critical illness-related corticosteroid insufficiency or CIRCI) is a condition in which the systemic availability of cortisol is assumed to be insufficiently high to face the stress of the illness, and is most typically thought to occur in the acute phase of septic shock. Researchers suggested that CIRCI can be diagnosed by a suppressed incremental cortisol response to an injection of adrenocorticotropic hormone, irrespective of the baseline plasma cortisol concentration. This concept triggered several randomized clinical trials on the impact of large 'stress doses' of hydrocortisone to treat CIRCI, which gave conflicting results. Recent novel insights in the response of the hypothalamus-pituitary-adrenal axis to acute and prolonged critical illnesses challenge the concept of CIRCI, as currently defined, as well as the current practice guidelines for diagnosis and treatment. These novel insights will be presented and integrated within a novel conceptual framework that can be used to re-appreciate adrenocortical function and dysfunction in the context of critical illness. This novel conceptual framework opens perspectives for further research and for preventive and/or therapeutic innovations.

DOI: 10.1530/endoabs.77.PL6

Clinical Endocrinology Trust Lecture

PL7

The yin and yang of hormones and glucose

Márta Korbonits
Professor of Endocrinology and Metabolism, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

The balanced hormonal regulation of metabolism is the cornerstone of endocrinology. One of the most elegant aspects of our discipline is that increased or decreased hormone activities lead to predictable changes and diseases. We

were surprised, therefore, to identify a novel disease where the same genetic alteration, a missense change in the beta-cell transcription factor *MAFA*, causes two very opposite conditions: life-threatening hypoglycaemia due to numerous small insulin-secreting tumours, or noninsulin-dependent diabetes resembling MODY. The altered MAFA protein, which normally would have a very short half-life and thus can dynamically respond to the demand / cessation of demand for insulin secretion, showed reduced activity but a significantly prolonged half-life. The resulting two phenotypes showed a strong gender imbalance, with females typically developing insulinomatosis while males rather demonstrate diabetes. While this disease, familial insulinomatosis and diabetes, is extremely rare, elucidating its mechanisms may help us to understand the complex regulation and tumorigenesis of beta cells. At the other end of the disease frequency spectrum are patients with iatrogenic Cushing's syndrome due to corticosteroid treatment, some 3-11% of the general population. Based on our experimental data on the effect of cortisol on AMPK, the major metabolic enzyme influenced by metformin, we attempted to counteract the myriad of metabolic abnormalities associated with excess glucocorticoids using metformin. Our double-blind, randomised, placebo controlled trial on patients on steroid treatment, and no diabetes, receiving metformin or placebo resulted in better glucose, lipid, liver, thrombotic and bone parameters, and significantly reduced infections & hospital admissions. These data suggest the possibility, similar to bone and gastric protection, that we should consider the routine use of metformin for steroid-treated patients.

DOI: 10.1530/endoabs.77.PL7

Clinical Endocrinology Trust Visiting Professor Lecture

PL8

Abstract Unavailable

DOI: 10.1530/endoabs.77.PL8

Society for Endocrinology Medal Lecture

PL9

Revisiting Cushing's: The power of pre-receptor metabolism

Jeremy Tomlinson
University of Oxford, Oxford, UK

Glucocorticoids have potent effects on almost every tissue in the body and this is exemplified in patients with Cushing's disease. Whilst Cushing's disease is rare, glucocorticoids are commonly prescribed for their anti-inflammatory actions, but their use is associated with a series of undesirable adverse effects, including obesity, insulin resistance, hypertension, myopathy and osteoporosis. 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. Using combinations of cellular and rodent models, complemented by bespoke, proof-of-concept, clinical experimental medicine studies, we have been able to show that the isoforms of 5α-reductase (that inactivate cortisol and prednisolone), potently regulate exogenous glucocorticoid action. Inhibition of 5α-reductase increases cortisol and prednisolone availability and worsens adverse effects. Contrasting with this, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), regenerates active glucocorticoid (cortisol from cortisone and prednisolone from prednisone). Fuelled by observations in a patient with Cushing's disease who was protected from the development of adverse metabolic features due a defect in 11β-HSD1 activity, we tested the hypothesis that 11β-HSD1 inhibition may represent a novel approach to selectively limit the adverse effects of prescribed glucocorticoids. Rodent data, alongside evidence from a randomized, double-blind placebo-controlled trial have endorsed the hypothesis and identified a crucial role for active glucocorticoid regeneration specifically within adipose tissue. Taken together, these data not only demonstrate the critical importance of pre-receptor metabolism (perhaps over and above what we measure in the circulation) in regulating glucocorticoid action, but also highlight the potential of 11β-HSD1 inhibition as a strategy to limit the adverse effects of prescribed glucocorticoids.

DOI: 10.1530/endoabs.77.PL9

Society for Endocrinology Jubilee Medal Lecture

PL10

Cancer treatment endocrinopathies and growth hormone status throughout life

Stephen Shalet
Christie Hospital, Manchester, UK

Late effects of therapy can only become a meaningful concern, when the cure rate of the primary disorder is high enough to provide sufficient survivors. This happened for childhood cancer survivors around 50 years ago. The primary treatment modalities were surgery, radiotherapy, and combination chemotherapy. Amongst the most common treatment complications were dysfunction of the pituitary, thyroid, and gonad. The observation of gonadal damage and subsequent infertility led to studies exploring the timing between the damaging insults and future fertility potential, as well as the possibility of hormonal protection to preserve fertility

The pituitary dysfunction, seen classically in brain tumour survivors, was a consequence of radiotherapy (XRT) and consisted of various degrees of anterior hypopituitarism. The first hormone to be affected was always growth hormone (GH). These children grew poorly due to a number of factors, including impaired spinal growth (XRT) and early puberty, but GH deficiency (GHD) was a key contributor to the growth failure. Early studies investigated the relationship between the radiotherapy dose and the timing and degree of GHD, then moved on to search for the optimal biochemical method of diagnosing GHD with the increasing knowledge that the pathological insult was primarily hypothalamic rather than pituitary. Treatment with GH replacement began in the mid-1970s without, at that time, any safety data. Subsequently the efficacy of GH replacement in normalising linear growth was established, and the gradually acquired safety data reassuringly revealed no increase in tumour recurrence. Studies of the physiological profiles of GH secretion excluded any major prevalence of GH neurosecretory dysfunction, implying that pharmacological testing provided meaningful results. With the advent of DNA-derived GH, defining severe GHD in adolescence and various stages of adult life became important as well as determining response to GH therapy in adult life.

DOI: 10.1530/endoabs.77.PL10

Debate: To block or not to block

Controversies in peri-operative management of catecholamine-producing tumours

D1.1

Abstract Unavailable

DOI: 10.1530/endoabs.77.D1.1

D1.2

Abstract Unavailable

DOI: 10.1530/endoabs.77.D1.2

Society for Endocrinology Journal Awards

Society for Endocrinology Journal Award – *Journal of Endocrinology*

JA1

Estrogen accelerates heart regeneration by promoting the inflammatory response in zebrafish

Shisan Xu, Fangjing Xie, Li Tian, Samane Fallah, Fatemeh Babaei, Sinai H C Manno, Francis A M Manno III, Lina Zhu, Kin Fung Wong, Yimin Liang, Rajkumar Ramalingam, Lei Sun, Xin Wang, Robert Plumb, Lee Gethings, Yun Wah Lam & Shuk Han Cheng

Journal of Endocrinology, 2019, 245(1): 39–51 (DOI: https://doi.org/10.1530/-JOE-19-0413)

DOI: 10.1530/endoabs.77.JA1

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

JA2

STAT5 ablation in AgRP neurons increases female adiposity and blunts food restriction adaptations

Isadora C Furigo, Pryscila D S Teixeira, Paula G F Quaresma, Naira S Mansano, Renata Frazão & Jose Donato Jr

Journal of Molecular Endocrinology, 2019, 64(1): 13–27 (DOI: https://doi.org/10.1530/JME-19-0158)

DOI: 10.1530/endoabs.77.JA2

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

JA3

LDLR-mediated lipidome-transcriptome reprogramming in cisplatin insensitivity

Wei-Chun Chang, Hsiao-Ching Wang, Wei-Chung Cheng, Juan-Cheng Yang, Wei-Min Chung, Yen-Pin Ho, Lumin Chen, Yao-Ching Hung & Wen-Lung Ma

Endocrine-Related Cancer, 2019, 27(2): 81–95 (DOI: https://doi.org/10.1530/ERC-19-0095)

DOI: 10.1530/endoabs.77.JA3

Society for Endocrinology Journal Award – *Endocrine Connections*

JA4

Role of fasting duration and weekday in incretin and glucose regulation

Kim K B Clemmensen, Jonas S Quist, Dorte Vistisen, Daniel R Witte, Anna Jonsson, Oluf Pedersen, Torben Hansen, Jens J Holst, Torsten Lauritzen, Marit E Jørgensen, Signe Torekov & Kristine Færch

Endocrine Connections, 2020, 9(4): 279–288 (DOI: https://doi.org/10.1530/EC-20-0009)

DOI: 10.1530/endoabs.77.JA4

Society for Endocrinology Journal Award – *Clinical Endocrinology*

JA5

Metabolomics analysis in adults with high bone mass identifies a relationship between bone resorption and circulating citrate which replicates in the general population

April Hartley, Lavinia Paternoster, David M Evans, William D Fraser, Jonathan Tang, Debbie A Lawlor, Jon H Tobias & Celia L Gregson

Clinical Endocrinology, 2020, 92(1): 29–37 (DOI: https://onlinelibrary.wiley.com/doi/full/10.1111/cen.14119)

DOI: 10.1530/endoabs.77.JA5

Awards and Prizes

Teaching Achievement Award

TAA1

Developing a Career in Education

Niamh Martin
Imperial College, London, UK

I am committed to undergraduate and postgraduate education. As Endocrinology course lead, Imperial College Medical School, I have designed a course to consolidate key principles of Endocrine pathology and physiology. Clinical reasoning is a cornerstone of clinical practice and a key learning requirement in undergraduate medical education. I have focused on developing clinical reasoning skills throughout the Endocrinology course using interactive clinical cases. The students have consistently voted this course as the most popular in the early undergraduate years of the medical school. One of the challenges I have faced is maintaining student engagement and enthusiasm in a large student cohort. In 2015, I received the Society for Endocrinology Undergraduate Achievement Award to introduce Team Based Learning (TBL) in the Endocrinology course. Breaking down a large student cohort into 'teams' provides an opportunity for students to apply knowledge to answer questions and make collaborative decisions in interactive teaching sessions. TBL has been enormously successful, with excellent student feedback. I shared this innovation in an article for 'The Endocrinologist' in 2016. I am Head of Year 1, BSc in Biomedical Sciences at Imperial College, a new degree course which emphasises early development of laboratory skills. To increase confidence in the laboratory, particularly in team working and practical skills, I have developed 'The Biomedical Kitchen'. This is a new inter-departmental collaboration, drawing on parallels between cookery and science to support students starting in the molecular laboratory. In 2014 I designed and delivered the first annual Imperial Pituitary Masterclass, a multidisciplinary meeting to share best practice and explore challenging areas in pituitary disease. Many Endocrinology postgraduate trainees attend this meeting and are encouraged to present pituitary cases of interest. I received an Endocrine Network Grant from the Society for Endocrinology in 2018 to facilitate the development of the Masterclass as a national meeting.

DOI: 10.1530/endoabs.77.TAA1

Outstanding Clinical Practioner Award

OCP1.1

Outstanding Clinical Practitioner Award: Improving the care of patients with thyroid diseases

Kristien Boelaert
University of Birmingham, Birmingham, UK

Thyroid diseases are common with thyroid dysfunction affecting up to 10% of the population and thyroid nodules occurring in more than 50% of people. I currently lead an internationally unique and wide-ranging programme of translational thyroid research, which integrates clinical and laboratory research with rigorously conducted clinical trials. My research findings are incorporated in national and international clinical management guidelines and drive professional training in addition to clinical and patient decisions in the UK and beyond. I am responsible for national policy setting related to the optimal management of thyroid diseases in the UK through leadership of UK thyroid guidelines (NICE, RCOG, BTA, BAETS) ensuring clinical and cost-effective healthcare delivery. Close collaboration with national patient groups ensures direct involvement of patients in decision-making processes and in driving the national research agenda relating to thyroid diseases. I believe that dissemination of research and generation of impact to the lay community are crucial elements of improving patient care. I actively engage with a number of national patient support groups including the British Thyroid Foundation (BTF) and the Butterfly Thyroid Cancer Trust (BTCT), and I am a regular speaker at their meetings. In response the COVID-19 pandemic, I have written guidance on the management of thyroid dysfunction during COVID-19. I am co-chair for the Society for Endocrinology project on the Future of Endocrine Services following the pandemic. This aims to facilitate the seizing of new opportunities ensuring world-class care for patients with endocrine disorders in the UK by harnessing research, education, and new ways of working. I feel privileged to receive this award and I am delighted to share this with my friend and colleague, Helen Simpson, who has transformed the care of patients with adrenal disorders.

DOI: 10.1530/endoabs.77.OCP1.1

OCP1.2

Outstanding Clinical Practitioner Award 2021

Helen Simpson
Department of Diabetes and Endocrinology, University College London Hospitals NHS Foundation Trust, London, UK

It is a real honour to be named Outstanding Clinical Practitioner by the Society for Endocrinology, especially as I am sharing this with my award twin, Professor Kristien Boelaert. For my presentation I will talk about aspects described in the nomination and discuss how improving patient care is at the heart of all we do. This can be achieved at an individual patient level, organisational level, and a national systems level. I will describe work around the NHS steroid emergency card and National Patient Safety Alert, which illustrates how by working in partnerships different organisations, namely Society for Endocrinology, Royal College of Physicians, NHS Patient Safety team, Royal Pharmaceutical Society, British Thoracic society. Working with patient support groups such as the Addison's Disease Self Help Group, Pituitary Foundation and Living with CAH teams, we can devise and disseminate patient safety work. I will also reference 2 patients with phaeochromocytoma who kindly gave up time to write comments to highlight the need to individualise patient care, especially during a pandemic. I'd then like to link this to thinking about how we remodel our services now the world has changed, as we live and work through a pandemic. Alternatively I may just talk about cricket. Whatever my talk compromises of I hope we meet for a face to face meeting and look forward to seeing everyone.

DOI: 10.1530/endoabs.77.OCP1.2

Nikki Kieffer Medal

NKM1

Abstract Unavailable

DOI: 10.1530/endoabs.77.NKM1

Endocrine Nurse Award

ENA1

Abstract Unavailable

DOI: 10.1530/endoabs.77.ENA1

Early Careers and Plenary Orals

Early Career Prize Lecture Basic Science

EC1.1

Gene discovery in neonatal diabetes to uncover the mechanisms regulating human pancreas development

Elisa De Franco, Matthew Wakeling, Nick Owens, Matthew Johnson, Sarah Flanagan & Andrew T Hattersley
Institute of Biomedical and Clinical Sciences, University of Exeter College of Medicine and Health, Exeter, UK

Understanding how pancreatic beta-cells develop during human development is essential to advance current protocols aimed at developing insulin-producing beta-cells *in vitro* and highlight therapeutic targets for diabetes treatment. Identifying the single-gene mutations which result in individuals developing diabetes in the first 6 months of life (a condition called neonatal diabetes) has the potential to give unique insights into the genes regulating human beta-cells which would never be discovered by studying animal models alone. By performing genome sequencing analysis of >100 individuals with neonatal diabetes, we have identified mutations in genes which were not previously thought to be important within beta-cells. These include genes essential for preserving beta-cell function (like YIPF5 which encodes a regulator of endoplasmic reticulum to Golgi transport) and genes crucial for human pancreatic development (such as the gene encoding for the negative regulator of transcription and stem cell pluripotency factor, CNOT1). These results highlight the power of human genetic studies to pinpoint genes which are essential for human beta-cell function and development, improving our knowledge of the biological mechanisms leading to diabetes and highlighting new promising targets to be further investigated to develop better therapies for individuals living with diabetes.

DOI: 10.1530/endoabs.77.EC1.1

Early Career Prize Lecture Clinical

EC1.2

Cardiometabolic disease burden and urine steroid metabolome in benign adrenocortical tumours: a case-control study

Alessandro Prete[1,2,3], Anuradhaa Subramanian[4], Irina Bancos[1,5], Vasileios Chortis[12,3], Stylianos Tsagarakis[6], Katharina Lang[1,2,3], Magdalena Macech[7], Danae A Delivanis[5], Ivana D Pupovac[8], Giuseppe Reimondo[9], Ljiljana V Marina[10], Timo Deutschbein[11,12], Maria Balomenaki[6], Michael W O'Reilly[1,13], Tomasz Bednarczuk[7], Catherine Zhang[5], Tina Dusek[8], Aristidis Diamantopoulos[6], Miriam Asia[2,3], Agnieszka Kondracka[7], Dingfeng Li[5], Jimmy R Masjkur[14], Marcus Quinkler[15], Grethe A Ueland[16], M Conall Dennedy[17], Felix Beuschlein[18,19], Antoine Tabarin[20], Martin Fassnacht[11], Miomira Ivovic[10], Massimo Terzolo[9], Darko Kastelan[8], William F Young Jr[5], Konstantinos N Manolopoulos[1], Urszula Ambroziak[7], Dimitra A Vassiliadi[6], Angela E Taylor[1], Alice J Sitch[4,21], Krishnarajah Nirantharakumar[1,2,4] & Wiebke Arlt[1,2,3,21]
[1]Institute of Metabolism and Systems Research, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK; [3]Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. [4]Institute of Applied Health Research, University of Birmingham, Birmingham, UK. [5]Division of Endocrinology, Metabolism, Diabetes and Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA. [6]Department of Endocrinology, Diabetes and Metabolism, Evangelismos Hospital, Athens, Greece. [7]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland. [8]Department of Endocrinology, University Hospital Centre Zagreb, Zagreb, Croatia. [9]Division of Internal Medicine, University of Turin, San Luigi Hospital, Turin, Italy. [10]Department for Obesity, Reproductive and Metabolic Disorders, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. [11]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany. [12]Medicover Oldenburg MVZ, Oldenburg, Germany. [13]Department of Medicine, Royal College of Surgeons in Ireland, University of Medicine and Health Sciences, Dublin, Ireland. [14]Department of Medicine III and Institute of Clinical Chemistry and Laboratory Medicine, Technische Universität Dresden, Dresden, Germany. [15]Endocrinology in Charlottenburg, Berlin, Germany. [16]Department of Endocrinology, Haukeland University Hospital, Bergen, Norway. [17]Department of Endocrinology, University Hospital Galway, Newcastle, Galway, Ireland. [18]Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitäts-Spital Zürich (USZ) und Universität Zürich (UZH), Zurich, Switzerland. [19]Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Universität München, Munich, Germany. [20]Service d'Endocrinologie, Centre Hospitalier Universitaire, Hopital du Haut Leveque, Pessac, France. [21]NIHR Birmingham Biomedical Research Centre, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Background
The overwhelming majority of incidentally discovered adrenal tumours are benign adrenocortical adenomas. These can be non-functioning (NFAT) or associated with cortisol excess on a spectrum ranging from rare clinically overt adrenal Cushing's syndrome (CS) to much more prevalent mild autonomous cortisol secretion (MACS) without signs of CS. The 1mg-overnight dexamethasone suppression test (DST) further differentiates MACS-1 (possible MACS; post-DST cortisol 50–138 nmol/l) and MACS-2 (definitive MACS; post-DST cortisol >138 nmol/l). A recent systematic review and meta-analysis reported that benign adrenocortical tumours are associated with a high prevalence of metabolic disease; however, large-scale prospective data are lacking.
Methods
We analysed all patients with benign adrenocortical tumours and DST results recruited to the prospective ENSAT EURINE-ACT study ($n=1305$). The prevalence of hypertension, type 2 diabetes, and dyslipidaemia was compared to 5268 population controls from the 2014 cohort of the Health Survey for England using Poisson regression to obtain sex-, age- and BMI-adjusted prevalence ratios (aPR). In the patients, we also carried out multi-steroid profiling of 24-h urine by tandem mass spectrometry and compared results to 127 healthy controls using a sex-, age- and BMI-adjusted linear regression model.
Results
Cortisol excess was highly prevalent (MACS-1 34.6%, MACS-2 10.7%, CS 5%). Patients had higher rates of metabolic disease than population controls (hypertension: NFAT aPR 1.88 [95%CI 1.75–2.02], MACS-1 1.86 [1.74–1.99], MACS-2 2.08 [1.88–2.31], CS 2.97 [2.47-3.58]; type 2 diabetes: NFAT 4.11 [3.28–5.16], MACS-1 4.34 [3.47-5.44], MACS-2 5.30 [4.03–6.97], CS 10.17 [7.27–14.23]; dyslipidaemia: NFAT 1.76 [1.53–2.02], MACS-1 1.71 [1.49–1.97]), MACS-2 1.95 [1.52–2.50]; all $P<0.001$). Urinary multi-steroid profiling revealed a gradual increase in glucocorticoid excretion from NFAT over MACS-1 and MACS-2 to CS while androgen excretion decreased.
Conclusion
Patients with benign adrenocortical tumours – including NFAT – have an increased cardiometabolic disease burden that increases with glucocorticoid output.

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Clinical Endocrinology Trust Best Abstract Clinical

EC1.3

Phase 3 and extension study of modified-release hydrocortisone in the treatment of congenital adrenal hyperplasia

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Background
Patients with congenital adrenal hyperplasia (CAH) due to classic 21-hydroxylase deficiency have poor health outcomes. We compared disease control in CAH adults treated with modified release hydrocortisone (MRHC, Chronocort®, Diurnal Ltd) versus standard glucocorticoid (GC).
Methods
6-month, Phase 3 study in 122 patients randomised to either MRHC twice daily or standard GC followed by safety extension study on MRHC. Patients had 24-hr 17-hydroxyprogesterone (17-OHP) profiling at baseline 4, 12 & 24 weeks. The primary endpoint was change from baseline to 24 weeks in logarithm mean of 24-hr standard deviation score (SDS) 17-OHP profile.
Results
Both groups improved hormonal control on intensive monitoring; however, the mean 24-hour 17-OHP SDS was lower on MRHC compared to standard GC at 4

weeks ($P=0.007$) and 12 weeks ($P=0.019$), but not at 24 weeks. At 24 weeks, MRHC compared to standard GC showed greater reduction in: 17-OHP SDS morning & afternoon ($PP=0.044$), 24 h AUC ($P=0.025$), and variability ($P<0.001$). Good disease control (09:00h serum 17OHP <36.4 nmol/l) was 52% at baseline and at 6 months 91% for MRHC and 71% for standard GC ($P=0.002$). There were no adrenal crisis on MRHC and 3 on standard GC. In the ongoing extension study (221 patient years), there were 12 adrenal crises in 5 patients (5.4 / 100 patient years). Geomean 9am 17-OHP was within optimal range on median MRHC dose of 20mg daily. In 27 women aged <50yrs not using oral contraceptives or IUD, 9 patients reported improved menstruation, 4 became pregnant and there have been 4 partner pregnancies.

Conclusions

Twice daily MRHC improved control of CAH with most patients showing good disease control on an adrenal replacement dose of hydrocortisone and this was associated with patient reported clinical benefit, including restoration of menstruation and pregnancies.

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Clinical Endocrinology Trust Best Abstract Basic

EC1.4

The vagal Calcium Sensing Receptor mediates the effect of protein ingestion on insulin release and regulates macronutrient metabolism

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Protein stimulates insulin release and improves post-prandial glycaemic excursions. The underlying mechanism has previously been attributed to gastric emptying, incretin release and direct pancreatic stimulation. However, our studies suggest the calcium sensing receptor (CaSR) in the vagus nerve plays an important role. The CaSR has a well characterised role in calcium homeostasis, but also acts as a protein metabolite sensor. In response to the amino acid products of protein digestion it mediates the secretion of gut hormones including the incretin Glucagon-like peptide-1 (GLP-1). Peripheral administration of a CaSR antagonist blocked protein's ability to improve glucose tolerance and stimulate insulin secretion. This was independent of GLP-1 as neither CaSR knockdown in GLP-1 secreting cells of the gut or inhibition of the GLP-1 receptor with exendin 9-39 affected protein's ability to improve glucose tolerance. The vagus nerve provides bi-directional communication between the brain and key metabolic organs. Oral administration of amino acids in rodents increased neuronal activation in central nervous system regions directly innervated by the vagus. Pharmacological inhibition of vagal afferent and efferent pathways in mice blocked improvements in glucose tolerance, following a protein pre-load, in a nutrient specific manner. Moreover, inhibition of vagal efferent signalling blocked protein stimulated insulin secretion. Interestingly, the CaSR is one of the few nutrient sensors expressed in vagal afferents. CaSR knockdown in vagal afferents, using both germline and adult transgenic models, blunted protein stimulated insulin secretion. Though this did not affect glucose tolerance, it did lead to changes in circulating levels of amino acids. This suggests vagal CaSR may be important in mediating the effects of insulin on protein metabolism, and that there may be distinct entero-vagal circuits regulating different metabolic pathways. Overall this suggests the vagus nerve plays an important role in protein's ability to modulate insulin release and metabolic pathways.

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Symposia

Lifestyle hacks for metabolic disease

S1.1

Abstract Unavailable
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S1.2

Abstract Unavailable
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S1.3

Abstract Unavailable
DOI: 10.1530/endoabs.77.S1.3

Nuclear receptors in male reproduction

S2.1

Liver X Receptors (LXR)s and testicular function

Sheba Jarvis[1], Lee Gethings[2], Raffaella Gadaleta[1,3], Damien Leach[1], Emmanuelle Claude[2], Antonio Moschetta[3], Robert Winston[1], Catherine Williamson[4] & Charlotte Bevan[1]
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Liver X receptors (LXRs) are are ligand-dependent transcription factors, members of the nuclear receptor superfamily of transcription factors. In humans two LXR isoforms exist, LXRα (NR1H3) and LXRβ (NR1H2). LXRα is expressed predominantly in metabolically active tissues, while LXRβ is expressed in the majority of tissues. They have long been known to have critical roles in regulation of lipid metabolism, particularly cholesterol homeostasis; oxidised cholesterol metabolites are activating ligands for both LXRα and LXRβ. In the testis, tightly regulated lipid metabolism is crucial for male fertility. LXRs are highly expressed in the testis but their role in regulating lipid homeostasis in this tissue is not fully understood. *Lxrα/β* double knockout male mice (*Lxrα/β* DKO*)* exhibit aberrations in lipid metabolism and are sterile by 7 months. We used integrated wide-platform studies and imaging methods to identify specific disrupted cellular lipids and novel candidate target genes in the testis. In addition to *in vitro* and genetic models, we developed an *ex vivo* human testicular model in which to model LXR pathways in human testis and identify LXR deregulation in human subfertility. We confirm for the first time that LXR pathways are active in human testis. Our results suggest the conventional roles of LXRs in cholesterol homeostasis are important in human testis, as previously described in mouse, and implicate LXRs in novel lipid pathways critical for male reproductive function.
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S2.2

Bile acid metabolism and nuclear receptors in male reproduction

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Over the last decades, studies using pharmacological approaches and transgenic mouse models have defined the major roles of bile acids as signaling molecules. Bile acids control many physiological functions such as lipid homeostasis, glucose, and energy metabolisms. In the last years, bile acids have been demonstrated to control male reproductive function. Here, we will highlight the impacts of bile acids on testicular physiology focusing on the roles of the nuclear bile acid receptor FXRα (Farnesoid-X-Receptor α) on mouse spermatogonial cells as well as on steroidogenic Leydig cells and the interaction with the hypothalamus/pituitary axis. We will present data supporting a major role for the FXRα signaling pathway in the deleterious impacts of the oestrogenic endocrine disruptor Bisphenol-A on testicular physiology. Finally, we will show data on the regulation of bile acid homeostasis within the testis. All these data should define research perspectives to better define the links between metabolic pathologies (liver) and fertility disorders. This should allow proposing new innovative therapeutic tracks in the field of the biology of reproduction.
DOI: 10.1530/endoabs.77.S2.2

S2.3

Abstract Unavailable
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Novel approaches to the diagnosis and treatment of endocrine neoplasia

S3.1

Abstract Unavailable
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S3.2

Abstract Unavailable
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S3.3

Abstract Unavailable
DOI: 10.1530/endoabs.77.S3.3

Understanding pathogenesis: development of novel treatments

S4.1

Abstract Unavailable

DOI: 10.1530/endoabs.77.S4.1

S4.2

Thyroid eye disease

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Graves' orbitopathy or thyroid eye disease (TED) represents the most common extra thyroidal manifestation of Graves' disease. Smoking and radioactive iodine therapy are the most important modifiable risk factors. Thyrotropin receptor and insulin-like growth factor-1 receptor crosstalk, orbital inflammatory infiltration and activation of orbital fibroblasts lead to perpetuation of orbital inflammation and expansion of orbital tissues, and hence various adverse mechanical consequences. Patients suffer from significant disfigurement, disability and impaired qualify of life because of the pathological processes. Early referral to specialized multidisciplinary care allows prompt diagnosis and treatment, which improves patients' outcome. Selenium is useful in mild disease, while intravenous glucocorticoids (IVGC) are the mainstay of treatment in active or sight threatening cases. Novel immunomodulatory treatment can potentially overcome limitations of current therapies. It is reasonable to recommend the combination of IVGC and mycophenolate as the new standard of care in active moderate-to-severe TED in view of its practicability and superior efficacy to conventional treatment. Other combinations of widely available and affordable therapies may also be beneficial in TED, e.g. IVGC + orbital radiotherapy. Biologics (e.g. teprotumumab, tocilizumab) appear highly promising both in treatment naïve or resistant cases, although long term efficacy and safety data is still pending. The roles of other existing targeted therapies in TED are also worth exploring (e.g. anti-IL17 agents for the IL-23/IL-17/Th17 axis, sirolimus for the mTOR pathway). Furthermore, several novel therapeutic agents can potentially treat Graves' hyperthyroidism and associated TED simultaneously by targeting their shared immunological mechanisms (e.g. antigen-specific immunotherapy ATX-GD-59; anti-CD40 monoclonal antibody iscalimab; TSH-R antagonists). Nonetheless, all new treatments should be carefully examined in randomized controlled trials (versus placebo and/or standard of care), preferably with standardized primary and secondary outcomes, in order to draw sound conclusions on the efficacy of certain intervention and facilitate comparisons among different trials.

DOI: 10.1530/endoabs.77.S4.2

S4.3

Translational studies in thyroid hormone transport

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Thyroid hormone transporters at the plasma membrane govern intracellular thyroid hormone concentrations. MCT8 represents a key thyroid hormone transporter. MCT8 deficiency (also known as Allan-Herndon-Dudley syndrome) is a devastating developmental disorder caused by mutations in the *MCT8* gene (located on the X-chromosome), with an estimated prevalence of 1:70.000 males. The phenotype comprises (1) a 'metabolic' or endocrine component dominated by signs of toxic high serum T3 concentrations and (2) a 'neurocognitive' component due to impaired neurological development. As a consequence of impaired thyroid hormone entry into the brain, individuals with MCT8 deficiency exhibit severe intellectual and motor disability and fail to achieve early developmental milestones. The endocrine hallmark of MCT8 deficiency are high serum T3, low T4 and normal TSH concentrations. Peripheral tissues that rely on transporters other than MCT8 are exposed to elevated T3 levels. Such chronic thyrotoxicosis leads to tachycardia, muscle wasting, hypermetabolism and progressive reduction in body weight, constituting significant morbidity and mortality in this vulnerable population. Preclinical studies indicated that the T3 analog TRIAC can bypass MCT8 at the cellular level and, thus, restore thyroid hormone signaling in MCT8-deficient cells. Recently, the results were published from a multicentre, international clinical trial (Triac Trial I) in which patients were treated with TRIAC. Key clinical outcomes improved with TRIAC treatment in patients with MCT8 deficiency. Data in animal models showed that TRIAC can completely normalize the brain phenotype. An ongoing trial (Triac Trial II) investigates if TRIAC can ameliorate the neurocognitive phenotype when administered in young individuals.

DOI: 10.1530/endoabs.77.S4.3

What is new in calcium and bone

S5.1

Osteomorphs: a new cell entity regulating bone resorption

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Osteoclasts are long lived highly specialised bone resorbing cells which form through the fusion of mononuclear pre-cursor cells and are believed to follow a linear fate and undergo apoptosis at the end of their life cycle. A number of anti-resorptive therapeutics target these cells, either preventing their resorptive function, Bisphosphonates, or inhibiting their formation, Denosumab (Anti-RANKL-Dmab). These agents have achieved success in preventing bone loss and fractures in patients with osteoporosis, amongst other diseases, however complications from their long term use has led to treatment cessation. In the case of Denosumab, treatment cessation has led to rebound bone loss and increased fractures, providing new challenges for its clinical use. We visualised the dynamics of osteoclasts in real time within live bone tissue leading to the discovery of a new fate for these complex cells. Further, this novel cell biology provides an improved understanding of patient response to anti-resorptive therapy. We developed a novel intravital imaging methodology to visualize osteoclast dynamics on the intact endocortical surface of tibia in live mice. Employing a double reporter mixed bone marrow chimera model and using sRANKL to stimulate osteoclasts and osteoprotegerin-Fc (OPG:Fc) to mimic Dmab we examined osteoclast dynamics and function. We showed that in addition to apoptosis, osteoclasts undergo fission to form osteomorphs, a novel intermediate cell of the osteoclast lineage. These osteomorphs were then shown to re-fuse, confirming the process of osteoclast recycling as an alternative osteoclast fate to apoptosis. Using RNAseq we defined the osteomorph as a novel cell population, distinct from osteoclasts and osteoclast pre-cursors. Interestingly, osteomorph specific genes were associated with bone phenotypes in mice. We also showed accumulation of osteomorphs and their rapid re-fusion following withdrawal of OPG:Fc, providing a mechanism for the rapid bone loss and fractures suffered by patients following Denosumab therapy withdrawal.

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S5.2

Abstract Unavailable

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S5.3

Abstract Unavailable

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Characterising the cortex to improve clinical care

S6.1

Characterizing the Cortex to Improve Clinical Care. Single cell sequencing: lessons for the pathogenesis of adrenocortical tumours

Cristina L Ronchi
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Key learning points

- Adrenocortical tumors comprise frequent benign adenomas and rare aggressive carcinomas (ACC).
- cAMP/PKA pathway plays a central role in the pathogenesis of cortisol-producing adenomas - associated with Cushing syndrome, while molecular alterations in Wnt/β-catenin, Rb/p53 pathway and chromatin remodeling are frequent in ACCs.
- However, the pathogenic mechanisms underlying autonomous steroid secretion and adrenal tumourigenesis are in many aspects obscure.
- We aimed to gain a better understanding of these aspects utilizing single-cell transcriptomics (RNA-seq) that may provide fundamental insights in the architecture and functional consequences of cell subtypes within the human adrenal gland.
- This potentially paradigm-changing approach shall increase resolution of molecular events involved in the pathogenesis of autonomous steroid secretion and adrenocortical tumour development.

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S6.2

Abstract Unavailable

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S6.3

Abstract Unavailable

DOI: 10.1530/endoabs.77.S6.3

What is New?

WIN1

Abstract Unavailable
DOI: 10.1530/endoabs.77.WIN1

WIN2

Abstract Unavailable
DOI: 10.1530/endoabs.77.WIN2

Clinical Management Workshops

Pituitary challenges: Prompt, practical and post-op

CMW1.1

Apoplexy

Niki Karavitaki
Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. Centre for Endocrinology, Diabetes and Metabolism, Birmingham, UK. Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Pituitary tumour apoplexy is a condition that occurs as a result of acute haemorrhage and/or infarction within a pituitary tumour (most commonly non-functioning pituitary adenoma), which may or may not be previously known. The clinical presentation occurs within a few hours or days and is due to sudden expansion of the pituitary gland. Manifestations cover a wide range including very intense and frequently retro-orbital headache, nausea and vomiting, visual impairment, ocular paresis, pituitary dysfunction and altered mental state. These, combined with the typical imaging features establish the diagnosis. Management should be prompt and requires involvement of a multidisciplinary team (endocrinologist, neurosurgeon, neuro-ophthalmologist, neuro-radiologist).
Immediate administration of high-dose glucocorticoids should be initiated, even before laboratory results are available, covering not only the increased risk of hypoadrenalism but also offering anti-inflammatory and anti-oedematous effects. Further management strategy will depend on the clinical manifestations, as well as the presence of co-morbidities. Prompt surgical decompression is offered in cases with severe or progressive deterioration of the visual acuity or visual fields or in the presence of altered mental state, and it leads to visual and neurological recovery in most of the patients. Conservative management and careful monitoring are adopted in cases with mild, stable clinical picture (including those with isolated ocular palsies) resulting in favourable visual and neurological outcomes. If during monitoring progression of symptoms occurs, later surgery is indicated with potential benefit, especially in terms of visual prognosis. Despite the above recommendations, clear proof of optimal outcomes in the form of randomised controlled trials is lacking, and relevant studies are necessary to put the management of pituitary tumour apoplexy on a sounder scientific footing.

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CMW1.2

Abstract Unavailable

DOI: 10.1530/endoabs.77.CMW1.2

CMW1.3

Post operative management of pituitary patients – Keeping it straightforward and safe

Simon Cudlip
Department of Neurosurgery, Oxford University Hospitals NHSFT, Oxford, UK.

We live in a world where neurosurgeons still prescribe salt tablets and fludrocortisone for hyponatraemia, and think cerebral salt wasting syndrome happens on a weekly basis. Neurosurgeons clearly need help, and the world of endocrinology needs to stage an intervention
Pituitary surgery is almost exclusively based in tertiary referral centres where neurosurgical departments are sited, often with endocrinology departments on a different site in the same city. In addition, there remain large variations in practice regarding post-op management of pituitary patients, in some cases with post operative protocols varying between individual surgeons and endocrinologists within the same hospital. I will discuss the benefits of pituitary services getting on the same page regarding the postoperative management of pituitary patients. This principally involves agreed protocols and close collaboration between endocrinologists, ANPs and pituitary surgeons. By continued data gathering and fine adjustment of these protocols, continued improvements can be made in postoperative complications and thus patient outcomes, and significantly reduce length of hospital stay.
With a clear protocols, and close team working between surgeons and endocrinologists, clinicians and nurses with less experience of the postoperative management of pituitary patients but involved in the care of such patients, are better placed to deliver high quality care. And remember....right now in your hospital....a neurosurgeon is thinking of prescribing DDAVP without speaking to an endocrinologist....somebody make it stop!

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Widening perspective on reproductive health

CMW2.1

Endometrial health – the role of the specialist menstrual disorders service

Jacqueline Maybin
MRC Centre for Reproductive Health at the University of Edinburgh, Edinburgh, UK.

Abnormal uterine bleeding (AUB) is a debilitating symptom that affects up to one in three women at some point in their reproductive lives. It may result in anaemia that necessitates blood transfusion and has a significant negative impact on quality of life. In addition, AUB has a detrimental economic impact on those who experience it, health services and the wider economy. A number of medical treatment options for AUB are currently available, but their success is limited by side effects and lack of effectiveness. This means many patients progress to fertility removing surgical management. This session will define typical and problematic menstrual bleeding before reviewing the benefits and limitations of existing treatment options for AUB. The role of the specialist menstrual disorders service in improving clinical care will be explored, with a focus on better diagnosis and more specific treatment of the underlying cause of AUB. The unanswered questions and unknowns in menstrual physiology and pathology will be signposted throughout, alongside discussion of the latest research to develop novel therapeutic strategies for AUB.

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CMW2.2

Abstract Unavailable

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CMW2.3

Abstract Unavailable

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Basic Physiology Workshops

New techniques and approaches

BPW1.1

Abstract Unavailable

DOI: 10.1530/endoabs.77.BPW1.1

BPW1.2

Research Facilitation or Management

Tim Giles
University of Birmingham, Birmingham, United Kingdom

There are many opportunities for those who pursue a career in science. This can include a direct route through academia and ultimately becoming a professor and leading your own research group. However, very few people go all the way through with this and therefore it is important to consider other options. Further career paths could include working in industry, government or in a research support setting amongst others. A career in research support is a rewarding one, often being a strong source of support for academics, from early-career researchers all the way to professor level. You can still maintain those connections with cutting edge research and use the skills you have developed during a PhD or post-doc. The knowledge gained during a PhD or post-doc can include strong analytical skills, time management and coping with pressure. These are all very important for a career in research support where applications come thick and fast. Research support is becoming an increasingly important area of University development, with competition for funding becoming more challenging, any additional support an academic has access to is welcomed.

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BPW1.3

Abstract Unavailable

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Model systems

BPW2.1

Modelling diabetes using iPSCs and adult derived organoids

Rocio Sancho
King's College London, London, United Kingdom

Loss of beta cell mass in the pancreas characterises type 1 and late-stage type 2 diabetes, resulting in a reduction of insulin levels. The pancreas has a very limited regenerative potential during homeostasis. Despite its quiescent nature, recent in vivo models suggest that a certain degree of regeneration and cellular interconversion is possible in the adult pancreas. The molecular regulation of this plasticity shares remarkable similarities with pancreas beta cell differentiation during development, however, the identity of the plastic cells remains elusive. Using iPSCs and adult ductal derived organoids we have uncovered new fundamental regulatory networks and cell populations involved in pancreatic cell fate decisions during homeostasis and diabetes. The use of iPSCs- and adult-derived organoids offers novel therapeutic avenues and new strategies for modelling diabetes *in a dish*.

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BPW2.2

Abstract Unavailable

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BPW2.3

Abstract Unavailable

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How Do I? Sessions

How do I…? 1

HDI1.1

Dr Claire Higham
Claire Higham
Christie Hospital NHS Foundation Trust, Manchester, UK.

This talk will cover the currently available evidence describing the endocrine and metabolic consequences of radiotherapy treatment to the hypothalamus and pituitary. A practical approach to surveillance, diagnosis and management of these consequences in childhood and adult cancer survivors will be provided.

DOI: 10.1530/endoabs.77.HDI1.1

HDI1.2

How do I investigate a young person with a low trauma fracture?
Jennifer Walsh
University of Sheffield, Sheffield, UK.

Long bone fractures are quite common in teenagers during rapid growth, due to the lag between longitudinal growth and cortical consolidation and trabecular structure. Vertebral fractures are uncommon in young people, and should always raise concern. A low trauma fracture is defined as a fall from standing height or less, but it is important to take a good history of the mechanism of fracture, and any previous fractures. Family history is important too. Causes of bone fragility in young people include malabsorption or poor nutrition, inflammatory disease and steroid treatment. Less common are postpartum osteoporosis and inherited disorders of bone metabolism. Look for clinical features of osteogenesis imperfecta or hypermobility syndromes and endocrinopathies. Measure bone mineral density and test for underlying causes of bone fragility (Calcium, phosphate, alkaline phosphatase, vitamin D, FBC, ESR, coeliac antibodies, TSH). Bone turnover markers are not very helpful in people before peak bone mass, because bone turnover is still high. Bone biopsy can be helpful in quantification of bone turnover and identification of mineralisation defects and rare diseases if there is real diagnostic and management uncertainty, but often doesn't add new information.

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HDI1.3

Abstract Unavailable

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HDI1.4

Abstract Unavailable

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HDI1.5

Abstract Unavailable

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HDI1.6

How do I optimise thyroid status after RAI therapy?
Nicola Zammitt
Edinburgh Centre for Endocrinology and Diabetes, Edinburgh, UK.

First, it is pertinent to ask WHY we should optimise thyroid status after RAI therapy. The links between poorly controlled thyroid function and patients' wellbeing, weight and thyroid eye symptoms will be discussed. This talk will also outline the use of block and replace therapy to reduce the risk of thyroid hormone instability following RAI.

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How do I…? 2

HDI2.1

How do I investigate abnormal alkaline phosphatase?
Rachel Crowley
St Vincent's University Hospital, Dublin, Ireland. University College Dublin, Dublin, Ireland.

Alkaline phosphatase is a widely-ordered test from the clinical laboratory. This brief clinical overview will cover the considerations an endocrinologist should make when assessing a patient referred with an incidental finding of either low or elevated alkaline phosphatase. Some discussion from a laboratory perspective will be included, with a clinic visit and the many caveats for interpretation of alkaline phosphatase in mind, as well as the patient factors to be assessed at clinical review. A practical approach to review and investigation will be outlined.

DOI: 10.1530/endoabs.77.HDI2.1

HDI2.2

A low testosterone level in a man with obesity – what to advise based on current evidence
Richard Quinton
University of Newcastle-upon-Tyne, Newcastle, UK. Newcastle-upon-Tyne Hospitals, Newcastle, UK.

Male Hypogonadism (MH) is a clinical and biochemical diagnosis, comprising pathologically low serum testosterone (T) levels and clinical features of androgen deficiency, of which low muscle mass and increased fat mass are features. The diagnosis is most secure when framed in the context of a recognised clinical syndrome, or with male factor infertility from impaired gonadal function. Testosterone levels in individual males are subject to considerable variation, according to nutritional status (both acute and chronic), sleep-wake periodicity and general state of health. Therefore, unless gonadotrophin levels are raised (signalling primary gonadal insufficiency), a low T level in the absence of corroborative clinical context is of itself insufficient to establish a verified diagnosis. Men with obesity and metabolic syndrome can represent a particular diagnostic challenge in that T and gonadotrophin levels may be low-normal for physiological, rather than pathological reasons. These comprise non-fasted or afternoon venepuncture; hyperinsulinaemic suppression of hepatic SHBG secretion giving rise to apparently low total-T with normal free-T, and suppression of gonadotrophin secretion through hyperglycaemia, hyperoestrogenaemia (mediated by aromatisation of T in adipose tissue), inflammatory adipokines and the effects of general ill health. Men with simple obesity can also exhibit clinical features that overlap with those of MH, including sexual dysfunction, fatigue and gynaecomastia, which adds to the confusion, albeit generally in the absence of key features such as anaemia, osteopaenia, or reduction in testes volume. In men with physiologically low T relating to simple obesity, the reproductive axis normalises with weight loss, whether achieved through lifestyle-change or bariatric surgery. Nevertheless, there are also clinical trial data to support a role for testosterone therapy in mitigating the risk of developing type 2 diabetes in men with simple obesity. However, this comes at the cost of an unacceptable rate of erythrocytosis that may predispose to arterial and venous thrombosis.

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HDI2.3

How do I manage pituitary macroadenoma in pregnancy?

Rebecca Reynolds
University of Edinburgh, Edinburgh, UK.

Pregnancy is associated with changes in both size and function of the pituitary gland. Thus diagnosing pituitary dysfunction during pregnancy can be challenging. For women with a pre-existing adenoma, there is limited evidence regarding safety in pregnancy for medical therapies used to control hormonal excess. Management includes optimisation of hormonal function and close monitoring for signs of tumour progression. Most women can be managed conservatively until delivery. The existing evidence will be discussed with illustration through some case studies.

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HDI2.4

Abstract Unavailable

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HDI2.5

How do I confirm biochemical diagnosis of primary aldosteronism?

Marie Freel
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Primary Aldosteronism (PA) is the commonest secondary cause of hypertension. Multiple studies worldwide suggest a prevalence of approximately 10% in an unselected hypertensive cohort and up to 20% in resistant hypertension. This does not correlate with real world experience and PA remains a significantly under-recognised condition. There is a myth that the biochemical diagnosis of PA is complex and requires significant alterations to drug therapy and very specific diagnostic sampling conditions. In this short presentation, I hope to alter this perception and demonstrate to the audience that screening for PA should be simple and possible in any secondary care setting. Subsequent confirmatory testing is not always required but the most straightforward options to confirm the diagnosis will be discussed in detail. The aim is to lower the diagnostic threshold and improve treatment and cure of this common condition.

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HDI2.6

Abstract Unavailable

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Meet the Expert Sessions

Adrenal and Cardiovascular

MTE1

Abstract Unavailable

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Bone and Calcium

MTE2

Bone turnover markers in the management of osteoporosis

Nicola Peel
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In common with other chronic conditions, persistence with treatment for osteoporosis is poor, with fewer than 50% of patients continuing treatment by 12 months. Reasons for this are multifactorial; treatment does not lead to symptomatic benefit, may be difficult to take and can cause adverse effects. Furthermore, poor compliance may not be overt and may be unintentional. Monitoring an individual's response to treatment can identify those with suboptimal response. Potential tools to monitor osteoporosis treatment include serial measurement of bone mineral density (BMD) and the use of bone turnover markers (BTM). BTM reflect the processes of bone resorption and formation. They have been shown to be determinants of fracture risk and predictors of accelerated bone loss in cohort studies. However, in the management of the individual patient with osteoporosis the main role for BTM is as a tool to monitor treatment response. BTM can be used to evaluate response to both anti-resorptive and anabolic therapies and have the advantage over serial measurements of BMD of showing large, early changes, enabling identification of treatment response within just weeks of initiating therapy. Care is required in sample collection, analysis and interpretation to optimise clinical utility. An attenuated or absent response to treatment may indicate poor compliance or the presence of an untreated underlying cause of osteoporosis. Poor compliance is the most common reason for poor treatment response and monitoring may be effective in enhancing compliance and clinical efficacy. However, it remains to be established whether this approach is cost-effective.

References

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Thyroid

MTE3

Meet the Expert (Thyroid): Thyroid Disease Assessment and Management; controversies in the NICE Guidelines.

Kristien Boelaert
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The NICE guidelines on the assessment and management of benign thyroid disorders were published in November 2019. They provide evidence based guidance on how to investigate thyroid dysfunction and thyroid enlargement as well as on the management and follow-up of these conditions. In addition, they include a chapter on important information to be provided to patients with thyroid diseases. The guidelines propose a cascading approach to measurement of thyroid function with measurement of TSH only and determination of fT4 and fT3 if this is abnormal. They propose that repeated TPO measurements are not needed in those with raised TSH. NICE proposes to treat primary hypothyroidism with levothyroxine monotherapy but advises against routine use of liothyronine alone or in combination in view of insufficient evidence of benefit and concerns about potential adverse effects of combination therapy. They propose that subclinical hypothyroidism be treated with levothyroxine if TSH is $\geqq 10$ mIU/L on repeated occasion and to give a trial of levothyroxine replacement if TSH is greater than the reference range but below 10 mIU/L and the patient has symptoms of hypothyroidism. NICE emphasises the importance of TSH-receptor antibody measurement in distinguishing thyrotoxicosis with and without hyperthyroidism and they propose to offer radioiodine as first-line treatment for Graves' disease unless remission with antithyroid drugs is likely. They also advise that radioiodine or thyroidectomy is offered for relapsed Graves' thyrotoxicosis and for toxic nodular hyperthyroidism. NICE advises that specialist advice is sought for patients with subclinical hyperthyroidism with evidence of thyroid disease and TSH <0.1 mIU/l on repeated occasion. NICE guidance emphasises the need for use of a recognised ultrasound grading system to classify thyroid nodules. The different sections of the NICE guidelines and the controversies arising from the guidance will be discussed in the session.

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Endocrine Cancer and Late Effects

MTE4

Abstract Unavailable

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Reproductive and Neuroendocrinology

MTE5

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.MTE5

Metabolism, Obesity and Diabetes

MTE6

Abstract Unavailable

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Nurse

MTE7.1

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.MTE7.1

MTE7.2

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.MTE7.2

Clinical Skills

Genetics for the endocrinologist

SK1.1

Abstract Unavailable

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SK1.2

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.SK1.2

Basic Skills

Grants and teaching

SK2.1

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.SK2.1

SK2.2

How to make meaningful improvements to your teaching with common and accessible technologies

James Moss
Imperial College London, London, United Kingdom

Abstract
You don't have to be a digital native to use technology effectively in teaching. Even self-confessed technophobes can make meaningful improvements in their use of digital learning with only a little bit of guidance and support. Technology is a ubiquitous feature of higher education, which has been consolidated during the COVID-19 pandemic. However, with so many options on the market it can be incapacitating to try and choose. This is further complicated by local institutional regulations, subscription costs, and steep learning curves, not to mention that many students already perceive they are inundated with too many learning platforms.
For example, Microsoft PowerPoint is the stalwart of the 21st century classroom, being used to deliver tens of millions of lectures, seminars, and tutorials every year across the world. Despite its prevalence, only a minority of educators have received any instruction or training on how to use it effectively to support students to learn. Probably because it's easy, right? Unfortunately, this attitude means that 'death by PowerPoint' is a common diagnosis for many disengaged learners in higher education. Atop of the potential student learning benefits that training could bring, there are tangible benefits for teachers too, including being able to develop better presentations with less effort and in less time.
This session will explore the use of PowerPoint to create presentation slides and two other accessible educational approaches, the theories, concepts and principles underpinning them, and how you might be able to incorporate them into your teaching practice (without extensive training or financial cost).

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Early Careers Session

Broadening your Career Pathway – What else can you do with your skills?

ECS1.1

Abstract Unavailable

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ECS1.2

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.ECS1.2

ECS1.3

Influencing at scale: NHS leadership and shaping policy

Neil Gittoes
CEDAM, Birmingham, UK.

Clinical interactions with patients are fulfilling and rewarding. We can make a difference to patients' health and lives by tuning care and attention to their individual needs on a 1:1 basis. Frustrations sometimes emerge from clinicians due to perceived restrictions and limitations in the healthcare system that appear to perversely impact patient care. Those frustrations are often exacerbated by lack of transparency around how to resolve the system issues for the greater good; often the language is different, the organisations are unfamiliar and can appear bureaucratic. While remaining firmly embedded in direct patient care, taking a leap into senior NHS leadership roles can by enormously rewarding, where it is possible to positively impact patient care well beyond the 1:1 interactions in clinic. Detailed insights and awareness of the structures, drivers, agendas and language of national healthcare leadership allows ones influence to be felt and shape national policy to facilitate high quality patient care. The time is ripe for strong medical leadership at all levels within the stressed NHS environment. Endocrine services must have strong representation nationally so we remain with clear identity and in control of our own destiny as a clinical service.

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ECS1.4

Clinical Teaching Careers

Niamh Martin
Imperial College, London, UK.

As a clinical trainee, you may be presented with teaching opportunities, but these are often opportunistic. Clinical training rarely provides sufficient flexibility to commit to developing substantial teaching roles. As you progress towards CCT and into a consultant post, you may be interested in developing a clinical teaching career but feel unclear about how to navigate this. Many skills that you have developed in your clinical training including communication, organisation and team working are really valued for teaching roles. Teaching provides a wide variety of opportunities depending on your skill sets and what you enjoy. For example, involvement in curriculum development and assessment can allow you to focus on academic progression, but many teaching roles involve pastoral care and mentoring, supporting students or trainees in difficulty. I have really enjoyed my involvement in undergraduate and postgraduate education. I will describe my own experiences in developing a clinical teaching career, combining clinical work with teaching roles at Imperial College London. I will discuss how to find out what teaching opportunities are available and how to develop a portfolio of teaching, including recommended teaching qualifications.

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ECS1.5

Abstract unavailable

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Nurse Sessions

Acromegaly

NS1.1

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.NS1.1

NS1.2

Biochemical cure – is this enough?

Niki Karavitaki
Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; Centre for Endocrinology, Diabetes and Metabolism, Birmingham, UK; Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Acromegaly is a condition associated with many co-morbidities and increased mortality. Over the last decades, advances in the management of this condition have led to improvement of the prognosis of the patients. Nonetheless, achievement of biochemical targets by various treatment modalities does not always translate to reversal of acromegaly-related morbidities. These include alterations in cardiovascular function, sleep apnoea syndromes, negative impact on bone health with high risk of fractures, arthropathy with joint pains and limitations in mobility, disorders in glucose metabolism and compromised quality of life (physical, emotional and mental aspects). Duration and severity of acromegaly have been proposed as factors associated with persistence of co-morbidities suggesting that not only effective but also early biochemical control should take priority in the management algorithm of the patients. Furthermore, long-term follow-up of the adverse sequelae of growth hormone excess on body systems and appropriate management of them by a multi-disciplinary team are considered key elements for the optimal care of patients in apparent biochemical remission.

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NS1.3

Addressing the unmet psychosocial needs of patients with treated Acromegaly

Sue Jackson
Independent Chartered Psychologist, Bristol, UK.

Each patient experience of diagnosis and treatment for Acromegaly is unique. For some the process is simple and straightforward, for others it is more challenging. For patients the condition is more than just the identification and treatment of the tumour: there are several important psychosocial issues with potentially far-reaching effects. Patients may feel disempowered from raising concerns about the wider psychosocial aspects of Acromegaly with healthcare professionals (HCPs), feeling that only physical symptoms related to the disease, or its medical management are the only issues worthy of discussion at clinic appointments. HCPs who provide care consistent with the biomedical model may unwittingly reinforce this message. Research has suggested that patient distress associated with these wider psychosocial issues may not be identified by healthcare professionals (HCPs), resulting in patients with problems with treatment adherence, significant morbidity, additional use of primary and secondary care services, as well as patient dissatisfaction with care. This session will briefly review the key psychosocial issues faced by patients with Acromegaly before turning to consider what tools and techniques are available to help HCPs identify these issues with their patients. It is not reasonable to expect a busy endocrine clinic to act as a one-stop-shop for all the psychosocial difficulties that can affect patients with Acromegaly, and so we will also consider what other services and resources are available that patients can be directed towards.

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The past, present and future of endocrinology within a District General Hospital (DGH)

NS2.1

Abstract Unavailable

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NS2.2

Abstract Unavailable

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NS2.3

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.NS2.3

Management of endocrine conditions in the time of COVID

NS3.1

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.NS3.1

NS3.2

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.NS3.2

NS3.3

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.NS3.3

Future of Endocrinology Post COVID-19 Update

FOE1

Abstract Unavailable
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Cutting Edge Session

Use and abuse endocrinology – enhancing performance at any cost?

CE1.1

Abstract Unavailable

DOI: 10.1530/10.1530/endoabs.77.CE1.1

CE1.2

GH as a performance enhancing drug

Richard Holt
Professor in Diabetes and Endocrinology, University of Southampton, Southampton, UK.

Anecdotal evidence suggests that athletes have been misusing growth hormone (GH) for its anabolic, lipolytic, psychological and cardiovascular effects since the early 1980s, at least a decade before endocrinologists began to treat adults with GH deficiency. There have been on-going debates about whether GH is performance-enhancing. Although many of the early studies were negative, randomized controlled studies are not sensitive enough to distinguish the small performance benefits that athletes are seeking. More recent studies suggest that GH improves strength and sprint capacity, particularly when combined with anabolic steroids. Insulin-like growth factor-I (IGF-I) has also been used as an alternative performance-enhancing drug to growth hormone (GH) because IGF-I mediates many of the anabolic actions of GH. The IOC recognized the need for an effective test to detect GH misuse as early as 1992 but the challenges involved in the detection of GH meant that the first test was not introduced until the Athens Olympic Games in 2004. WADA has approved two methods to detect GH misuse based on blood samples. The first is based on the measurement of pituitary GH isoforms while the second relies on the measurement of two markers of GH action, insulin like growth factor-I (IGF-I) and the amino-terminal pro-peptide of type III collagen (P-III-NP).

GH-2000 team

Richard Holt, Peter Sonksen, David Cowan, Dankmar Böhning, Nishan Guha, Christiaan Bartlett, Tan Böhning.

Acknowledgements

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CE1.3

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Senior Endocrinologists' Session

SE1.1

Are gonadotrophins more than gonadotrophins?

Ilpo Huhtaniemi
Institute of Reproductive and Developmental Biology, Department of Digestion, Metabolism and Reproduction, Imperial College London, London, UK.

There is a plethora of information about the extragonadal expression of gonadotrophin receptors (R), i.e. for LH/hCG and FSH, many of the studies published in high-profile journals. LHCGR has been found to be expressed in almost all organs of the body, and FSHR is expressed in fat and bone tissues, as well as in multiple malignant tumours. On the basis of these findings it has been proposed that direct gonadotrophin action participates in the regulation of extragonadal reproductive organs, bone and fat tissue metabolism in post-menopausal women and in malignant tumour growth. Most of the findings come from single research groups and have not been confirmed by independent investigators. Another problem has been the paucity of good-quality antibodies for gonadotrophin receptors and the reluctance of the investigators to share their reagents with others. Furthermore, methodological problems of many of the reports are a concern. I will present in this talk some of our own findings on the topic, as well as a critical evaluation of the current stage of the saga of extragonadal gonadotrophin action.

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SE1.2

Abstract Unavailable

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SE1.3

INSL3: a new index of testis function in puberty and aging

Richard Ivell & Ravinder Anand-Ivell
University of Nottingham, Sutton Bonington, UK.

Insulin-like peptide 3 (INSL3) is a peptide hormone secreted exclusively in boys and men by the mature Leydig cells of the testes. It acts through a unique G-protein-coupled receptor, called RXFP2. In the female INSL3 regulates ovarian antral follicle growth. Whereas INSL3 in the male foetus is responsible for the first phase of testicular descent, in the adult it appears to support spermatogenesis and bone health. Importantly, it is expressed constitutively, is independent of acute regulation by the HPG axis, and effectively measures the product of Leydig cell numbers and their differentiation status, i.e. the functional capacity of Leydig cells to make testosterone, correlating with the T/LH ratio. We have developed very specific time-resolved fluorescence immunoassays and show that INSL3 has low within-individual and technical variance. In humans, rodents, and bulls, as a mature Leydig cell biomarker, INSL3 effectively monitors the dynamics of puberty, acting much like a biochemical Tanner scale, without any of the fluctuation seen with testosterone, to achieve a stable final level in early adulthood. This adult peak varies up to 10-fold in the normal human population, reflecting a wide range of Leydig cell functional capacity. The causes of this variance are unknown, though we have shown that it may in part depend on childhood BMI, early nutrition, and possible maternal impacts. Studies in large aging male cohorts indicate that INSL3 declines consistently at 15% per decade from age 40 and measures the decline of testis function independently of compensation by the HPG axis. The 10-fold range of INSL3 in young men persists as men age, suggesting that low INSL3 in young adulthood will predict low INSL3, hypogonadism, and related morbidity in older age.

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Oral Communications

Reproductive and Neuroendocrinology

OC1.1

Melanocortin-4 receptor agonism improves sexual brain processing in women with low sexual desire

Layla Thurston[1], Tia Hunjan[1], Edouard Mills[1], Matthew Wall[2,1], Natalie Ertl[2,1], Maria Phylactou[1], Beatrice Muzi[1], Bijal Patel[1], Emma Alexander[1], Sofiya Suladze[1], Manish Modi[1], Pei Eng[1], Paul Bassett[3], Ali Abbara[1], David Goldmeier[4], Alexander Comninos[1,4] & Waljit Dhillo[1,4]
[1]Imperial College London, London, United Kingdom; [2]Invicro, London, United Kingdom; [3]Statsconsultancy Ltd., Amersham, United Kingdom; [4]Imperial College Healthcare NHS Trust, London, United Kingdom

Hypoactive sexual desire disorder (HSDD) is the most prevalent female sexual health complaint worldwide, affecting 1-in-10 women. It is characterised by a persistent lack of desire for sexual activity and sexual fantasies, causing distress or interpersonal difficulties. Treatment options are limited, however, melanocortin-4 receptor (MC4R) agonists have emerged as a promising therapy for HSDD, through unclear mechanisms. Investigating the pathways involved is crucial for our understanding of normal and abnormal sexual behaviour. We conducted a randomised, double-blind, placebo-controlled, crossover clinical study using psychometric, functional neuroimaging and hormonal analyses to assess the effects of MC4R agonist administration, compared to placebo, on sexual brain processing in 31 premenopausal women with HSDD. MC4R agonism significantly increased sexual desire for up to 24-hours post administration, compared to placebo ($P = 10.007$). During functional MRI, MC4R agonism enhanced cerebellar and supplementary motor area activity, and deactivated the secondary somatosensory cortex, specifically in response to visual erotic stimuli, compared to placebo ($Z = 2.3$, $P < 0.05$). In addition, MC4R agonism enhanced functional connectivity between the amygdala-insula during visual erotic stimuli, compared to placebo ($P = 0.025$). MC4R agonism resulted in a small mean increase in LH of 1.1iU/l (F [1,58] = 13.38, $P = 0.0005$) and FSH of 0.35iU/l (F [1,60] = 10.97, $P = 0.0016$) across the 300-minute duration of the study, with no effect observed on downstream circulating estradiol or progesterone levels. These findings identify novel neural substrates and connections through which MC4R agonism modulates sexual brain processing to increase sexual desire. These changes in brain activation may serve to reduce self-consciousness, increase sexual imagery, and disinhibit sexual responses in women with HSDD. Our data have widespread implications as understanding the effects of MC4R agonism on sexual behaviour is important, not only for the ongoing development of melanocortin-based therapies for psychosexual disorders but also for obesity medicine, where related MC4R agonists are rapidly being developed.

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OC1.2

Hyper-phosphorylation of β-catenin at Serine552 correlates with invasion and predicts recurrence of Non-Functioning Pituitary Tumours (NFPTs)

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Background
No predictive biomarkers for NFPT recurrence have been identified, apart from Ki67. We employed high-throughput mass spectrometry-based analyses to examine the phosphorylation pattern of different subsets of NFPTs.
Methods
Based on histopathological, radiological and surgical features, NFPTs were sub-grouped into three groups: non-invasive ($n = 15$), invasive ($n = 10$) and recurrent ($n = 5$) subtypes. Invasiveness was determined by radiology (Knosp classification 3&4), histopathological invasion (bone, dura and mucosa) and intraoperative findings. Tumour recurrence was based on radiological data for a mean follow-up of 10y (SD ± 5.4y). Proteins were extracted from frozen tissues, phosphopeptides enriched using TiO_2 and labelled with tandem mass tags and subjected mass spectrometry (Orbitrap) for quantification. Candidate hyper-phosphorylated proteins were validated in NFPTs by immunohistochemistry ($n = 200$) on tissue microarray and immunoblotting ($n = 36$).
Results
Out of 3185 identified phosphopeptides, phospho-serine showed the highest level of difference (90.3%) among the tumour subtypes, followed by threonine (8.9%) and tyrosine (0.8%). One of the identified group of phosphoproteins with subtype-specific expression pattern was Ser552 of β-catenin showing significant hyper-phosphorylation in recurrent ($P < 0.001$) and invasive ($P < 0.001$) NFPTs. We performed receiver operating characteristics curve analysis to find the optimal cut-off value of β-catenin pSer552 H-score in patients who had recurrence ($n = 44$) or non-recurrence ($n = 156$) and observed an area under curve of 0.717 (95% CI: 0.610-0.797), indicating a good prognostic ability of the β-catenin pSer552H-score. A cut-off value of 160 for the β-catenin pSer552 H-score gives a sensitivity of 68.8% and a specificity of 72.6% for tumour recurrence. Kaplan-Meier survival curve analysis shows strong statistical correlation in the recurrence free survival ($P < 0.0001$) and the nuclear positive staining of β-catenin pSer552 with a hazard ratio of 3.1 (95% CI 1.5-6.3).
Conclusion
Our results suggest that the phosphorylation status of β-catenin at Ser552 could act as predictive biomarker of tumour recurrence and invasion in NFPTs.

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OC1.3

Acromegalic cardiomyopathy in pituitary-specific aryl hydrocarbon receptor interacting protein (Aip) gene knockout animals

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Introduction
Patients with a germline loss-of-function mutation in *AIP* are predisposed to young-onset GH excess resulting in gigantism or acromegaly. Acromegaly leads to disease-specific cardiomyopathy with biventricular hypertrophy and diastolic dysfunction progressing to fulminant cardiac failure if left untreated, therefore it is vital to have a tractable animal model to investigate the disease
Findings
Our $Aip^{Flox/Flox}$;$Hesx1^{Cre/+}$ model abrogates *Aip* in cells expressing the early pituitary transcription factor *Hesx1*, specifically targeting cells of the anterior pituitary from embryonic day (e)8.5. These animals develop functional pituitary adenomas with 85% penetrance by the age of 15 months. Our data on these mice suggest that the excess GH from these tumours recapitulate the phenotype similar to human acromegaly. This includes an increase in weight and body size of mutant animals, increased IGF-1 circulating levels and enlargement of the pituitary gland and other organs, particularly the heart. The hearts of these mice are significantly larger (mean (base to apex) ±SD: 10.8±1.0mm,$n = 7$) than wild-type controls (9.2±0.4mm,$n = 7$), p-value <0.0001. We observe hypertrophy of the left ventricular wall, apex and nodes of the heart as well as areas with increased fibrosis compared to controls. Cardiac ultrasound on the hearts of these animals has revealed a significant reduction in stroke volume in knockout animals (mean±SEM: 31±0.07µl) compared to controls (51±1.36µl, $P < 0.005$) observed at 9 months of age. At this age, we also observed a trend towards reduced cardiac output and ejection fraction and are currently increasing our replicates for these experiments.
Conclusions
Data from our $Aip^{Flox/Flox}$;$Hesx1^{Cre/+}$ model shows development of pituitary tumours and consequently cardiac abnormalities. These data support the clinical observations and overall provides an effective model to study cardiac disease in acromegaly.

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OC1.4

Intranasal Kisspeptin Administration Stimulates Reproductive Hormone Secretion in Healthy Men

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[1]Imperial College London, London, United Kingdom; [2]King's College London, London, United Kingdom; [3]Imperial College Healthcare NHS Trust, London, United Kingdom

Background
Kisspeptin is a critical activator of hypothalamic gonadotrophin-releasing hormone neurons, inducing release of downstream reproductive hormones. Intravenous or subcutaneous kisspeptin administration has been shown to have

significant potential to treat reproductive disorders. However, intranasal administration could offer a novel non-invasive delivery route, which would be clinically preferable. We therefore sought to determine the effects of intranasal kisspeptin on reproductive hormone release in healthy men for the first time.
Methods
Randomised, double-blinded, placebo-controlled, cross-over study in 12 healthy men (mean age 28.3 years, BMI 24.5 kg/m^2). After intranasal delivery of kisspeptin-54 (3.2, 6.4, 12.8 and 25.6 nmol/kg) or 0.9% saline, serum luteinising hormone (LH), follicle stimulating hormone (FSH) and testosterone were measured every 15-minutes for 4-h. Mean $\pm$ standard deviation are presented.
Results
Intranasal kisspeptin dose-dependently increased mean LH at doses from 3.2-12.8 nmol/kg ($P = 0.008$ and <0.0001 for 6.4 and 12.8 nmol/kg, respectively), with the maximal rises occurring 30-45 minutes post-administration. Correspondingly, the area under the LH curve was significantly elevated following all doses of kisspeptin compared to saline (3.2 nmol/kg: 172.2 $\pm$222.6 h.IU/l [$P = 0.03$]; 6.4 nmol/kg: 300.2 $\pm$274.3 h.IU/l [$P = 0.002$]; 12.8 nmol/kg: 595.7 $\pm$340.4 h.IU/l [$P = 0.001$]; 25.6 nmol/kg: 549.0 $\pm$376.2 h.IU/l [$P < 0.0001$]). FSH levels followed a similar trajectory to LH in response to intranasal kisspeptin. Kisspeptin 12.8 nmol/kg significantly increased serum testosterone from 120-minutes onwards ($P = 0.02$), with a peak change from baseline of 5.5 $\pm$5.5 nmol/l ($P = 0.03$).
Conclusion
We report the first investigation of the effects of intranasal kisspeptin delivery on reproductive hormone release in humans. Our results demonstrate that intranasal kisspeptin robustly and dose-dependently stimulates reproductive hormone release in healthy men. Given the ongoing development of kisspeptin therapeutics, intranasal kisspeptin delivery therefore offers a novel, effective and non-invasive administration route for the management of reproductive disorders.

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OC1.5

Is radiotherapy for pituitary adenoma or craniopharyngioma associated with increased risk of second brain tumour? A long-term multicentre study of 3,679 patients

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Background
Current conclusions on risk of second brain tumour following radiotherapy for pituitary adenoma or craniopharyngioma are challenged methodologically by small patient sample size, selection biases or lack of appropriate controls.
Objective
To ascertain whether radiotherapy for pituitary adenoma or craniopharyngioma is associated with increased second brain tumour risk, through use of appropriate methodology.
Design
Multi-centre, retrospective cohort study (6 centres; 5 within UK, 1 from Italy).
Methods
4,292 patients with pituitary adenoma or craniopharyngioma detected until 31/12/2013 were identified from departmental registries. Patients with one image, unknown radiotherapy exposure status, genetic predisposition, or history of brain tumour prior to study entry were excluded ($n = 532$). Recipients of proton or stereotactic radiotherapy ($n = 81$) were excluded from statistical analyses and data were explored for 996 patients exposed to conventional, 3D-CRT or IMRT and 2,683 controls.
Results
During 45,246 patient-years, second brain tumours were reported in 61 patients (30 radiotherapy, 31 controls); 7 malignant (5 radiotherapy, 2 controls), 2 atypical (1 radiotherapy, 1 control) and 52 benign (24 radiotherapy, 28 controls). Age at pituitary tumour diagnosis and radiotherapy were associated with increased risk of second brain tumour (HR 1.031, 95%CI 1.014-1.049, $P < 0.0001$, and HR 1.731, 95%CI 1.046-2.864, $p = 0.034$, respectively), but tumour type and gender were not. After adjusting for age, radiotherapy exposure was associated with increased risk of second brain tumour (HR 1.824, 95%CI 1.100-3.020, $p = 0.020$) . Relative risk ratio of irradiated to controls was 2.18 (95%CI 1.31-3.62). Median latency after radiotherapy was 8.3 (7.5-27.3) for malignant and 17.7 years (3-50.8) for atypical or benign tumours, respectively.
Conclusions
This is the first study assessing the risk of second brain tumour in a cohort of non-selected irradiated patients and appropriate controls with confirmed long-term imaging surveillance. Risk is increased in irradiated patients, although much less than previously reported and these data can inform clinical practice.

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OC1.6

Differential follicle stimulating hormone glycosylation modulates pre-antral follicle growth and survival rates

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Ovarian ageing is a naturally occurring physiological process, marked by dynamic changes in ovarian function and hormone secretion. A key endocrine regulator of ovarian function is the heterodimeric glycoprotein hormone, follicle stimulating hormone (FSH). FSH is secreted as two glycosylation variants: partially glycosylated FSH (FSH21) and fully glycosylated FSH (FSH24). These variants have different *in-vitro* activities, with FSH21 more bioactive than FSH24. Interestingly, analysis of human pituitary extracts has shown that the ratio of FSH21:FSH24 changes with age, with FSH21 predominant in women of reproductive prime, and FSH24 predominant in menopausal women. However, how differential FSH glycosylation modulates ovarian functions remains unknown. This study therefore aimed to determine the effects of FSH21 and FSH24 on follicle growth and survival. To do this, mouse ovarian follicles were isolated from 3-5wk-old-C57/BL6 mice and treated +/- 10ng/ml, FSH21 ($n = 85$), FSH24 ($n = 80$), a ratio of FSH21:FSH24 at 80:20 (to mimic reproductive prime;$n = 77$), FSH21:FSH24 at 50:50 ($n = 53$), or FSH21:FSH24 at 20:80 (to mimic late peri-menopause;$n = 78$). Follicles were cultured for up to 96hrs and imaged daily to evaluate follicle morphology, and were snap frozen at 24-hour time intervals for qPCR analysis. In the presence of FSH21 dominant conditions, follicle growth was markedly increased at all time points, in comparison to control and FSH24 alone and 20:80 FSH21:FSH24 conditions. Treatment of follicles with FSH24 or 20:80 FSH21:FSH24 resulted in increased basement membrane rupture and oocyte extrusion, with survival rates significantly decreased. qPCR analysis revealed markers of apoptosis were increased in follicles treated with FSH24 alone and 20:80 FSH21:FSH24, while FSH-responsive genes including hormone receptors and steroidogenic enzymes were increased in FSH21 or 80:20 FSH21:FSH24 conditions. These data suggest that the nature of FSH glycosylation modulates the follicular microenvironment to control follicle growth and survival.

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Endocrine Cancer and Late Effects

OC2.1

Outcomes of surgery and treatment with selective RET TK inhibitor Selpercatinib in children with MEN2 and advanced MTC.

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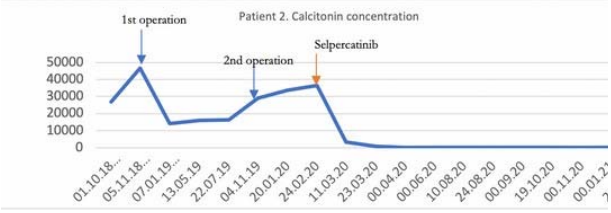
Background
Patients with Multiple Endocrine Neoplasia type 2 (MEN2) without previous family history often present late with advanced Medullary Thyroid Cancer (MTC). Surgery is not always curative but RET tyrosine kinase pathway is a potential target for molecular treatment for progressive MTC.
Methods
Retrospective review of clinical, genetic, biochemical (calcitonin, CEA) and imaging (US, CT/MRI, Gallium Dotate) data of children with MEN2 who developed recurrent and progressive MTC after surgery and were treated with Selpercatinib, a selective RET TK inhibitor. The main parameters were safety, efficacy and objective treatment response.
Results
Six children (3M,3-1 years) presented with palpable lymphadenopathy (5) and elevated calcitonin (median 6560ng/L,140-46850) and were subsequently diagnosed with MEN2 (4x2B, 2x2A, RET 918,804). Five had metastatic disease on imaging. All had total thyroidectomy with unilateral (2) and bilateral (2) levels 2,3,4,5,6 lymphadenectomy and resections of JV (1), RLN (2), Vagus (1). Post-operative complications included transient (3) and permanent (1) hypoparathyroidism and Horner's syndrome (2). Two children had second surgery and one external beam radiotherapy (EBRT) complicated by delayed oesophageal perforation (surgery) and stridor requiring tracheostomy (EBRT). None of the children were cured and all had disease progression evidenced by clinical deterioration, rising calcitonin and CEA (3) and worsening radiology (5). All children received Selpercatinib (92 mg/m2/dose) orally twice daily. The objective clinical, radiological and biochemical response was 100% with complete resolution of all clinical symptoms (third month) and significant decrease of calcitonin (Graph 1) and CEA within 4 weeks. Four had partial radiological response (1-3months). No child had to discontinue Selpercatinib because of a drug toxicity. Median follow up was 13 months (10-20months).
Conclusions
Children with MEN2 and advanced MTC can't be cured by surgery and EBRT alone, but Selpercatinib has shown remarkable therapeutic efficacy with clinical, biochemical and radiological improvement and minimal toxicity.



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OC2.2

An emerging role for proteostasis modulators targeting NIS activity to enhance radioiodide therapy in thyroid cancer

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Introduction
New therapeutic strategies are urgently needed to improve radioiodide (RAI) uptake and efficiently ablate thyroid cancer cells, thereby reducing the risk of recurrent disease. We recently utilised high throughput screening and identified FDA-approved compounds capable of inducing sodium iodide symporter (NIS) function to enhance iodide uptake. Categorisation revealed a high proportion of drugs that modulate proteostasis, with 6 of the top 15 targeting activity of VCP–a critical component of the proteasome system. A better understanding of how proteostasis genes such as VCP modulate NIS function is now needed prior to clinical evaluation.
Methods
NanoBiT assays were used to assess the stringency of NIS:VCP interaction. NIS function was monitored by RAI (^{125}I) uptake assays. The Cancer Genome Atlas (TCGA) was appraised for proteostasis genes.
Results
We undertook rigorous evaluation of proteostasis inhibitors CB-5083 and disulfiram to understand their mechanistic impact on NIS function. CB-5083 and disulfiram induced NIS expression and ^{125}I uptake in multiple cell types (1.5-5-fold), including human primary thyrocytes. Importantly, NanoBiT showed that CB-5083 significantly decreased VCP binding to NIS. In contrast disulfiram failed to impact stringency of the NIS:VCP interaction but retained the ability to enhance NIS function in VCP-ablated thyroid cells. Disulfiram also failed to impact expression of autophagy marker LC3B-II but increased p62, indicating its effect on NIS was likely via VCP-independent proteasomal pathways. We next appraised TCGA and identified a 13-proteostasis gene riskscore classifier, including VCP, as an independent predictor of recurrence in RAI-treated papillary thyroid cancer (PTC). Critically, the predictive model showed a significantly worse prognosis for high-risk RAI-treated PTC [Hazard Ratio = 35.9, 95%CI 4.8-267.4; $P < 0.001$;$n = 137$].
Conclusions
These results demonstrate differential mechanisms of emerging proteostasis modulators that target NIS activity to enhance radioiodide uptake. We further reveal the clinical relevance of proteostasis genes associated with an increased risk of recurrence.

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OC2.3

A novel *in vivo* platform for studying tumour vascularization and endocrine responses

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Background
Tumour growth is critically dependent on blood perfusion, its source of oxygen and nutrients. Therefore, tumour vascularization has become an attractive target for the treatment of many cancers types. The study of endocrine-responsive tumours, in particular, needs improved platforms to screen drugs targeting vascularization that have better resolution and that do not compromise on inter-individual variability.
Aim
Hence, we've set out to develop a novel *in vivo*longitudinal platform that allows us to directly track both tumour growth and vascularization in the same individual overtime.
Methods
This was achieved by, firstly, fluorescently tagging a mouse renal adenocarcinoma cell line (Renca) that has been shown to mimic the human renal cell carcinoma growth, which is known to have a hormone-related aetiology. Secondly, in order to keep the tumour size uniform across experiments, we've generated tumour spheroids *in vitro* out of Renca cells following previously published protocols. Then, the spheroids were transplanted into the anterior chamber of the eye (ACE), a known immune-privileged site and natural window to the body, of host transgenic mice that have fluorescent blood vessels. Lastly, tumour growth and vascularization were monitored in each individual overtime through repeated intra-vital fluorescent imaging.
Results
So far, we've verified that upon transplantation into the ACE, the *in vitro* generated Renca spheroids can successfully engraft, vascularize and grow overtime. In future experiments we aim to evaluate the tumours response to predefined hormones that are known to impact renal cell carcinoma growth, and to test how already validated anti-vascularization drugs affect these tumours.

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OC2.4

PBF phosphorylation regulates cell motility of thyroid and breast cancer cells

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The proto-oncogene pituitary tumor transforming gene binding factor (PTTG1IP/PBF) is overexpressed in multiple tumours and associated with tumour progression. One of the tumourigenic processes that PBF can mediate is cell motility. PBF can induce cell invasion in both thyroid and breast cancer cell lines. However, in contrast to wild-type (WT) PBF, the Y174A PBF mutant was not able to induce the invasiveness of thyroid or breast cancer cells. The Y174 residue is highly phosphorylated and these findings implicated that phosphorylation mediates the induction of breast and thyroid cancer cell invasion by PBF. Mutation of Y174 also causes retention of PBF at the plasma membrane due to disruption of an endocytosis motif. To better understand the impact of PBF phosphorylation and localisation on cell motility, a mutant with a disrupted Src consensus sequence (EEN170-172AAA;'PBF-EEN') and another with a substitution at F177 (F177A) were also employed. PBF-EEN shows largely vesicular localisation, similar to WT PBF, but with reduced phosphorylation. F177A accumulates at the plasma membrane due to the disruption of the endocytosis motif but is still phosphorylated. Our preliminary data again demonstrate significant induction of cell migration with PBF overexpression using both scratch wound and Transwell migration assays in thyroid and breast cancer cells. In contrast, neither Y174A, PBF-EEN nor F177A were able to stimulate cell migration. This further suggests that PBF phosphorylation is important for PBF induction of cell motility and also suggests that the endocytosis of PBF is essential. This study provides more insight into the mechanism of PBF induction of cell motility and supports PBF pY174 as a potential therapeutic target. Understanding the impact of PBF phosphorylation may help to develop new treatment approaches for cancer progression

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OC2.5

A novel MiR-346-Directed DNA damage mechanism is regulated by its interaction with long non-coding RNA, NORAD, in prostate cancer

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MiR-346 is an Androgen Receptor (AR)-activating miR that associates with DNA damage response (DDR)-linked transcripts in prostate cancer (PC). MiR-346 induces rapid and extensive DNA damage in PC cells through chromatin association, activation of transcription, R-loop formation and DNA replication stress, leading to checkpoint activation and cell cycle arrest. MiR-346 interacts with lncRNA, NORAD, in PC cells, which functions to maintain mitosis, DDR, and chromosomal integrity, and rescues miR-346-induced DNA damage. High NORAD expression/activity are strongly correlated with adverse disease outcome, and with increased DDR in primary, but not metastatic PC. In contrast, miR-346 is associated with improved PC survival. Further, NORAD activity is regulated by miR-346, which disrupts NORAD:PUM2 interaction, leading to PUM2 destabilisation and derepression of PUM1/2 DDR targets in PC cells. RNA-seq reveals widespread miR-346 and shNORAD dysregulation of DNA damage, DNA replication and cell cycle processes. High resolution, amplification-free genome-wide mapping of double strand DNA breaks (DSBs) (INDUCE-seq) reveals that miR-346-induced DSBs occur preferentially at binding sites of the most highly-active transcription factors in PC cells, including c-Myc, FOXA1, HOXB13, and importantly, AR, resulting in target transcript downregulation. Contrastingly, NORAD drives target-directed miR decay (TDMD) of miR-346 as a novel genome protection mechanism: NORAD silencing increases mature miR-346 levels by several thousand-fold, and WT but not TDMD-mutant NORAD significantly rescues miR-346-induced DNA damage. Thus balance between NORAD and miR-346 activities determines DDR in PC. This first demonstration of DNA damage induced by a miR is of direct therapeutic relevance: miR-346 sensitizes PC cells to chemotherapy/PARP inhibition and induces *in vivo* tumour regression. It may be particularly effective as a therapeutic in the context of decreased NORAD observed in advanced PC, and in transcriptionally-hyperactive cancer cells. Its induction of DSBs at AR binding sites may synergise with androgen-deprivation therapy as a novel PC treatment strategy.

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OC2.6

Transcriptomic analysis of succinate dehydrogenase subunit deleted cells to identify molecular mechanisms underlying the increased metastatic potential of SDHB-deficient tumours

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Mutations in each of the 4 subunits of succinate dehydrogenase (SDH) – *SDHA, B, C* and *D* predispose to development of phaeochromocytomas and paragangliomas. Loss of SDH function leads to accumulation of succinate which acts as an oncometabolite to drive tumourigenesis. However, mutations in *SDHB* have an increased likelihood of causing metastatic disease, compared to mutations in the other SDH subunits. The reasons behind this increased risk remain elusive due to the rarity of these tumours and heterogeneity in patient phenotype. To address this, we have used CRISPR/Cas9 to generate a series of isogenic *SDH* knockout cell lines as a tool to investigate the cellular consequences of loss of specific subunits. Characterisation of these cell lines demonstrates that they recapitulate the phenotypes reported for previous *SDH* knockout models and tumour tissue. Transcriptomic analysis has identified differentially expressed gene signatures that are unique to *SDHB* knockout cells, potentially identifying mechanisms responsible for the increased risk of metastasis in *SDHB*- deficient tumours.

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Metabolism, Obesity and Diabetes

OC3.1

The serotonin transporter SLC6A4 protects human brown adipose tissue from serotonin-mediated suppression of thermogenesis.

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The recent discovery of brown adipose tissue (BAT) in adult humans, which generates heat to maintain body temperature in a cold environment, offers an exciting new strategy to treat obesity and metabolic disease, but our knowledge of human BAT activation is limited. To identify novel pathways regulating human BAT, we undertook RNA sequencing of human brown and white adipocytes. The gene *SLC6A4* (encoding the serotonin transporter SERT) was one of the most highly differentially expressed genes in brown adipocytes (>15-fold). *In vitro*, there was substantial ^{3}H-serotonin uptake by human brown but not white adipocytes, this was abolished by the selective serotonin reuptake inhibitor (SSRI) sertraline. Serotonin inhibited uncoupled respiration in human primary brown adipocytes and decreased mRNA levels of uncoupling protein 1, this effect was mediated through the $5HT_{2B}$ receptor. *In vivo*, SERT mRNA and protein levels were increased in human BAT versus white adipose tissue. Cold exposure acutely decreased circulating serotonin concentrations by ~40% in lean healthy subjects. A retrospective analysis of patients who had undergone PET/CT scanning at room temperature, revealed that no patients taking SSRIs had detectable ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake by BAT compared with ~5% of matched controls, suggesting that SERT inhibition suppresses human BAT activation. Finally, we recruited 15 normal weight healthy subjects (age 24.7+/-1.0y, BMI 22.0+/-0.4kg/m^2) to a double-blind randomised crossover study using the SSRI sertraline (50 mg daily for 7 days or placebo). BAT activity was quantified using ^{18}F-FDG PET/MRI, thermal imaging and indirect

calorimetry during cold exposure (17°C). Sertraline reduced ^{18}F-FDG-uptake by BAT by ~40%, reduced supraclavicular skin temperature during cold and cold-induced thermogenesis compared with placebo, in keeping with decreased BAT activity. This research has identified a possible new mechanism of SSRI-driven weight gain and inhibition of peripheral serotonin synthesis may be a novel strategy to treat obesity-associated metabolic disease.

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OC3.2

Comparing the transcriptional landscape between lean and obese mice within the small intestinal segments

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Background
Obesity is a complex metabolic disease characterised by excess adipose tissue, that increases the risk of comorbidities such as type II diabetes. Interventions that rearrange the gut architecture or exclude nutrients from the duodenum promote immediate and long-term anti-diabetic effects, placing the gut front and centre in obesity and diabetes pathology and treatment. Currently, little is known about the pathological changes which occur in the small intestine (SI) in obesity. This study aims to determine the transcriptional signatures of each small intestinal segment and how obesity may pathologically alter these footprints.
Methods
RNA sequencing followed by differential gene expression (DE) analysis was performed on the three SI segments of mice that were fed a 60% high fat diet (DIO) ($n = 10$) and a chow diet (CTL) ($n = 10$) for 13 weeks. Standard physiological tests, such as a glucose tolerance test, confirmed the mice as metabolically obese at 13 weeks ($p < 0.05$).
Results
Principal component analysis using the top 200 DE genes revealed distinct transcriptional footprints for each intestinal segment. In response to diet induced obesity, the duodenal signature shifts to more closely resemble the transcriptional landscape of the jejunum. Additionally, the jejunum exhibited the greatest number of DE genes in obese mice followed by the duodenum and ileum respectively. Finally, gene set enrichment analysis revealed that multiple significantly enriched pathways ($p < 0.1$) that defined the difference between lean duodenum and jejunum, such as the adipocytokine signalling pathway, fatty acid metabolism and interferon alpha/gamma response, were no longer significant in obesity.
Conclusion
Altogether, this suggests that the obese duodenum may undergo transcriptional changes that cause it to more closely resemble the jejunum. Further analysis, such as leading-edge analysis, may identify specific gene sets that could enable us to gain a better understanding of underlying mechanisms of obesity.

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OC3.3

Sex-specific risk of obesity and cardiometabolic disease in low- and middle-income countries (LMICs): a meta-analysis in 681929 individuals

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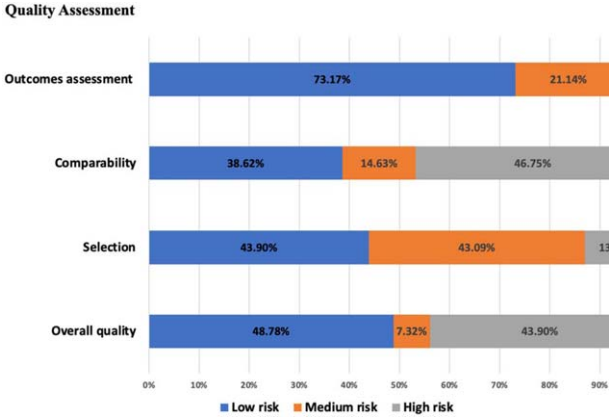
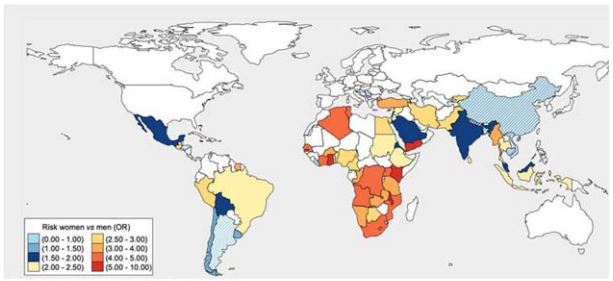
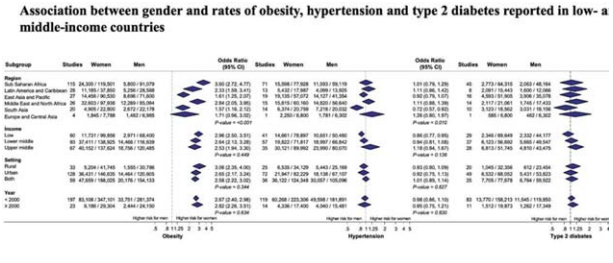
Introduction
Obesity is a global health challenge with more than 60% of the worlds population with obesity living in LMICs. Studies have demonstrated that women are more affected by obesity than men. However, the risk of obesity and obesity-related cardiometabolic diseases in women in LMICs have not been documented. The aims of this meta-analysis are: to evaluate the risk of obesity and obesity-related cardiometabolic disease in women compared to men in LMICs and to evaluate the risk of obesity and cardiometabolic disease in women with obesity compared to those without obesity in LMICs.
Methods
PubMed, EMBASE and Cochrane were searched from inception to December 2020. MESh terms on 'women', 'obesity' and 'cardiometabolic diseases' were used in the search without restrictions. Studies reporting obesity rates according to BMI in LMIC according to World Bank Region were included. Case-control studies, children, adolescents, pregnancy, infections, and cancers were excluded. Two reviewers undertook study selection, quality assessment, and data extraction. Odds-ratios were calculated for obesity in both women and men, and for risk of cardiometabolic diseases in women with obesity. Results were pooled using a random effects model in the meta-analysis.
Results
236 primary studies (376405 women) reported rates of obesity in women in LMICs. Women presented with almost a 3-fold increase in the odds of obesity (OR:2.75 [95% CI:2.50-3.02]) compared to men, independent of age. Highest risk was observed in Sub-Saharan Africa (OR:3.60 [95% CI:2.71-4.77]). There was a 2-fold increase in the odds of hypertension (OR:2.43 [95% CI:2.19-2.80]) and diabetes (OR:2.84 [95% CI:2.16-3.74]) in women with obesity compared to women without obesity.
Conclusion
We provided the evidence on sex-related disparities in obesity prevalence and increased risk of obesity-related cardiometabolic diseases in women in LMICs. Call for global and local actions on obesity prevention and treatment in women in LMICs is urgently needed.







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OC3.4

Hepatic choline deficiency underpins amelioration of visceral obesity and diabetes in ectonucleotide pyrophosphatase (Enpp)-6$^{-/-}$ mice

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The global prevalence of obesity continues to rise, creating a growing need for new effective medicines. Selective targeting of visceral obesity (fat around the internal organs) would be particularly advantageous because it carries a greater risk for cardiometabolic diseases. The ectonucleotide pyrophosphatase (ENPP) enzyme family participates in several pathological conditions including diabetes (ENPP1, and ENPP2, also known as autotaxin) and vascular dysfunction (ENPP3-4). Of these, ENPP6 is a lysophospholipase-C-type enzyme recently linked to regulation of local phosphocholine availability. The role of ENPP6 in fat distribution and metabolism in the context of obesity is unknown. Here we investigated the metabolic profile of mice lacking the *Enpp6* gene (*Enpp6*$^{-/-}$) when exposed to an obesogenic high-fat-diet (HFD) and tested whether choline deficiency (CD) represented an underlying mechanism contributing to their phenotype. HFD-fed*Enpp6*$^{-/-}$ mice exhibited selectively reduced visceral adiposity with higher white adipose expression of "beigeing" markers (indicative of enhanced lipid burning), improved glucose tolerance and resistance to fatty liver compared to *Enpp6*$^{+/+}$ mice. HFD-fed *Enpp6*$^{-/-}$ mice also exhibited significantly decreased hepatic choline levels and evidence for impaired *de novo* phosphatidylcholine biosynthesis through reduced hepatic phosphatidylethanolamine N-Methyltransferase *(Pemt)* expression. Dietary choline supplementation reversed the improved metabolic phenotype of *Enpp6*$^{-/-}$ mice in parallel with restored hepatic *Pemt* mRNA levels. Dietary choline deficiency (CD) did not augment the improved phenotype of HFD-fed *Enpp6*$^{-/-}$ mice. Instead, CD-HFD increased liver fat accumulation to a greater extent in *Enpp6*$^{-/-}$ mice. This suggests ENPP6-regulated endogenous choline production plays a novel role in body-fat distribution distinct to dietary choline. ENPP6 is a novel anti-visceral obesity target through its effects on endogenous hepatic choline production.

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OC3.5

Microbial tryptophan metabolites modulate L-cell induced GLP-1 secretion to improve glucose homeostasis

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Growing evidence implicates gut microbiota-derived metabolites in metabolic homeostasis. Gut microbial dysbiosis occurs in obesity, while high-fibre and high-protein diets, which improve glucose tolerance and induce weight loss, are associated with the generation of microbial metabolites. Understanding how the gut responds to microbial metabolites may identify mechanisms that induce satiety and improve glucoregulation, revealing novel therapeutic targets. Indole is generated following bacterial catabolism of the essential amino acid L-tryptophan, and can act as an agonist of the aryl hydrocarbon receptor. Indole has been reported to modulate glucagon-like peptide 1 (GLP-1) secretion *in vitro*, while recent epidemiological studies found that indole metabolites are inversely associated with type 2 diabetes incidence. We investigated the effect of indole on food intake, glucose tolerance and gut hormone secretion in mice. Acute oral but not intraperitoneal administration of indole significantly improved glucose tolerance *in vivo*, but orally administered indole had no effect on food intake in mice. In accord with this improvement in glucose tolerance, indole stimulated the secretion of GLP-1 from STC-1 cells and primary murine colonic crypts *in vitro*, an effect that did not appear to involve the aryl hydrocarbon receptor, but was attenuated by Transient Receptor Potential A1 ion channel inhibition. Additionally, using murine intestinal organoids which express a fluorescent calcium reporter in enteroendocrine L-cells, we found that indole dose dependently increased calcium mobilization in L-cells. Single bolus oral supplementation of indole also caused an improvement in glucose tolerance which lasted for several days. In line with this, increased expression of *Gcg*, which codes for GLP-1, was detected in the ileum of indole-treated mice. Further work is needed to elucidate how indole metabolites acutely and sub-chronically modulate the enteroendocrine system to determine whether this pathway is conserved in humans, and whether it can be exploited therapeutically.

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OC3.6

Stimulation of motilin secretion by bile, free fatty acids and acidification in human duodenal organoids

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Objective
Motilin is a proximal small intestinal hormone with roles in gastrointestinal motility, gallbladder emptying and hunger initiation. The molecular mechanisms underlying motilin release in response to fats, bile and duodenal acidification are poorly understood, in part due a lack of suitable cellular and rodent models. We therefore generated a novel human intestinal organoid model with fluorescently labelled motilin-expressing M-cells, which we used to establish the key signalling pathways involved in the regulation of motilin secretion.
Methods
CRISPR-Cas9 homology donor repair was used to insert the fluorescent protein Venus or the Ca^{2+} sensor GCaMP7s under control of the endogenous motilin promoter in human duodenal organoids. This enabled identification and purification of M-cells for bulk RNA sequencing, peptidomics, calcium imaging and electrophysiology. We also developed a liquid chromatography tandem mass spectrometry (LC-MS/MS) assay to measure secretion of motilin and other gut hormones from 2D organoid-derived cultures.
Results
Human duodenal M-cells express a range of nutrient-sensing and neurohormonal receptors. Agonists of the bile acid receptor GPBAR1, long chain fatty acid receptor FFA1 and monoacylglycerol receptor GPR119 stimulate motilin secretion by 3.4-, 2.4- and 1.5-fold, respectively. Acidification at pH 5.0 was a potent stimulus of acute M-cell calcium elevation and electrical activity, an effect attributable to acid-sensing ion channels, and a modest inducer (1.6-fold) of motilin release.
Conclusions
This study presents the first in-depth transcriptomic and functional characterisation of human duodenal motilin-expressing cells. We identify several receptors important for the postprandial and interdigestive regulation of motilin release.

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Adrenal and Cardiovascular

OC4.1

Development of [18F]AldoView as the first highly selective aldosterone synthase PET tracer for imaging of patients with Primary Hyperaldosteronism.

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Background
Inappropriately high aldosterone in patients with primary hyperaldosteronism (PHA) is due to increased aldosterone synthase (CYP11B2) activity. Selective *in vivo* imaging of overexpressed CYP11B2 in adrenals with positron emission tomography (PET) has not yet been achieved due to close homology of enzymes involved in aldosterone and cortisol (CYP11B1) synthesis.
Aim
Synthesize a fluorine-18 labelled highly selective CYP11B2 inhibitor, [18F] AldoView, and assess its potential for the detection of aldosterone producing adenomas (APAs) and aldosterone producing cell clusters (APCCs) with PET in patients with PHA.
Methods
[18F]AldoView was synthesised in high radiochemical yields using a proprietary radiochemistry platform.[1] Dynamic PET/CT imaging, biodistribution studies and metabolite analysis was performed in wild type female BALB/c mice. [18F] AldoView binding to CYP11B2 was characterised by quantitative phosphorimaging in tissue sections prepared from adrenalectomy specimens of patients with PHA, Cushing, phaeochromocytoma and incidentaloma. CYP11B2 specific immunohistochemistry (IHC) was performed in directly adjacent sections.
Results
In mice, [18F]AldoView showed a favourable pharmacokinetic profile, including rapid distribution and clearance. In tissue sections, [18F]AldoView binding was

visually consistent with CYP11B2 IHC staining. Specific tracer binding to CYP11B2 positive areas ranged from 8.6 to 19.1 kBq/cm^2 and was evenly distributed across tissue identified as APA, in contrast to cortex, which had diffuse patterns with hot spots in keeping with APCCs. There was no evidence of elevated tracer uptake in CYP11B2 negative areas in patients with or without PHA (3.2 ± 1.1 kBq/cm^2 and 2.6 ± 1.8 kBq/cm^2, respectively).[2]

Conclusion

Our results strongly suggest that [18F]AldoView can image CYP11B2 expression in human adrenals and could become first highly selective radioactive tracer to be used to stratify patients with PHA for adrenalectomy.

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OC4.2

Somatic mutations of GNA11 and GNAQ in CTNNB1-mutant aldosterone-producing adenomas presenting in puberty, pregnancy or menopause.

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Most aldosterone-producing adenomas (APAs) have gain-of-function somatic mutations of ion channels or transporters. However, their frequency in aldosterone-producing cell-clusters of normal adrenals could suggest the existence of co-driver mutations which influence the development or phenotype of APAs [1]. Gain-of-function mutations in both *CTNNB1* and the G-protein coupled receptor *GNA11* were found by whole exome sequencing in 3/10 APAs. Further sequencing of known *CTNNB1*-mutant APAs from UK/Irish patients led to 10/10 with a somatic p.Gln209His, p.Gln209Pro or p.Gln209Leu mutation of *GNA11/Q*. Nine out of ten patients presented at times of high LH/HCG (puberty, pregnancy, menopause). Their double-mutant APAs had >10-fold higher expression of multiple transcripts, including LHCGR, than other APAs. Transfections of NCI-H295R cells (an immortalised adrenocortical cell line with S45P mutation of *CTNNB1*) with *GNA11* Q209H, L or P increased aldosterone secretion and *CYP11B2* expression (encoding aldosterone synthase) by 2.5-6.1-fold and 8.0-9.8-fold ($P = <0.0005$) respectively, compared to vector-transfected cells. H295R cells, and one double-mutant APA, did not express *LHCGR,* and pointed to alternative mediators of the double-mutant phenotype, e.g. TMEM132E. Fresh adrenal adenoma cells harvested post adrenalectomy were transfected with *CTNNB1* and *GNA11* mutants, alone or together, and compared with cells transfected with vector or wild-type genes. Aldosterone secretion, *CYP11B2* expression and *LHCGR* were increased substantially more by the combination than by single mutant, or wild-type transfections ($P = <0.0001$). *LHCGR* expression was also assessed via immunofluorescence, which showed cells harbouring both mutations to stain the most intensely. In conclusion, somatic mutations of the Q209 residue of *GNA11/Q* appear always to co-exist with exon 3 mutations of *CTNNB1* and to cause a unique clinical and APA phenotype. These experiments are part of a larger study, which also compared APAs with single- or double-mutation of *CTNNB1*, from French and Swedish cohorts [2].

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OC4.3

[^{11}C]Metomidate PET/CT can aid decision-making in patients with primary aldosteronism

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Background

Primary aldosteronism (PA) is the leading, potentially reversible, cause of secondary hypertension. For most patients in whom surgery is being considered, adrenal vein sampling (AVS) is recommended to distinguish unilateral and bilateral causes. However, AVS remains technically challenging, and a significant proportion of patients are unable to progress to surgery because AVS is unavailable or unsuccessful. We have explored whether [^{11}C]Metomidate PET/CT (MTO-PET), used alone or in combination with AVS, can increase the proportion of patients proceeding to surgery.

Methods

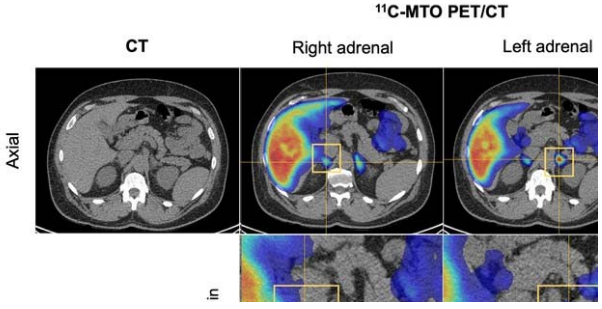
We report a retrospective case series of 111 consecutive patients referred to Cambridge for MTO-PET between January 2016 and December 2019. Patients recruited to clinical trials and those included in previous published case series were excluded from the analyses. MTO-PET/CT was interpreted jointly by two experienced clinicians and assigned a probability (low, medium or high) of unilateral disease. Where available, findings from AVS were not disclosed until scoring of MTO-PET/CT was complete. Biochemical and clinical success following surgery were judged according to PASO criteria.

Results

47 (42.3%) patients were recommended for surgery, of which 31 (27.9%) proceeded to adrenalectomy. In the surgical cohort, 19 patients had a high probability of unilateral disease on MTO-PET and complete biochemical success was observed in 18/19, with all achieving at least partial clinical success. 12 patients were assigned an intermediate probability of unilateral disease, with five proceeding to surgery based on MTO-PET/CT alone. In seven patients, findings from MTO-PET/CT were combined with AVS to inform decision-making. Complete biochemical success was achieved in 11/12 patients, with partial clinical success in all patients.

Conclusion

In a subgroup of PA patients previously unable to progress on the management pathway due to challenges with AVS, we have shown that MTO-PET can reliably identify patients with unilateral disease to allow successful surgery.



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OC4.4

24-hour dynamics of free tissue adrenal hormones: A description of healthy normal variation

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Adrenal hormones possess both circadian and ultradian rhythms, making interpretation of single time point measurements difficult, particularly in the context of suspected endocrine disease. Attempting to capture either normal or pathological rhythms in detail by traditional measurement of blood is impractical and generally unfeasible. However, minimally invasive microdialysis sampling of free tissue hormones coupled with a portable fraction collector (U-RHYTHM), and a targeted LC-MS metabolomics approach offers the ability to sample at high resolution without blood and in ambulatory settings. Using these methods, we examined the dynamics of tissue free adrenal steroids in healthy volunteers as part of the ULTRADIAN multi-centre clinical trial (ultradian.eu). Inter-individual variability of subcutaneous free adrenal steroid rhythms was characterised by U-RHYTHM collection of 24-hour hormone profiles in$n = 223$ participants (age 18-68, males = 100) in ambulatory free-living conditions. In a separate cohort, simultaneous plasma samples were collected and hormone rhythms in blood and tissue were compared ($n = 7$). Finally, intra-individual variability was examined in$n = 24$ healthy volunteers who completed outpatient U-RHYTHM hormone profiles on multiple occasions. During analysis, we used mathematical techniques including conventional metrics (range, area under the curve, etc.), non-stationary statistics and time series analyses to create novel dynamic biomarkers of normality. Consequently, we have been able to characterise for the first time the healthy range, dynamic features, and plasma correlations that define normal variation of adrenal hormones in subcutaneous tissue. Key hormones identified include cortisol, cortisone, corticosterone, aldosterone and 18-hydroxycortisol. Results have been stratified in several ways including by age, sex, and BMI. This knowledge is a step towards a deeper understanding of the dynamic physiology of adrenal steroids in healthy people, and furthermore provides normative reference data that will enable the possibility of comparison with disease conditions.

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OC4.5

Circulating cell-free DNA-based biomarkers as a tool for disease surveillance in adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare aggressive cancer with heterogeneous behaviour. Disease surveillance relies on frequent imaging, which comes with significant radiation exposure. Here we investigated the role of circulating cell-free DNA (ccfDNA) in ACC monitoring. We extracted ccfDNA from 1-4 ml EDTA-plasma using the Nonacus Cell3^{TM}Xtract or the Qiagen QIAamp MinElute kit and quantified by fluorimeter. We investigated 63 patients with ACC (25M/38F, 52 ± 15yrs; 25 primary tumours [ACC-P] and 38 recurrences [ACC-R]); while 26 patients with adrenocortical adenomas (8M/18F, 55 ± 17yrs) and 19 healthy subjects (9M/10F, 37 ± 9yrs) served as controls. Targeted next generation sequencing (Illumina NextSeq500) was performed on 34 ccfDNA samples (12 ACC-P, 14 ACC-R, 8 adenomas) using a customised panel of 30 ACC-specific genes (Cell3^{TM}Target Nonacus). Leucocyte DNA was sequenced to discriminate germline from somatic variants. Sequencing data from matched tumour-DNA were available for 13 ACC. ACC-P had the highest ccfDNA concentrations (0.99 ± 1.46 ng/µl) compared to ACC-R (0.23 ± 0.22 ng/µl, $P < 0.05$), adenomas (0.17 ± 0.13 ng/µl, $P < 0.005$) and healthy subjects (0.11 ± 0.07 ng/µl, $P < 0.005$). In ACC, ccfDNA levels correlated with the tumour burden, i.e. size of tumour manifestations plus number of metastasis ($P < 0.001$, R = 0.57). In ACC-P, ccfDNA concentrations correlated with ENSAT stage ($P < 0.05$) and were negatively associated with recurrence-free survival ($n = 14$, $P = 0.039$, HR 7.54, 95%CI 1.2-47.5). Among sequenced ccfDNA samples, 6 ACC-P (50%) and 3 ACC-R (21%), but no adenomas, showed somatic mutations in at least one ACC driver gene (4 *CTNNB1*, 4 *TP53*, 3 *ZNRF3*, 2 *MEN1*, 1 *DAXX*, 1 *RB1*). CcfDNA sequencing matched with tumour-DNA results in 69% of cases. In conclusion, ccfDNA concentrations correlate with tumour burden and may predict disease recurrence in patients with ACC. Targeted ccfDNA sequencing detected ACC-specific mutations in half of the patients. Thus, ccfDNA-based liquid biopsy may represent a promising, non-invasive tool complementing imaging in disease surveillance.

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OC4.6

Glucocorticoids and the Vascular Molecular Clock: Implications in Vascular Function Control

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Glucocorticoids synchronise peripheral clocks with the master clock in the suprachiasmatic nucleus of the brain. In humans and mice, abnormal glucocorticoid rhythms induce blood pressure abnormalities accompanied by vascular dysfunction. The mechanisms of this remain unclear. We hypothesise that excessive activation of the glucocorticoid receptor (GR) disrupts circadian clock signalling, altering vascular function and inducing non-dipping blood pressure. We characterise the vascular molecular clock and define the rhythm of vascular reactivity in control mice and mice with smooth muscle specific deletion of the GR (SMGRKO). Mice were kept under 12:12 light: dark conditions. Plasma was sampled every 2 h across the light cycle and analysed for corticosterone by ELISA. Renal and mesenteric arteries were isolated at ZT0 and 12 (ZT0 lights on) to assess molecular clock transcripts by qPCR. Renal and mesenteric arteries from SMGRKO mice and controls were mounted on a wire myograph and subject to increasing doses of phenylephrine or sodium nitroprusside starting at ZT0 and ZT12 Data are mean ± SD. Corticosterone had a circadian rhythm in control mice with peak at ZT 10. Clock genes *Per1* and *Bmal1* were expressed in the renal and mesenteric artery with a circadian rhythm peaking at ZT12 and ZT0 respectively. Vascular reactivity as assessed by wire myography showed in control mice the response to phenylephrine was elevated during the inactive period (ZT0, 86.2 ± 9.21 % of the maximum constriction) compared to the active period (ZT 12, 72.3 ± 7.52%). Relaxation in response to sodium nitroprusside was more pronounced during the active period (ZT12, 23.2 ± 8.74% of pre-construction vs ZT0, 36.71 ± 5.15%). The temporal differences in response to phenylephrine and SNP was absent in SMGRKO mice. These data suggest that glucocorticoids regulate the molecular components that control vascular function's timing. Further investigations will identify glucocorticoid-related pathways that control vascular function and assess their impact on blood pressure rhythm.

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Bone and Calcium

OC5.1

Successful adeno-associated virus mediated neonatal gene therapy treatment of hypophosphatasia murine model resulted in bone maturation and increased survival to at least 18 months

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Hypophosphatasia (HPP) is an inherited skeletal disease characterized by defective bone mineralization due to a deficiency in tissue-nonspecific alkaline phosphatase (TNALP). Patients with the severe infantile form of HPP have a poor prognosis that often results in high mortality by one year. Asfotase alfa is an approved therapy for HPP, while requires chronic injections to maintain efficacy. To develop a one-time gene therapy for HPP, we examined the safety and efficacy of AAV-TNALP-D10 (adeno-associated viral vector expressing TNALP-D10) in an *Akp2*$^{-/-}$ HPP mouse model. Neonatal *Akp2*$^{-/-}$ mice were injected with AAV-

TNALP-D10 intramuscularly. Wild type mice were injected with AAV-GFP vector ($1.0x10^{12}$ vector genome (vg)/body) as a control. Plasma ALP activity was assessed and the organs of the mice were examined for any possible macroscopic lesions. Following treatment of neonatal *Akp2*$^{-/-}$ mice with a single local injection of AAV-TNALP-D10-vector ($1.0x10^{12}$ vg/body), high plasma ALP levels (19.38 $\pm$ 5.02 U/ml) were detected and persisted for up to 18 months. Computed tomography analysis showed mature bone mineralization. 5/7 of the animals survived until the end of the study (18 months). Histochemical staining for ALP activity in the knee joint revealed ALP activity on the surface of the endosteal bone of mice. Throughout their lives, the treated *Akp2*$^{-/-}$ mice exhibited normal physical activity and a healthy appearance, whereas untreated controls died within 3 weeks. No ectopic calcification or abnormal calcium metabolism together with unusual cell growth was detected in the treated mice. AAV-TNALP-D10-mediated neonatal gene therapy is both safe and effective. The current study demonstrates durability and survival up to 18 months, the longest ever demonstrated in this animal model. The study supports the development of AAV-TNALP-D10 as one-time treatment of the severe infantile form of HPP. AAV-TNALP-D10 has the potential to shift HPP treatment paradigm from chronic to one-time dose.

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OC5.2

Gastric inhibitory polypeptide (GIP) reduces human osteoclast activity by suppressing multiple signalling pathways

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Gastric inhibitory polypeptide (GIP) is a post-prandially secreted gut hormone that acts upon the GIP-receptor (GIPR), to stimulate insulin secretion. Animal studies indicate that GIP influences bone remodelling, and in humans, GIP administration decreases levels of bone resorption markers. However, the mechanisms by which GIP influences resorption remain to be elucidated. Therefore, we investigated how GIP (10nM) affects bone cell activity using primary human osteoclasts, human osteoblasts, and osteoclast-osteoblast co-cultures. We confirmed that GIP reduces bone resorptive activity in osteoclast ($P < 0.01$) and osteoclast-osteoblast cultures ($P < 0.01$), and showed reduced tartrate-resistant acid phosphatase (TRAcP) activity in mature osteoclasts, demonstrating that GIP reduces osteoclast differentiation. Signalling was then assessed in cells (5-9 donors) stimulated with GIP for 30 minutes, and compared to vehicle-treated cells. Direct stimulation of GIPR on osteoclasts and osteoblasts was shown by GIP-mediated elevations in cAMP ($P < 0.01$), which was reversed by pre-treatment with a GIPR antagonist, GIP(3-30)NH_2. AlphaLISA assays showed phosphorylation of c-Src, Akt1/2/3 and NFκB p65, which regulate cytoskeletal reorganisation necessary for resorption, osteoclast survival and differentiation, were all reduced by GIP in osteoclasts ($P < 0.01$). Furthermore, confocal microscopy revealed that GIP-treated osteoclasts had reduced levels of nuclear phosphorylated-NFATc1 ($P < 0.0001$), a key modulator of osteoclast differentiation and osteoclast-specific gene expression. Pre-exposure of cells to inhibitors of GIPR and the cAMP-induced protein kinase A (PKA) prevented these GIP-mediated effects on p-Akt1/2/3, p-p65 and NFATc1. RNA-sequencing revealed downregulation of >30 genes involved in osteoclast function, including genes for cathepsin K, TRAcP5 and carbonic anhydrase-2, known regulators of osteoclast resorption. Moreover, >70 cell survival genes were differentially expressed by GIP treatment. Assessment of caspase-3/7 activity showed that GIP also increases osteoclast apoptosis ($P < 0.01$). In summary, GIPR activation on osteoclasts suppresses c-Src, Akt1/2/3, NFκB and NFATc1 signalling, leading to decreased bone resorption, likely by reduced expression of osteoclast-specific genes and increased apoptosis.

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OC5.3

Role of Intact and C-Terminal FGF-23 Assays in the Investigation of Metabolic Bone Disease.

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Fibroblast growth factor 23 (FGF-23) is a phosphatonin produced by osteocytes in response to serum phosphate concentration. Immunoassays are widely employed to detect C-terminal fragments of FGF-23 (cFGF-23). Quantitative assays for intact FGF-23 (iFGF-23) measurement are also available. Causes of increased FGF-23 include Tumour Induced Osteomalacia (TIO), X-linked hypophosphataemic rickets (XLH) and end stage renal disease (ESRD). We observed that some individuals, with no identifiable classical cause of elevated FGF-23, have elevated cFGF-23 and normal iFGF-23. 561 individuals, with elevated cFGF-23 and normal iFGF-23, were identified from a metabolic bone clinic at our centre. 361 patients were included in our final analysis and were further characterised using their bone-metabolic biochemical parameters and clinical data. Patients with a confirmed diagnosis of TIO, XLH, hypophosphataemia (PO_4 <0.8 mmol/l) and ESRD on renal replacement therapy were excluded. Each patient's primary clinical diagnosis was correlated with their biochemical results. In the final cohort, the mean cFGF-23 was 224RU/mL (RR <100RU/mL, range 100 – 6720); mean iFGF-23, 63pg/mL (RR 33 – 110pg/mL, range 0 – 109); mean PTH, 8.0 pmol/l (RR 1.6 – 6.9pmol/l); mean eGFR, 69 ml/min/1.73m^2 (range 20 – 90); mean 25-OH vitamin D 68.9 nmol/l; mean albumin adjusted calcium 2.6 mmol/l (RR 2.2 – 2.6 mmol/l); and inorganic phosphate 1.0 mmol/l (RR 0.8 – 1.5). As expected, negative correlations between eGFR and C-terminal and iFGF-23 concentrations were observed (r^2 value -0.035 and -0.121 respectively). The major associated co-morbidities in the cohort were osteoporosis on treatment ($n = 63$), primary hyperparathyroidism (PHPT) ($n = 90$) and vitamin D deficiency ($n = 90$). A significant proportion of cases with elevated cFGF-23 have normal iFGF-23 measurements. The commonest causes of this biochemical picture in our cohort were PHPT, osteoporosis on treatment, and vitamin D deficiency. Thus, it appears that cFGF-23 assays may be more susceptible to confounding by non-classical causes of FGF-23 elevation than iFGF-23 assays.

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OC5.4

Nuclear factor I/X (NFIX) regulates the transcriptional activity of the cellular retinoic acid binding protein 2 (CRABP2) promoter and alters CRABP2 expression in Marshall-Smith Syndrome (MSS) patients.

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Marshall-Smith syndrome (MSS) is a congenital disorder affecting skeletal and neural development, due to mutations in the nuclear factor I/X (*NFIX*) gene. *NFIX* encodes a ubiquitously expressed transcription factor that regulates the expression of viral and cellular genes. To identify novel genes that are misregulated by *NFIX* mutations, RNA sequencing and proteomics analyses were performed on mouse embryonic fibroblast (MEF) cells derived from a representative *Nfix* mutant mouse model for MSS (*Nfix*$^{Del2/Del2}$) and wild-type mice. This revealed that cellular retinoic acid binding protein 2 (*Crabp2*) was upregulated at both the RNA and protein levels (2.59-fold and 2.83-fold, $P < 0.012$, respectively). Validation studies using qRT-PCR and Western blot analyses confirmed that *Crabp2* was upregulated at the RNA and protein levels (2.4-fold and 5-fold, $P < 0.0001$, respectively) in *Nfix*$^{Del2/Del2}$ MEFs compared to wild-type MEFs and that 60% of the 5 MSS patients' fibroblasts had altered *CRABP2* transcript ($P < 0.05$) and protein ($P < 0.001$) levels, compared to 3 normal fibroblasts. We identified a putative nuclear factor I (NFI) binding site, to which NFIX binds, in the *CRABP2* 5' untranslated region (UTR). To investigate its effect on promoter activity, luciferase reporter constructs under the transcriptional control of either the wild-type or mutant (with a mutated or deleted NFI binding site) *CRABP2* promoter were transfected into monkey kidney fibroblast (COS-7) cells. Mutation and deletion of the NFI binding site resulted in 1.3-fold ($P < 0.001$) and 0.6-fold ($P < 0.0001$) change in luciferase expression compared to the wild-type promoter, respectively. Furthermore, co-transfection of COS-7 cells with wild-type *CRABP2* promoter-driven luciferase reporter constructs and N-terminal-FLAG tagged wild-type and MSS-mutant *NFIX* cDNA constructs showed that the MSS-associated NFIX mutants significantly increased luciferase reporter activity at the *CRABP2* promoter (1.5-fold, $P < 0.05$) compared to wild-type NFIX. Thus, our results suggest that NFIX directly regulates the activity of the *CRABP2* promoter and alters *CRABP2* expression in MSS patients.

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OC5.5

Diacylglycerol kinase delta haploinsufficiency in mice causes hypocalcaemia: relevance to human Autosomal Dominant Hypoclacemia (ADH)

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Diacylglycerol kinase delta (DGKD) has been implicated in calcium homeostasis and nephrolithiasis by genome-wide association studies. We have previously demonstrated that alterations in expression of DGKD cause biased calcium-sensing receptor (CaSR) signalling *in vitro*. To further elucidate the physiological role of DGKD we examined the biochemical phenotype of a *Dgkd*-haploinsufficient (+/-) mutant mouse developed by the International Mouse Phenotyping Consortium. *Dgkd* (+/-) animals were found to be hypocalcaemic when compared to wildtype mice (+/+) (serum calcium +/+ = 2.42 mmol/l ± 0.01 vs. +/- = 2.34 mmol/l ± 0.02, $P = 0.008$ male mice, +/+ = 2.39 mmol/l ± 0.01 vs. +/- = 2.30mmol ± 0.04, $P = 0.02$ female mice) with inappropriately normal parathyroid hormone concentrations indicating an alteration in the homeostatic set-point for extracellular calcium (serum PTH +/+ = 61.89pmol/l ± 17.48 vs. +/- = 58.47pmol/l ± 9.24 male mice, +/+ = 106.3pmol/l ± 27.42 vs. +/- = 35.54pmol/l ± 5.76 female mice). In addition, *Dgkd* +/- mice were hyperkalaemic (serum potassium +/+ = 4.28 mmol/l ± 0.04 vs. +/- = 4.68 mmol/l ± 0.08, p = 0.0009 male mice, +/+ = 3.81 mmol/l ± 0.07 vs. +/- = 4.63 mmol/l ± 0.14 female mice, $P = 0.0009$ female mice), female mice were hyperphosphatasic (serum ALP +/+ = 65.78U/l ± 2.26 vs. +/- = 79.50U/l ± 2.41 male mice, +/+ = 107.9U/l ± 1.98 vs. +/- = 128.0U/l ± 4.08 female mice $P = 0.0009$), and male mice had a reduced bone mineral density (BMD) (+/+ = 2.480mg/cm^2 ± 0.008 vs. +/- = 2.18 mg/cm^2 ± 0.068, $P = 0.0009$ male mice, +/+ = 3.00 mg/cm^2 ± 0.012 vs. +/- = 2.94 mg/cm^2 ± 0.045 female mice). These studies have established a mouse model of *Dgkd*-haploinsufficiency with hypocalcaemia due to a homeostatic set-point abnormality in keeping with Autosomal Dominant Hypocalcaemia (ADH), a human disorder due to gain-of-function mutations in components of the CaSR-signalling pathway and associated with hypercalciuria. However, in contrast to previously reported mouse models and human cases of ADH, alterations in serum potassium, ALP, and BMD were detected suggesting that alterations in DGKD expression may also affect signalling pathways other than the CaSR.

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OC5.6

The role of vitamin D supplementation in critically ill patients with COVID-19

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Background
Studies have established a link between vitamin D deficiency and susceptibility to and severity of COVID-19. Our study aims to evaluate the role of vitamin D supplementation in intensive care units (ICU) in patients with COVID-19.
Methods
We conducted a retrospective analysis of patients admitted to ICU in a large tertiary centre. Data on serum vitamin D concentration and supplementation, mortality, hospital and ICU stay, electrolyte replacement and organ support days was analysed using chi-square, Mann-Whitney and Spearman rank coefficient tests where appropriate.
Results
There was no association between vitamin D deficient patients and mortality (26.4% vs 25.9% $P = 0.934$). Patients that received vitamin D supplementation during their admission had a lower mortality than those who did not (19% vs 30% respectively, $P = 0.032$), however there was no difference in mortality in those that had vitamin D replaced within 4 days from admission and those that did not (28% vs 26% $P = 0.469$). Patients who received supplementation within 4 days had a shorter ICU stay (2.85 vs 4.7 days, $P = 0.004$) and hospital stay (13 vs 16.05 days, $P = 0.028$). There was a moderate positive correlation between the time between admission and vitamin D supplementation and length of ICU and hospital stay ($r_s = 0.581$ and $r_s = 0.561$ respectively). Those given vitamin D within 4 days were less likely to require IV phosphate infusions (18.8% vs 31.3% $P = 0.043$, RRR = 12.46%) and advanced respiratory support (29.0% vs 45.5% $P = 0.014$, RRR = 36.3%).
Discussion
Our findings suggest that early replacement of vitamin D in critically ill patients with COVID-19 may reduce hospital and ICU stay, and reduce the requirement for more advanced management. This was a single centre, retrospective study with notable implications for the role of vitamin D supplementation. To further clarify this role prospective studies are needed.

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Thyroid

OC6.1

Adjuvant Rituximab – exploratory trial in young people with Graves' disease

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Objective
Remission rates in young people with Graves' hyperthyroidism are <25% after a 2-yr course of thionamide antithyroid drug (ATD). Immunomodulatory agents might improve outcome by facilitating immune tolerance. We explored whether rituximab (RTX) would increase remission rates when administered with a short course of ATD.
Design
This was an open label multi-centre single arm phase 2 trial in newly presenting young people (12-20y) with Graves' hyperthyroidism. The trial used an A'Hern design to distinguish an encouraging remission rate of 40% from an unacceptable rate of 20%, with power of 80% and Type I error of 10%. Participants received 500 mg dose of RTX followed by up to 12 months of ATD. The primary endpoint was relapse at 24 months (suppressed serum TSH and raised FT3), needing to restart ATD or to undergo thyroidectomy/radioiodine therapy.
Results
Twenty-seven participants were recruited (6 UK centres). All completed the trial and there were no serious side effects linked to treatment. The daily Carbimazole dose at 12 months was 5 mg or less in 20/27 participants (1/27 on 50 mg propylthiouracil). 13 of 27 participants were in remission at 24 months (48%, 90% one-sided confidence interval 35%, 100%); this number exceeded the critical value (9) for the A'Hern design, providing evidence that the remission rate exceeded 40%. B lymphocyte count at 28 weeks (percentage of baseline value) was 18.0 in the remission group versus 46.5 in the relapse group (95% CI for difference; 8.1,48.0). There was no significant difference between remission/relapse groups in terms of total ATD dose or time to non-suppressed TSH.
Conclusions
Adjuvant RTX, administered with a 12 month course of ATD, may increase the likelihood of remission in young people with Graves' hyperthyroidism. A formal randomised trial of adjuvant rituximab in young people with Graves' hyperthyroidism is warranted.

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OC6.2

Concerted action of TH transporters MCT8 and OATP1C1 regulates adult hippocampal neurogenesis and hippocampal function in mice

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Inactivating mutations in the thyroid hormone (TH) transporter monocarboxylate transporter 8 (MCT8) result in a severe form of psychomotor retardation (known as Allan-Herndon-Dudley syndrome, AHDS) due to compromised TH access to the CNS. Consequently, TH-dependent processes both during brain development and in the adult CNS such as adult hippocampal neurogenesis are impaired. Using mice deficient in Mct8, we recently demonstrated a diminished neurogenesis in the adult hippocampus due to combined cell-autonomous and non-autonomous requirements for Mct8. To further investigate alterations in adult neurogenesis in Allan-Herndon-Dudley syndrome, we addressed the question whether T4-specific organic anion transporting polypeptide 1c1 (Oatp1c1) acts in concerts with Mct8 in regulating adult neurogenesis in Mct8/Oatp1c1 double knockout (dko) mice, the currently most suitable mouse model for AHDS. We first defined Oatp1c1 expression in a subset of hippocampal progenitor cells and granule cell neurons. Then, analysing distinct stages within the cell lineage leading to adult hippocampal neurogenesis in Mct8/Oatp1c1 dko and single transporter mutant mice by immuno-histochemistry, we showed that Mct8/Oatp1c1 dko mice replicated the impaired neuroblast differentiation and neuron formation capacity previously attributed to cell-autonomous Mct8 function. In addition, however, we demonstrated that absence of Oatp1c1 results in a further increase in the number of earlier progenitor cells within the lineage (stage 2 and stage 3 cells) at 6 months of age. Importantly, in all knockout models, we observed selective impairments in hippocampus-related functions and a depression-anxiety like phenotype in the open field arena. Together, our results point to a function of Oatp1c1 in the adult hippocampal neurogenic programme and substantiate the concept that TH transport is required at multiple levels in this process.

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OC6.3

Failure of Radioiodine Remnant Ablation to Improve Postoperative Outcome in 2668 Adult Patients with AJCC/pTNM Stage I Papillary Thyroid Carcinoma

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Background
To determine whether radioiodine remnant ablation (RRA) reduces cause-specific mortality (CSM) or tumor recurrence (TR) rates after bilateral thyroidectomy (BT) in low-risk adult papillary thyroid carcinoma (APTC) patients treated with curative intent, we compared outcome in 1836 stage I patients having BT alone with 832 having BT+RRA.
Methods
THEN cohort (1966-1990) comprised 809 patients; 36% having RRA within 6 postoperative months. NOW cohort (1991-2015) comprised 1859 patients (29% having BT+RRA); statistical analyses of differences in occurrence rates between BT alone and BT+RRA performed with SAS software.
Results
During 1966-90, when RRA rates rose tenfold, 20-year CSM and TR rates after BT alone were 0.6 and 7.9%; rates after BT+RRA higher at 1.2% ($P = .66$) and 11.7% ($P = .04$). When compared to rates after BT alone, RRA did not significantly improve CSM or TR rates at local, regional, or distant sites ($P > .1$). During 1991-2015, when RRA rates fell, no NOW cohort patient died of PTC. The 20-year TR rate after BT alone was 7.6%; after BT+RRA significantly higher at 20.0% ($P < .0001$). RRA in NOW cohort was administered to 49% of pN1 patients but only 17% of pN0/NX patients ($P < .0001$). TR rates were examined separately for node-negative and node-positive patients. In 1157 pN0 cases, 20-yr loco-regional recurrence (LRR) rates were 3.1% after BT and higher ($P = .049$) at 8.6% after BT+RRA. In 702 pN1 patients, 20-yr LRR rates were higher at 27.0% after BT+RRA, when compared to 19.4% after BT alone ($P = .045$); in four pN1 groups, stratified by nodal burden, RRA did not significantly ($P > .5$) reduce the LRR rates observed after BT with curative intent.
Conclusions
RRA given to adequately treated stage I patients did not reduce CSM or TR rates. Therefore, we do not recommend RRA for APTC patients who have stage I disease and undergo potentially curative BT.

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OC6.4

AP-2 and Moesin Regulate the Internalisation of the Sodium-Iodide Symporter and Affect I^{125} Uptake in Thyroid Cancer Cells.

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Dysregulation of sodium-iodide symporter (NIS) function is common in differentiated thyroid cancer, resulting in sub-optimal radioiodide therapy and poorer clinical outcome. Recent developments in identifying proteins that regulate the function of the sodium iodide symporter have highlighted two proteins involved in internalisation of NIS from the plasma membrane: AP-2 and moesin. Clathrin-mediated endocytosis (CME) of NIS is facilitated through the adaptor protein 2 (AP2) complex which selectively sorts membrane proteins for recycling or fusion with early endosomes. Moesin has an established role in regulating CME by bridging integral membrane proteins with actin filaments to facilitate the cytoskeletal rearrangements necessary for internalising proteins. Our studies have shown that AP2°1 gene knockdown effectively inhibits CME causing NIS retention at the plasma membrane and a significant increase in ^{125}I uptake (3.4-fold; $P < 0.001$). Blocking dynamin-mediated scission via the GTPase inhibitor Dynasore (100uM) resulted in a significant increase in ^{125}I uptake (2.34 to 2.89- fold; $P < 0.001$) in TPC1-NIS and 8505C-NIS cells and significantly increased NIS protein expression. Additionally, we investigated the ability of moesin to interact with NIS, and assessed potential functional consequences. NanoBiT protein-protein interaction assays confirmed a stringent interaction between moesin and NIS in HeLa cells ($P < 0.05$ compared to controls. Critically, a functional role for moesin in regulating NIS was indicated as depletion of moesin significantly increased I^{125} uptake in NIS-expressing thyroid cell lines (TPC-1-NIS cells: 2.01-fold, $P < 0.05$; 8505C-NIS cells: 1.74-fold, $P < 0.001$). These studies have further outlined the processes that regulate the internalisation of NIS which can be dysregulated in differentiated thyroid cancer and may contribute to a radioiodide refractory tumour phenotype.

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OC6.5

Effects of *in utero* thyroid hormone exposure on human neurodevelopment: MRI analysis from the Controlled Antenatal Thyroid Screening Study

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Background
The Controlled Antenatal Thyroid Screening II (CATS) study, a large randomised trial of thyroxine supplementation for suboptimal gestational thyroid function (SGTF), reported a higher prevalence of elevated attention deficit hyperactivity disorder (ADHD) scores in 9 year-old children exposed to higher thyroid hormone (TH) *in utero*. Here we investigated if this was accompanied by altered neurodevelopment.
Methods
85 children aged 11-16 years (exposed to untreated SGTF ($n = 21$), normal GTF ($n = 24$), or treated SGTF (optimally replaced ($n = 21$), over-treated ($n = 19$)) recruited from the CATS cohort underwent quantitative characterisation of white matter microstructure and regional brain volumes using 3.0T diffusion MRI. Fractional anisotropy (FA) was measured along white matter tracts known to be influenced by TH and/or implicated in ADHD risk, including the corpus callosum and superior longitudinal fasciculus (SLF).
Results
Maternal TH at 12 weeks' gestation was not correlated with median FA values for any of the tracts studied, except between TSH and the posterior segment of the corpus callosum (correlation coefficient (τ) -0.2,$P = 0.018$). The only significant correlation with T4 was found in the right SLF-1 (r -0.57, p 0.028) at 30 weeks' gestation in the overtreated SGTF group. Weak, but statistically significant positive correlations were found between TSH and brain volume in over 30 regional volumes, notably the nucleus accumbens (r +0.25, $P < 0.008$) and total cortical volume (r +0.19, p 0.01).
Conclusions
This is the first imaging study to explore tract-specific white matter microstructure in adolescents exposed to both extremes of maternal thyroid function. Weak but consistent correlations suggest maternal TSH levels, but not T4, have an effect on certain cortical volumes. Analysis of free T4 in the treated group suggest that SLF-1, a regulator of motor behaviour, may be a target of TH action in the developing human brain later in pregnancy.

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OC6.6

Forty years' experience of national screening programme for congenital hypothyroidism in Northern Ireland.

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Northern Ireland was one of the first participating sites for the UK screening programme for congenital hypothyroidism (CHT) started 40 years ago. This study aimed to explore any changing patterns in incidence over time. Enrolment in the programme has remained high throughout the 40 years (> 98%). The cut-off value for neonatal thyroid stimulating hormone (nTSH) on day 5-8 of life reduced in ~1995 from 10 mU/l to 8 mU/l to improve sensitivity and specificity. There was a steady increase in incidence of CHT over time with an incidence of 26 cases/100,000 livebirths in 1981 vs 71/100,000 in 2019 ($P < 0.00001$). Results are similar to recent Republic of Ireland data (65/100,000). In ten year blocks the average incidence rose from 28 to 42, 65 and 73/100,000 live births (1980s, 1990s, 2000s and 2010s respectively). Similar increases have been reported in North America, Australia, Italy and Greece. Possible explanations include changes in cohort gestational age or ethnicity, more survivable associated conditions, iodine nutritional status, unquantified environmental changes (e.g., perchlorate exposure), assay cut off change or assay drift. The median gestational age of affected babies did not change significantly e.g. 40 weeks (IQR 39-41) in 1980s vs 39 weeks (IQR 38-40) in 2010s. Ethnicity is not captured in screening data, but census data shows no significant change (95% British/Irish). The most common associated chromosomal abnormality was Trisomy 21 (4.4% overall) with little change over last 30 years. When the data was reanalysed excluding cases with TSH 8-10 mU/l there was still a significant increase in incidence ($P < 0.00001$). Assay drift is possible but unlikely as our laboratory is UKAS accredited and quality assured. Our data confirms a similar increase in CHT found in other Western countries against a background of a relatively stable population.

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Poster Oral Presentations

Thyroid

OP1.1

Factors predicting long-term outcome and the need for surgery in Graves Orbitopathy extended follow-up from the CIRTED Trial

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Context
Thyroid eye disease is disabling and disfiguring and has a substantial negative impact on quality of life. Medical therapies to reduce inflammation are widely used, but there is limited data from clinical trials beyond 6 months of follow-up.
Methods
3 year follow-up of a subset of the CIRTED trial ($n = 68$) which randomized patients to receive high-dose oral steroid with azathioprine/placebo and radiotherapy/sham radiotherapy. We compared baseline severity scores and changes in clinical assessments (including CAS, Ophthalmopathy Index and Total eye score) over the first year to 3 year outcomes including quality of life (GOQOL visual function and visual appearance) and need for surgical intervention.
Results
CAS, Ophthalmopathy Index and total eye score improved over 3 years ($P < 0.001$). 24/64 individuals (37.5%) with surgical outcome data required surgical intervention. Quality of life at 3 years remained poor, 25% of patients had a GOQOL-Visual Function of 75 or lower and 54.2% had a GOQOL-Visual Acuity of 75 or lower. Over 3 years CAS fell to 0 or 1. Ophthalmopathy Index fell from 9.45 to 6.02, thyroid eye score fell from 14.9 to 6.33. Disease duration of greater than 6 months before treatment was associated with increased need for surgery OR = 16.8 (95%CI 2.95, 95.0)$P = 0.001$. Baseline levels of CAS, Ophthalmopathy Index and total eye score were associated with requiring surgery, although early improvement in CAS was not associated with a reduced need for surgery.
Conclusion
In this first long-term follow-up from a clinical trial of thyroid eye disease, 3 year outcomes remained suboptimal with ongoing poor quality of life and high numbers requiring surgery. Importantly, reduction in CAS to low levels in the first year, a commonly used surrogate outcome measure, was not associated with improved long-term outcomes. Further studies are required to determine if early intervention results in improved outcomes.

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OP1.2

Long term Management of Thyrotoxicosis with Anti thyroid Drugs (ATDs)

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Background
Recent NICE guidance recommends radioactive iodine as the first line treatment for relapsed thyrotoxicosis as it reportedly produces better control than long-term anti-thyroid drugs (ATDs).However, almost all studies of long-term ATDs relapse occurs after discontinuation of a medication. We present a retrospective analysis of efficacy of ATDs.
Methods
Data of all patients with hyperthyroidism, attending Endocrinology clinic at Morriston Hospital were collected from electronic database (Leicester database). Thyroid function test results obtained from the pathology.
Results
Total of 695 patients with thyrotoxicosis were identified between 1997 to 2020. Of 695, 476(68%) patients were diagnosed with autoimmune hyperthyroidism (Graves disease) and 99(14%) with toxic multinodular (TMNG) /solitary goitre 99(14%) and other aetiology 120(17.2%). The median length of follow up was 2.75 years(1month to 22 years). Of 476 patients with autoimmune disease, 385 were treated with ATDs. Out of 385 patients, 85 continued on long term ATDs and 300 discontinued after 12-18 months of treatment. Out of 300 who discontinued ATDs, 108 relapsed and the median time of relapse was 11.5 months. Out of 108 who relapsed, 87 were re-started on ATDs and continued on long term treatment. In total 167(97%) patients with autoimmune hyperthyroidism on long-term ATDs remained in remission with normal TSH after a median period of follow up of 37 (range 2-263) months. Of 99 patients with toxic goitre, 75 were treated with ATDs. Out of 75 patients, 39 continued on long term ATDs and 36 discontinued after 12 to 18 months. Out of 36 patients in remission after 12-18 months treatment 14 relapsed. Out of 14 relapsed patients10 were restarted on long term ATDs. In total 49 patients with toxic goitre were treated with long term ATDs. These patients maintained remission after median period of follow up of 38 (range 1 to 204) months with no relapse. Of 120 patients in other aetiology, 116 out of 120 were started on ATD. Out of 116,34 patients went into remission after 12-18 months and discontinued treatment and 10 continued on longterm treatment. No data available for 71 patients. Out of 10 relapsed patients 4 were restarted on ATD. In total 14 patients in non-specific group were treated with long term ATDs.
Discussion
Our study demonstrates that long-term maintenance dose of ATDs are effective in maintaining euthyroidism in both Graves' disease and TMNG.

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OP1.3

Thyroid Endocrine Nurse Service: Improving patient experience

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Aims
Within Imperial College Healthcare Trust, St Mary's Hospital has a large one-stop shop thyroid service. On average, 700 encounters have been recorded per annum in the St Mary's thyroid nurse-led service since its inception in June 2017. We aimed to critically evaluate the role of the specialist nurse within safe and robust monitoring clinical parameters, to determine the conditions managed in the nurse-led service and assess attendance rate.
Methods
Patients attend clinic for monitoring of blood pressure and thyroid function levels. A discussion of the presenting condition and a mutually agreed management plan takes place between the nurse and patient, with supervising consultant involvement as necessary. The data profile of those who were referred to the nurse led service over a one-year period were collated (2019 to 2020).
Results
Over the one-year period, 733 encounters were recorded for 269 patients. 61.7% (452) attended their appointments: 13.2% (97) did not attend (DNA rate in consultant thyroid service 10.5%), 15.6% (114) of patients cancelled their appointments and 9.5% (40) of appointments were cancelled by the trust. Of the 269 patients within the service, 62.8% (168) were diagnosed with autoimmune thyrotoxicosis (Graves' disease): 23% were attending the service for other thyroid conditions including surveillance monitoring for toxic multi-nodular goitres, toxic autonomous nodules, subclinical hyper/hypothyroidism and post-radioiodine treatment. An additional 2.2% (6) had a diagnosis of thyroid cancer (incorrectly booked into the service): the remainder of encounters related to further specified endocrine conditions e.g. growth hormone monitoring (32.0%,$n = 12$).
Conclusion
This service offers an enhanced and improved patient experience where an effective point of contact delivers a safe and efficient mechanism for thyroid follow up. It does not only create appointment slots for the consultant led-clinics but also enables patient to be closely involved in their care and treatment journey.

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OP1.4

Autoimmune thyrotoxicosis: Is first line treatment with anti-thyroid medication good enough?

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Introduction
Autoimmune thyrotoxicosis (AT) affects 2-5% of the Western population. Despite current NICE guidelines recommending radioiodine as first-line treatment for AT, practical considerations such as licensing often prevent this. Typically, anti-thyroid medication (carbimazole or propylthiouracil) is initially offered. Patients are usually counselled that the remission rate following a 12-18 month course of anti-thyroid medication is approximately 50%.
Aims
1. To determine whether maintenance of remission using anti-thyroid medication coincides with the current consensus. 2. To determine if a difference exists in maintenance of remission between genders. 3. To determine whether a difference exists in the maintenance of remissionbetween patients with TSH-R Ab positivity vs TPO Ab positivity (at the start of treatment).
Methods
Our population comprised secondary care patients diagnosed with AT between 2014-2017, receiving a minimum of 18 months of anti-thyroid medication and at

least 12 months of post-treatment follow-up. Failure to achieve remission was defined as patients who had 18 months of anti-thyroid medication without achieving euthyroidism, or those who achieved euthyroidism but became hyperthyroid thereafter.
Results
Comparing 68 females and 17 males, we found 71.67% ± 1.04% of people failed to achieve remission (females 70.58%, males 76.47%). Binomial distribution analysis showed statistical significance vs a null hypothesis of 50% remission ($P < 10.0001$). No significant differences in remission rates were found between antibody status ($P > 0.05$ for both TPO and TSH-R Ab positivity) or between gender ($P > 0.05$). 61.29% of patients who achieved euthyroidism and stopped anti-thyroid medication at 18 months subsequently relapsed.
Discussion
Failure to achieve remission with anti-thyroid medication was >50%, implying that we ought to counsel our patients as such. Contrary to the established literature, our small study did not demonstrate that gender or antibody status at diagnosis predicts the outcome following a course of anti-thyroid medication. Our data validates NICE recommendations that first-line treatment for AT should be radioiodine therapy.

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Adrenal and Cardiovascular

OP2.1

A phase 1 clinical trial evaluating the safety and efficacy of up to two administrations of the adrenal PET tracer [^{18}F]CETO in healthy volunteers and patients with primary aldosteronism

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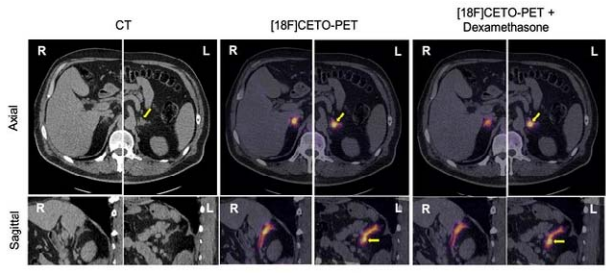
Background
Primary aldosteronism (PA) is an important, potentially curable, cause of hypertension. Distinguishing unilateral and bilateral causes is a critical step in determining who should be considered for adrenalectomy. Adrenal vein sampling (AVS) remains the gold standard for lateralisation. However, AVS is technically challenging with limited availability. To address this, we have introduced molecular imaging using PET/CT with the radiotracer [^{11}C] Metomidate (MTO-PET) as an alternative for lateralisation/localisation of aldosterone-producing adenomas and nodules. However, its utility is limited by the short tracer half-life, restricting its availability to centres with an on-site cyclotron. Here, we report initial findings with a related radiotracer with a longer half-life, [^{18}F]CETO.
Methods
We conducted a phase 1, single-centre, open-label, micro-dosing study. The primary objective was to evaluate the safety of up to two administrations of [^{18}F] CETO in six patients with PA (three unilateral, three bilateral) and five healthy volunteers. Safety assessments included a 250mcg Synacthen test at screening and morning after initial [^{18}F]CETO administration. The secondary objectives were to assess normal adrenal uptake, and to evaluate findings in unilateral versus bilateral PA in patients undergoing two scans – with and without dexamethasone pre-treatment.



Results
No serious adverse events/reactions occurred; a single adverse event (minor flushing) was observed following Synacthen injection in one patient unrelated to tracer administration. All subjects had preserved adrenal function. [^{18}F]CETO-PET demonstrated selective adrenal uptake in healthy volunteers and patients with PA. Following dexamethasone, [^{18}F]CETO was able to distinguish unilateral and bilateral disease.
Conclusion
In this first-in-human study, [^{18}F]CETO was shown to be safe and exhibited selective adrenal uptake. Preliminary findings in a small number of patients with PA suggest it can distinguish unilateral and bilateral causes of PA. If these findings are confirmed in larger studies, [^{18}F]CETO may provide a more widely available alternative to AVS.

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OP2.2

Single-centre analysis of 900 short synacthen tests: do pre-test clinical or biochemical variables predict failure?

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Short synacthen test (SST) is the most widely used dynamic test of hypothalamic-pituitary-adrenal (HPA) axis function. It's simple to conduct but requires nursing time and is relatively costly given 15-fold price increase in synacthen since 2015. We audited our SST use with the aim of reviewing clinical indications for testing and identifying useful predictors of test outcome. Baseline referral, clinical and biochemical data were retrospectively collected for individuals undergoing SST between June 2018 and December 2020. Binomial logistic regression and ROC curves analysis were performed using SPSS27. Nine hundred SSTs were performed in 767 patients (female 61%, mean age 51 ± 19 years) and comprised patients with known pituitary disease (60.56%), GP-referrals (25.67%) with possible symptoms of adrenal insufficiency (AI) and referrals queried tertiary AI (9.44%). From 900 SSTs, 658 (73.11%) resulted in a pass (30minute cortisol ≥430nmol/l) with 90.47% of GP referrals and 45.88% referrals for possible tertiary AI passing the SST. No specific symptom, clinical or biochemical pre-SST parameter could predict test outcome. However, a pre-test 9am cortisol ≥273 nmol/l in the GP referral cohort predicted a definite 'pass' with 100% specificity (ROC AUC 0.804, $P < 0.001$). Delta cortisol level (SST baseline cortisol-30mins cortisol) was a better predictor (ROC AUC 0.873, $P < 0.001$) of SST outcome in the suspected tertiary AI group when compared to pre-test 9am cortisol. In keeping with the non-specific clinical phenotype of AI, common symptoms, clinical and biochemical variables are unhelpful predictors of SST outcome. A pre-test 9am cortisol is a useful predictor and we propose to lower our 9am cortisol threshold for SSTs where pre-test probability is low. Tertiary AI is common and the pre-test 9am cortisol is less predictive in this group than delta cortisol, which could help identify which patients are more likely to later recover HPA axis function.

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OP2.3

PLK1 inhibitors as a new targeted treatment for adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is an aggressive malignancy with limited treatment options. We identified polo-like kinase 1 (*PLK1*) as one of the most overexpressed genes and potential drug target in ACC. PLK1 inhibitors (PLK1i) are under evaluation in clinical trials for other malignancies, being more effective in *TP53*-mutated tumours. Here we test PLK1i efficacy in four ACC cell lines with different genetic background. Efficacy of three PLK1i (i.e. Volasertib, Vol, multi-targeting Rigosertib, RGS, and PBD-PLK1-specific Poloxin) was evaluated

in NCI-H295R (*TP53* deletion) and MUC1 (frameshift *TP53* mutation) cell lines. RGS and Poloxin were also tested in CU-ACC1 (*TP53* wild-type) and CU-ACC2 (missense *TP53* mutation) cells. Increasing concentrations were used at different time-points (24h-48h-72h) and compared with vehicle control. Cell proliferation was analysed using DNA fluorescence and cell apoptosis by Caspase Glo 3/7 assay. NCI-H295R cells showed a significant time- and dose-dependent reduction of cell proliferation after 72h with all PLK1i with maximum effect at 100nM Vol and RGS and 10μM Poloxin ($P < 0.05$). In MUC1 cells a less pronounced effect on proliferation was observed with best effect at 72h 1000 nM RGS and 48h/72h 30uM Poloxin ($P < 0.001$). Regarding cell apoptosis, NCI-H295R cells showed significant increase at 100nM of both Vol and RGS ($P < 0.01$), but not with Poloxin. No effect was observed in MUC1 cells. In CU-ACC2 cells, both RGS and Poloxin had limited effect on cell proliferation ($P < 0.05$ at 1000nM and $P < 0.0001$ 30μM, respectively) and apoptosis ($P < 0.05$ only at 3000nM RGS). Finally, in *TP53* WT CU-ACC1 cells, a reduced proliferation was observed only with 100 μM Poloxin ($P < 0.001$). In conclusion, ACC cells with *TP53* variants demonstrated greater response to PLK1i than *TP53* WT CU-ACC1, with the most impressive efficacy seen in NCI-H295R. Thus, PLK1i might represent a promising targeted treatment of a subset of ACC patients with a specific tumour molecular pattern.

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OP2.4

Modelling changes in the control, secretion and metabolism of cortisol during and after heart surgery

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Control mechanisms of adrenocorticotrophic hormone (ACTH) and cortisol (CORT) secretion and metabolism during acute systemic inflammation (e.g. major surgery) have never been clearly elucidated. We sampled blood every 10 minutes for 12 h during and after coronary artery bypass grafting (CABG) in 10 patients to create profiles of ACTH, CORT and inflammatory mediators and compared these to healthy controls. Patients' ACTH and CORT responses were classified into one of three groups:

- **Single-pulse**: single peak in 12 h, strong peak dissociation (m_{lag} = 77min) and unstable peak synchrony,
- **Two-pulse**: prolonged periodicity (T_u = 5-6 h), peak association (m_{la} = 13 min), stable peak synchrony, or
- **Multiple-pulses** (normal periodicity (T_u = 2 h), peak dissociation (m_{lag} = 106 min) and partial peak synchrony.

We used an ACTH-dependent, two-compartment mathematical model of CORT activity to investigate the physiological changes underlying these patterns. The model has six parameters representing the fast and slow adrenal maximum secretory capacity, fast and slow CORT turnover rates, the adrenal sensitivity to ACTH stimulation, and a Hill coefficient indicating the steepness of the non-linear adrenal response to ACTH. By fitting the model parameters to control and patient groups, we identified the physiological processes regulating CORT activity that are likely disrupted by surgery. Patients in the **single-pulse** group had a greater slow adrenal secretory capacity and very prolonged slow turnover rate for CORT compared to controls. Those in the **two-pulse** group had similar adrenal secretory capacity and a slightly increased slow turnover rate compared to controls. Those in the **multiple-pulse** group had a slightly increased slow adrenal secretory capacity and slightly increased slow turnover rate. This study shows that patients' ACTH and CORT responses to CABG fit one of three phenotypes which exist due to differential changes in the underlying secretion, distribution and metabolism of cortisol. A suitably powered study is now required to establish whether these affect clinical outcome.

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Reproductive and Neuroendocrinology

OP3.1

Discordant growth hormone and insulin like growth factor-1 values are associated with an increased mortality over concordant normal values in patients treated for acromegaly

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Background
Growth hormone (GH) and Insulin like growth factor 1 (IGF-1) discordance in patients with acromegaly is a well-recognised phenomenon. It is unclear whether this is associated with increased mortality and morbidity compared to patients with concordant normal results.
Methodology
A retrospective study was conducted on the United Kingdom Acromegaly Registry (UKAR). A comparison of mortality and morbidity was performed among four groups categorised according to the latest simultaneously available GH and IGF-1 pair; 1) normal GH and IGF-1 ($normal_{conc}$), 2) high GH and IGF-1 ($high_{conc}$), 3) discordance with high GH and normal IGF-1 (GH_{disc}) 4) discordance with normal GH and high IGF-1 ($IGF\text{-}1_{disc}$). High IGF-1 level was considered as >1.3 times upper limit of normal for age, gender matched centre specific reference range, while high GH level was considered as >1μg/dl.
Results
Out of all the patients (n = 2138, 41331 person-years of follow up) there were 1210,326,429,173 in $normal_{conc}$, $high_{conc}$, GH_{disc} and $IGF\text{-}1_{disc}$ groups, respectively. Overall mean discordance rate was 28.2% (range = 5-47.4%) across 29 centres in the UK. Majority of discordance noted in GH_{disc} (71%). Both discordant groups showed lower median survival (GH_{disc} [35.5yrs,95%CI = 32.4-38.7] and $IGF\text{-}1_{disc}$ [37.9yrs,29.6-46.1]) compared to $normal_{conc}$ (41.8yrs,37.7-45.8).Age and gender adjusted Hazard ratio (aHR) for mortality rate was higher in $high_{conc}$ (aHR = 1.57;1.24-2.0; $P < 0.001$) and GH_{disc} (aHR = 1.25;1.01-1.62;p = 0.045) than $normal_{conc}$, but was not significantly higher in $IGF1_{disc}$ group (aHR = 1.41;0.98-2.02;p = 0.062). No difference noted between the causes of death among groups. Morbidity analysis revealed, diabetes mellitus was higher in the $IGF\text{-}1_{disc}$ group than $normal_{conc}$ group ($p < 0.05$).
Conclusions
This is the first data in a large number of acromegaly patients to show that discordance in GH and IGF-1, especially with high GH and normal IGF-1 is associated with a higher mortality than patients with normal levels. These findings have a significant implication in the management as they may require treatment escalation.

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OP3.2

An ex-vivo human placental model demonstrates that temporal fluctuations in maternal glucose in gestational diabetes alter placental transcriptome networks associated vascular development and angiogenesis

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Aims
Women with gestational diabetes (GDM) who deliver large-for-gestational age (LGA) infants have subtle (1-1.5mM) differences in temporal maternal glucose control detectable by continuous glucose monitoring (CGM), compared to women who deliver appropriate-for-gestational-age (AGA) infants. It is unclear how these subtle changes cause LGA, but LGA has been linked to placental dysfunction. We aimed to develop an ex-vivo human placental model to mimic subtle differences in temporal maternal glucose in GDM and assess the impact on the placental transcriptome and function.
Methods
Human term villous explants (n = 7) from uncomplicated pregnancies were cultured for 48-h with medium changes every 6-18 h in variable (5/5.5mM) or constant (7 mM) glucose. Glucose concentrations assessed in medium at each timepoint were compared to CGM profiles from women with GDM/AGA/LGA. mRNA sequencing was performed on explants (n = 5). Functional enrichment was performed on differentially expressed genes (DEGs; $P < 0.05$, $\log_2$-foldchange -0.5< or >0.5) by over representation analysis (ORA) and ingenuity pathway analysis (IPA).

Results
Input levels of 5-5.5 mm glucose represented CGM profiles from GDM women with stable/appropriate glucose control (normoglycaemia) delivering AGA infants, whereas 7 mM glucose reflected CGM profiles from GDM women with suboptimal glucose control (hyperglycaemia) delivering LGA infants.Hyperglycaemia altered the placental transcriptome (456 downregulated and 128 upregulated genes). ORA revealed that DEGs were associated with gene ontology terms and pathways including response to chemokines (P = 2.36E-06), regulation of vascular development (P = 4.97E-06), angiogenesis (P = 1.23E-04) and regulation of insulin-like growth factor (IGF) transport/uptake (P = 4.40E-05). IPA revealed several associated canonical pathways including atherosclerosis (P = 8.99E-06), type II diabetes signalling (P = 1.21E-02) and pathways associated with IL-17a signalling.
Conclusions
The altered placental transcriptome observed using this physiologically relevant model suggests that subtle changes in maternal glucose may lead to LGA by influencing key developmental and inflammatory pathways in the placenta.

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OP3.3

'Suppression imaging' – a novel PET technique for increasing confidence in the localisation of secretory pituitary microadenomas

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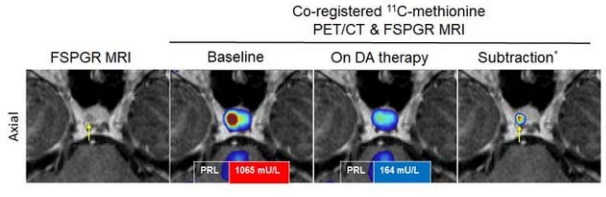
Background
In a sub-group of patients with newly diagnosed pituitary adenomas, conventional MRI will fail to confidently localise the tumour. The role of molecular imaging for these patients is increasingly being recognised, both in terms of confirming diagnosis and in guiding targeted therapy; ^{11}C-Methionine PET co-registered with volumetric MRI (Met-PET/MR^{CR}) can enhance decision making in this group of patients. However, in some cases distinguishing tumoral tracer uptake from that of the normal gland can still be challenging (especially for small microadenomas). Additionally, co-existent incidental non-functioning adenomas can demonstrate a confounding focus of tracer avidity. We hypothesised that performing PET on two occasions, with targeted suppression of tumour activity in the interim, can permit greater confidence in determining tumour localisation.
Methods
In 14 patients with secretory microadenomas (including prolactinomas, somatotropinomas, thyrotropinomas & corticotropinomas) we performed Met-PET/MR^{CR} pre-and-post appropriate endocrine suppression. We developed a novel algorithm which permitted calculation of the normalised difference in signal between pre-and-post scan datasets – this allowed the creation of a '*subtraction image*'.
Results
In 13 patients we observed a significant reduction in focal tracer uptake at the site of the suspected adenoma following endocrine suppression. In each of these cases the '*subtraction image*' clearly demonstrated a focus of suppressible tracer uptake (Figure 1). Six patients elected to continue with medical management. In six patients, the location of the tumour was confirmed at subsequent transsphenoidal surgery with histopathological correlation. One patient is awaiting surgery.



Conclusion
For the first time we report a novel approach to molecular imaging in which imaging pre-and-post suppression of tumour activity allowed precise localisation of the site of a functioning microadenoma.

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OP3.4

Stem cell heterogeneity and regulation in the postnatal pituitary gland

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The anterior pituitary gland is a critical endocrine organ responsible for many important physiological processes including puberty, fertility, metabolism and the stress response. It is derived from, and maintained by, a population of SOX2+ progenitor/stem cells which become more quiescent with age until their direct contribution to tissue turnover becomes negligible. Previous research has demonstrated that the postnatal SOX2+ population exhibits heterogeneity in terms of marker expression, but how this translates to their proliferative capacity during homeostasis remains unknown, as do the molecular mechanisms that regulate their commitment and differentiation. By performing single cell RNA sequencing of EGFP positive cells from the mouse pituitary of *Sox2*$^{Egfp/+}$ mice, we have identified three distinct subsets of SOX2+ stem cells, which exhibit dynamic heterogeneity from the early postnatal period into adulthood. Here we show that these subtypes have unique transcriptional signatures and differences in their proliferative states and differentiation potential. In addition, we identify the presence of distinct early committing progenitors across the *Pou1f1*, *Tbx19* and *Nr5a1* expressing populations, which still retain low levels of *Sox2* expression. These newly distinguished early progenitor subsets are crucial for the identification of the extrinsic and intrinsic mechanisms involved in cell lineage specification, necessary to fully comprehend cellular events in normal pituitary homeostasis and of relevance to disease states and regenerative approaches.

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Metabolism, Obesity and Diabetes

OP4.1

Investigating the role of the gut metabolome in appetite and obesity

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Overweight and obesity is an escalating global health problem, affecting 40% of the population and being the 5th largest cause of death worldwide. Treatment options are limited, with pharmaceutical approaches being inadequate and the success of bariatric surgery being limited by its invasive nature. The regulation of appetite by small bioactive compounds in the gastrointestinal tract is an important target in antiobesity research. Metabolites from diet and both host and microbial metabolism interact with G protein-coupled receptors in the gut epithelium, triggering the release of hormones that act on the appetite regulatory centres in the brain to promote satiety. Understanding how gut metabolites influence appetite could lead to novel antiobesity strategies. Here, 10 participants (Age 47.40 $\pm$ 3.70 years, body mass index 25.69 $\pm$ 0.84 kg/m^2) attended the clinical research facility for a 4-day inpatient stay. Nasoenteric tubes were inserted to allow sampling of gut content from the distal ileum and the proximal colon. Following ingestion of a high-protein and high-fibre test meal (695 kcal, 55% protein, 27g fibre), gut samples were collected every 30 minutes for 6 h. Visual analogue scales were used to measure subjective appetite, and blood samples drawn for the measurement of appetite hormones. Comprehensive 1H-NMR metabolomic analysis provided novel information about the metabolic environment of different regions of the intestine that accompanies the enhanced satiety from this type of meal. Analysis showed distinct metabolite processing over a timeline from baseline until 360 minutes after ingestion, including perturbations to various amino acids, such as isoleucine, leucine and aspartate, carbohydrates such as glucose, sucrose and lactose, and bile acids such as cholic acid. The correlation of these NMR datasets with appetite and gut hormone data revealed important information about the role of nutrient sensing in appetite regulation, which could have implications in the treatment of obesity.

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OP4.2

3 mg Liraglutide ameliorates inflammation and improves hypothalamic regulation of energy homeostasis by modulation of Sphingosine-1-Phosphate signalling in super-responders

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Background
Growing evidence suggests that hypothalamic lipid sensing plays a key role in controlling food intake, fat deposition and energy balance and that its dysregulation could lead to obesity and type 2 diabetes (T2D). Recent investigations reported that sphingosine-1-phosphate (S1P) is involved in the hypothalamic control of energy homeostasis. Intra-cerebroventricular administration of S1P decreased food intake and increased energy expenditure in rodents.
Methods
We conducted a 24-week, open-label real-world study involving 62 participants with a BMI $>30 kg/m^2$, without T2D. Patients received once-daily subcutaneous liraglutide 3.0 mg, alongside a reduced calorie diet based on individual estimated basic metabolic rate. The primary outcome was change in body-weight. Secondary outcomes included changes in anthropometrics, proinflammatory cytokines (IL1b, IL6, IL-8 and TNFa) and plasma metabolome using Ultra Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) providing untargeted study of water-soluble metabolites (HILIC-LCMS) and lipid metabolites (C18 reversed-phase LCMS).
Results
Participants were aged 38.6 ± 9.8 years (mean $\pm$ SD) and 87.1% of participants were women. They weighed 117.5 ± 24.5kg with BMI of $41.33 \pm 6.9 kg/m^2$. At week 24, participants had lost 12.85 ± 8.4 kg or 9.9 ± 5.8 % body weight ($P < 0.001$). 55.1% of participants lost 5-10% and 18.4% lost >10% body weight ($P < 0.001$). According to weight loss (WL) response, participants were divided into non-responders (<5% WL,$n = 21$), good responders (5-10% WL,$n = 19$) and super-responders (>10% WL,$n = 9$). At week 24, oxidised lysoglycerophospholipid metabolic pathway was heavily enriched. Metabolites phosphatidylcholine and triglycerides were significantly ($P < 0.001$) downregulated, and S1P was upregulated ($P < 0.005$) comparing super-responders to non-responders. IL-6 had significant positive correlation ($r = 0.732$, $P < 0.001$) with WL. In all super-responders, IL-6 concentration was significantly decreased and S1P expression was significantly higher.
Conclusions
In this study, administration of liraglutide was associated with upregulation of S1P and reduction of IL-6 in super-responders. S1P signalling may be key in determining response to treatment with liraglutide.

DOI: 10.1530/endoabs.77.OP4.2

OP4.3

The Chemerin-CMKLR1 Axis is Functionally Important for Central Regulation of Energy Homeostasis

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Chemerin is a newly discovered chemoattractant adipokine and is a natural ligand for the G protein coupled receptor CMKLR1. Its role in the regulation of energy metabolism and inflammation makes it a promising candidate for urgently needed pharmacological treatment strategies for obesity. To demonstrate a central role of chemerin, we manipulated chemerin signalling in the arcuate nucleus, a specific hypothalamic region associated with appetite regulation. We designed a short-hairpin-RNA (shRNA) lentivirus construct targeting expression of *Cmklr1* and tested for efficiency to reduce expression of this receptor mRNA *in vitro* in characterised mouse NPY-AgRP hypothalamic cell lines. This shRNA construct or a control construct was injected bilaterally into the arcuate nucleus of adult Sprague Dawley rats on high-fat diet (45 % fat; n = 8 / group). After surgery, these rats were maintained on high fat diet for 2 weeks and then switched to chow diet for a further 2 weeks. The novel object recognition test was performed at 2 and 4 weeks following surgery. The rats were humanely killed at 28 days following surgery and tissues were collected (hypothalamus, white adipose tissue, brown adipose tissue, blood). We found a significant inhibition of weight gain of arcuate nucleus-*Cmklr1* knockdown rats 28 days after injection, and this difference became apparent after the diet switch. Interestingly, this was not accompanied by a difference in blood glucose levels. Our behavioural analyses suggest that knockdown of *Cmklr1* had an impact on object recognition. We investigated mRNA expression of neuropeptides and chemerin receptors in the hypothalamus, and mRNA expression of chemerin, its receptors, and markers of adipogenesis, lipogenesis and brown adipocyte activation in adipose tissues. Together our data demonstrate that *Cmklr1* is functionally important for the central effects of chemerin on body weight regulation and implicate the chemerin-CMKLR1 axis in regulation of whole body metabolism and cognition.

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OP4.4

Audit of Clinical Outcomes with Dexamethasone in Patients Hospitalised with COVID-19

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Background
Dexamethasone significantly improved outcomes in patients requiring supplementary oxygen and in ventilated patients with COVID-19 in the RECOVERY trial. Consequently, dexamethasone is now routinely used in these patients. However, dysglycaemia is commonly associated with steroid use and is an established risk factor for poorer outcomes in COVID-19. In this study, we aimed to elucidate the effect of dexamethasone use in patients hospitalised with COVID-19 in a real-world setting.
Methods:
Data from Imperial College Healthcare NHS Trust hospitals were collected from 1372 consecutive patients hospitalised with COVID-19 between 01/11/2020 and 31/01/2021 (Wave 2) and 889 patients admitted between 09/03/2020 to 22/04/2020 (wave 1). The primary outcome was admission to intensive care (ICU) or death within 30 days of COVID-19 diagnosis. Secondary endpoints were post-dexamethasone glycaemic complications. Multivariate logistic regression analyses were performed to determine the factors associated with primary outcome and to determine impact of dexamethasone on the primary outcome.
Results
Mortality alone, without accounting for ICU admission, was significantly lower in wave 2 (wave 27.6%, wave 2 18.8%, 31.8% reduced risk of death, $P < 0.01$). Male gender, hypertension, increased frailty and lower eGFR were independently associated with the primary outcome. Dexamethasone significantly reduced the risk of death/ICU admission by 56%. In patients with diabetes, dexamethasone use is associated with increased risk of glycaemic complications (OR = 22.5, 95% CI 13.98-36.67, $P < 0.0001$). However, the risk of death/ICU admission was not increased in those with post-dexamethasone complications.
Conclusions:
Dexamethasone reduced the risk of death/ICU admission. There was no difference in ICU admission rates between waves 1 and 2, possibly driven by the dominance of new SARS-Cov2 variants. Patients with diabetes are more likely to develop steroid-induced dysglycaemia, but this did not increase mortality.

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Bone and Calcium

OP5.1

Parathyroid hormone (PTH) of 1.6 pmol/l or more at 6 months is associated with delayed recovery of parathyroid function in post-surgical hypoparathyroidism (PoSH)

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Introduction
Post-surgical hypoparathyroidism (PoSH) is common after thyroidectomy. Most cases recover within 6 months, but several require long-term supplementation

with calcium and activated vitamin D. When PoSH persists beyond 6 months, it is considered to be 'long-term' or 'permanent'. However, few studies have demonstrated recovery beyond this time period.
Aim
Aim of this study is to determine the frequency of late recovery in this group and factors that can predict this.
Methods
Adult patients undergoing total or completion thyroidectomy between 2009-2018 were included in this cohort prospective observational study. Records of patients who met certain inclusion criteria (started on calcium or activated vitamin D, or day 1 adjusted calcium <2.1 mmol/l, or day 1 PTH <1.6 pmol/l) were reviewed to identify those with PoSH at 6 months. Demographic, biochemical, surgical, pathological, and clinical follow-up data is described and analysed.
Results
Out of 911 patients undergoing thyroidectomy, 270 met inclusion criteria. Of these, 192 were started on supplements and 138 (71.9%) recovered within six months. From the remaining 54 patients (females: males = 46:8), 21 had ongoing PoSH (minimum follow-up 3 years, median follow-up 4.5 years). However, a significant number of patients ($n = 19$ [47.5%]) were weaned off all supplements and achieved remission (median recovery at 1.3 years, most delayed recovery at 4.8 years). All of those who recovered had a PTH of ≥ 1.6 pmol/l at/beyond 6 months. There was no difference in age, gender, diagnosis, type/extent of surgery, or calcium levels between the two groups.
Conclusions
Recovery from PoSH is common beyond 6 months, raising the question of whether 6-month threshold to define long-term PoSH is appropriate? In patients with PTH level of ≥ 1.6 pmol/l at/after 6 months, the chances of recovery are high. Therefore, attempts should be made to wean off supplements in this group.

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OP5.2

Society for Endocrinology / Parathyroid UK National Hypoparathyroidism Management Audit

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Individuals with chronic hypoparathyroidism sometimes receive suboptimal care with high frequency of unplanned hospitalisation and iatrogenic harm. In 2015 the European Society for Endocrinology published evidence base consensus guidelines on the management of chronic hypoparathyroidism. Using these consensus recommendations as audit standards we worked with the Society for Endocrinology and Parathyroid UK to conduct a national audit of management of chronic hypoparathyroidism in UK endocrine departments during the second half of 2020. Endocrine leads in 117 endocrine departments were written to inviting participation in the survey by completing a data collection tool on up to 5 sequential cases of chronic hypoparathyroidism seen in their department's outpatient clinics in the previous 6 months. Responses were received from 22 departments giving a response rate of 18.8% with each department contributing data on between 1 and 5 cases. A total of 80 valid returns were received. The main findings were that 62.5% of returns were compliant with the treatment standard that all cases should be treated with activated vitamin D and calcium supplementation and 60% with the standard that all should be supplemented with vitamin D. For monitoring standards, compliance rates were 63.8% for 3-6 monthly monitoring of renal function; 80% for 3-6 monthly monitoring for symptoms of hypocalcaemia; 23.8% for annual assessment of 24 hr urinary calcium excretion and 20% for renal imaging. We conclude that improvements in the UK national standard of management of chronic hypoparathyroidism could be made and that this will benefit both quality of life, morbidity and potentially mortality in this group of patients. Additionally, it may also benefit NHS services by reducing the number of unplanned hospital admissions of individuals with chronic hypoparathyroidism. We are indebted to those colleagues who generously gave their time to complete the data returns during a very difficult year in the NHS.

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OP5.3

Vitamin D deficiency is highly prevalent among patients who died from COVID-19 in the North-East of England.

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Background
Vitamin D deficiency (VDD) has been implicated in the pathophysiology of respiratory infections, including Coronavirus Disease 2019 (COVID-19). We assessed vitamin D levels of patients who died from COVID-19 during or following admission to Newcastle-upon-Tyne Hospitals.
Methods
We performed a retrospective survey of electronic patient records for 2,355 patients admitted to our institution between 04/02/2020 and 19/01/2021, who had a positive SARS-CoV-2 PCR on nasopharyngeal swab. 308 patients died and had COVID-19 included on their death certificate (mortality rate = 13%). 136 patients (44%) also had a serum 25-hydroxyvitamin D (25OHD) measurement within 3 months prior to admission and were included in the analysis.
Results
The median 25OHD was 34nmol/l (interquartile range 19-69.5nmol/l). 60% ($n = 81$) of patients who died from COVID-19 had 25OHD levels <50nmol/l (local laboratory definition of VDD, Table). 68% ($n = 93$) of patients who died would have been deemed as having "sufficient" vitamin D levels (≥ 25nmol/l) according to UK Scientific Advisory Committee on Nutrition (SACN) recommendations. Conversely, only 29 (21%) patients who died had 25OHD levels ≥ 75nmol/l, which is the definition of vitamin D adequacy used in Endocrine Society guidance. The prevalence of VDD was higher in male deaths compared to female deaths: 67% of males and 46% of females who died had 25OHD levels $<$ 50nmol/l ($P = 0.0185$ using Fisher's exact test).
Discussion
VDD was highly prevalent in patients who died from COVID-19 in Newcastle-upon-Tyne. Although our study is limited by the lack of a control group, we recommend that vitamin D supplementation aiming for levels of ≥ 75nmol/l is a safe and cost-effective intervention to mitigate COVID-19's morbidity and mortality.

Table 1 Deaths from COVID-19 by 25OHD quartile.

Admission 25OHD, nmol/l	Number of deaths (%)	Age at death, median (IQR)
<25	43 (32%)	83 (72–89)
25–49	38 (28%)	77.5 (73.75–84.25)
50–74	26 (19%)	80 (76.75–84.5)
≥ 75	29 (21%)	86 (80–89.5)

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OP5.4

Normocalcaemic hyperparathyroidism: Impact of assay and reference range differences on the diagnosis

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Approximately 70% of clinical laboratories in the United Kingdom use assays from Abbott Laboratories and Roche Diagnostics. We carried out a cross-sectional study between two neighbouring hospital laboratories in our regional pathology network, comparing the potential impact of Abbott and Roche PTH and calcium assays in the diagnosis of normocalcaemic hyperparathyroidism. Over 4 months, forty-one vitamin D replete (>50 nmol/l) normocalcaemic hyperparathyroidism patients (37 females, median age 69 years, IQR 63-77) with eGFR $>$ 60 ml/min/1.73m^2 were identified using the Abbott assays. The serum samples were aliquoted and stored at -80°C soon following the conclusion of requested tests, maximally within 8 h of receipt. Aliquots were thawed and analysed immediately by Abbott and Roche assays within one month of storage. Abbott PTH results were 57.6% (IQR 49.4-74.7) higher compared to Roche PTH results ($P < 0.001$). Roche adjusted calcium results were 3.8% (IQR 2.4-5.3) higher

compared to Abbott adjusted calcium results ($P < 0.001$). Of the 41 patients with normocalcaemic hyperparathyroidism by the Abbott assays, 22 (54%) had a normal PTH and adjusted calcium and 9 (22%) had results indicative of primary hyperparathyroidism when measured by Roche assays. Only 10 (24%) patients were concordant for normocalcaemic hyperparathyroidism by both assays. The manufacturer-provided assay-specific reference ranges used by the laboratories for Abbott and Roche PTH assays are similar at 1.6-7.2 pmol/l and 1.9-6.9 pmol/l respectively; however, Abbott PTH assays have a considerable positive bias compared to Roche PTH assays. The laboratories use the pathology harmony adjusted calcium reference range of 2.2-2.6 mmol/l; however, Abbott calcium assay has a 3.8% (median 0.09 mmol/l) negative bias compared to Roche calcium assay. In conclusion, the diagnosis of normocalcaemic hyperparathyroidism is strikingly different depending upon the assays used, highlighting a need for harmonisation and consideration of assay related factors in clinical practice.

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Endocrine Cancer and Late Effects

OP6.1

Incidental findings are common, but rarely clinically significant, in patients with Neuroendocrine Tumours undergoing Gallium68 Dotatate PET CT; results from a one year retrospective review

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Gallium[68]-Dotatate PET-CT is a somatostatin-receptor (SSTR) based imaging modality employed in the diagnosis and follow-up of Neuroendocrine Tumours (NET). We set out to investigate the incidence of incidental findings, some of which are related to SSTR expression, in our NET patient cohort in Oxford University Hospital. Sixty-eight patients underwent Gallium[68]-Dotatate PET-CT between June 2020 and June 2021. 40 patients (59%) were female, and median age was 64 (24-86) years. The most common primary disease site was small intestine (27, 40%); 46 patients (68%) had metastases and 36 patients (53%) were on somatostatin analogue treatment at the time of data collection. Twenty patients (29%) had at least one incidental finding on Gallium[68]-Dotatate PET-CT. The most common incidental finding was avidity inside the calvarium suggestive of meningioma, noted in 7 patients (10%). Of these, 5 had cranial MRI or CT and a corresponding meningioma was found in just one case, for which no clinical intervention or follow-up was required. One patient had uptake in the iliac bone; biopsy did not reveal any malignancy, and review of subsequent CT suggested it may represent an area of fibrous dysplasia. Gallium[68] uptake was present in the thyroid gland of four patients (6%), one of whom had a 15mm TR5 nodule and has opted for ultrasound surveillance. One patient had uptake in the pituitary, confirmed to be a non-functioning microadenoma. Another patient had uptake in the left ventricular wall; subsequent cardiac MRI was normal. Incidental findings of vertebral haemangiomata and wedge fracture were present in 3 and 1 patients, respectively. Incidental findings, unrelated to NET, are reported in almost one in three Gallium[68]-Dotatate PET-CT studies. Although rarely clinically significant, patients should be counselled about the possibility of incidental findings, and the potential need for further investigations including brain imaging.

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OP6.2

The evaluation of a musculoskeletal health package intervention to prevent bone toxicity in women with gynaecological malignancies undergoing pelvic radiotherapy. The RadBone randomised controlled feasibility study

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Background
Bone toxicity and more specifically Radiotherapy Related Insufficiency Fractures (RRIFs) are common late effects of pelvic radiotherapy, associated with increased morbidity and reduced quality of life, while their cost to the health system is currently unknown. The mechanisms underlying RRIFs are not well understood. Effective preventive techniques and management pathways need to be developed and validated with robust clinical and health economic analyses. The RadBone prospective randomized controlled trial (Clinical trial registration: NCT04555317) aims to determine the feasibility and acceptability of a musculoskeletal health package (MHP) intervention in women with gynaecological malignancies receiving pelvic radiotherapy and to preliminary explore the clinical effectiveness of the intervention.
Methods and Analysis
Eighty patients will be randomised to the MHP or standard of care/observational arm. The MHP consists of a three-month prehabilitation personalised exercise package (Prehab4cancer), DXA assessment of bone mineral density, fracture risk estimation using FRAX score and treatment according to the National Osteoporosis Guideline Group (NOGG) recommendations (patients will be divided into 3 risk groups: Low Risk will receive written advice about bone health; Intermediate Risk will receive the written information and Calcium/Vitamin D replacement; High risk will receive bisphosphonate treatment in addition to the above). Participants will be followed using Patient Reported Outcome Measures (PROMs), pelvic MRI scans and fasting blood tests at 6, 12 and 18 months. Baseline (pre-radiotherapy) samples will be taken for MS-SWATH proteomics and weekly during radiotherapy for longitudinal bone turnover markers. The primary outcome is feasibility; including eligibility, screening and recruitment rate, intervention fidelity and attrition rates; acceptability; and health economic variables. Clinical effectiveness and bone turnover markers will be assessed as secondary outcomes. The results of this trial will inform power calculations and the feasibility of an economic evaluation alongside a future multi-centre UK randomised controlled trial.

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OP6.3

An unusual presentation of hypoglycaemia: An investigative challenge

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Prohormone convertase 1/3 (PC1/3), encoded by protein convertase subtilisin kexin type 1 (PCSK1), converts inactive prohormones such as pro-opiomelanocortin, proinsulin, proglucagon into biologically active peptides. Inherited genomic mutations of PCSK1 present with malabsorptive diarrhoea, hyperinsulinemic hypoglycaemia, central adrenal and thyroid defects and severe obesity. Somatic mutations of insulinomas are associated with genetic defects interfering with insulin secretion from pancreatic beta-cells. However, somatic mutations in proinsulinomas have not been described. We report a case of a 70-year old woman with a 20-years history of frequent 'blackout' episodes. These episodes of syncope were manifestations of severe hypoglycaemia, caused by proinsulinomas in the head and tail of the pancreas. The diagnosis was initially missed as insulin levels were appropriately low in the presence of hypoglycaemia. A 72-hour fast was conducted and the blood glucose dropped to 1.9 mmol/l 24 h into the fast. Once again, plasma insulin and C-peptide levels were suppressed, but plasma proinsulin levels were measured and raised at 37 pmol/l (<10 pmol/l). CT

imaging and endoscopic ultrasound revealed three distinct lesions in the pancreas which were found to be DOTATATE-avid. A laparoscopic spleen-preserving distal pancreatomy was performed without any postoperative complications. Immunohistochemistry was positive for insulin. More than 6 years later, the patient remains very well without any episodes of hypoglycaemia. This case highlights the investigative challenge of patients harbouring a proinsulinoma. Appropriately suppressed insulin levels in the context of hypoglycaemia do not always indicate absence of a neuroendocrine islet cell tumour and measurement of proinsulin levels is indicated to solidify the diagnosis. If proinsulin levels are elevated, low insulin and C-peptide levels might be explained by absent PC1/3 activity. Whilst our patient's molecular analysis results are currently still pending, variants in the PCSK1 gene encoding PC1/3 expression causing hyperproinsulinemia need to be considered as a possible pathomechamism.

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OP6.4

Virtual Blood Pressure Monitoring in the Pre-operative Management of Phaeochromocytoma Patients in a Tertiary Centre during the COVID-19 Pandemic

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The usual management at our centre for patients awaiting phaeochromocytoma surgery involves pre-operative titration of alpha blockade with frequent clinic visits for blood pressure (BP) and heart rate (HR) monitoring. The COVID-19 pandemic restricted our ability to consult with patients frequently. To reduce infection risk, we incorporated virtual BP monitoring using a Microsoft Excel template coupled with regular remote consultations. We present a clinical case highlighting our adaptation. A 69-year-old woman with hypertension was incidentally found to have a 3.1cm left adrenal mass following the localised resection of a left arm dermatofibrosarcoma. Investigations revealed plasma normetanephrines of 7367 pmol/l (0-1180). Her plasma metanephrines, 3-methoxytyramine and aldosterone-to-renin ratio were normal. She suppressed cortisol adequately following dexamethasone. Functional imaging confirmed a solitary phaeochromocytoma. Genetic testing did not reveal abnormalities. The patient recorded home lying and standing BP using our virtual template and shared it weekly via secure email. Dose titration and side-effect assessment were done using remote telephone consultations. The patient later underwent an uncomplicated left-sided robot-assisted laparoscopic adrenalectomy with no significant post-operative hypotension and was able to stop antihypertensive therapy. Following the successful management of our patient's case, we expanded the use of our template to four further patients with phaeochromocytomas: 2 have been treated successfully surgically (uncomplicated) and 2 are awaiting surgery. All patients provided positive feedback with specific comments including ease of use and improvements in engagement, confidence and autonomy in relation to their condition. We subsequently updated our management pathway to incorporate enhanced home BP/HR monitoring and recording with the aim of reducing the number of face-to-face visits. We demonstrate that using a virtual monitoring pathway is feasible and convenient in the pre-operative management of patients with phaeochromocytoma. Our pathway may be incorporated into the standard pre-operative management of patients thereby potentially increasing efficiency and reducing risk.

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Featured Clinical Case Posters

CC1

Cinacalcet in the Treatment of Malignancy-Related Hypercalcaemia: A Case Report

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Malignancy-related hypercalcaemia occurs in over 20% of cancer patients. Most cases are due to enhanced production of parathyroid hormone-related peptide (PTHrP) by tumours and carry a poor prognosis of survival of weeks to months. A 74 year old man with a history of prostate cancer treated with radical radiotherapy in 2013 and androgen blockade until 2015 underwent CT and PET/CT scans in 2017, which showed liver and spleen abnormalities, suggestive of metastases, but unlikely to be related to prostate cancer due to radiological appearance. The patient declined further investigation, prioritising his good quality of life. In 2020 he presented with lethargy and tests showed adjusted calcium 3.1 mmol/l (2.2-2.6) and low PTH 1.0 pmol/l (1.6-6.9). He had multiple hospital attendances with recurring symptoms and hypercalcaemia, despite treatment with IV fluids and pamidronate. Further imaging and liver biopsy confirmed pancreatic neuroendocrine tumour. The patient's performance status deteriorated from 0 to 3 over months, no further oncological treatment was deemed possible and palliative care team were involved in anticipation of further decline. No bony metastases were seen and myeloma screen was negative, so PTHrP-mediated hypercalcaemia was suspected, although testing for this is not routinely available and costly. Hypercalcaemia continued to recur despite monthly zolendronic acid, so a trial of cinacalcet was started, successfully stabilising calcium. However, once the dose was titrated up to 30 mg twice daily, calcium fell to 1.8 mmol/l and cinacalcet was stopped. Calcium has since slowly risen to 2.61 mmol/l over several months. Over a year after his first presentation with hypercalcaemia, the patient continues to have a reasonable quality of life. Although no studies have yet been performed to evaluate the use of cinacalcet in PTHrP-mediated hypercalcaemia of malignancy, a growing number of case reports suggest it may be effective in stabilising calcium, thereby controlling symptoms and potentially improving prognosis.

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CC2

Familial hypocalciuric hypercalcaemia (FHH) type 3: A rare cause of parathyroid (PTH) dependent hypercalcaemia with associated learning disabilities and behavioural problems

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Case
A 25-year-old male with a history of Asperger's syndrome, not on regular medication, with no family history of endocrinopathy; was referred with mild hypercalcaemia found during routine investigations for fatigue, weight loss, diarrhoea and vomiting. A normal PTH suggested PTH-dependent hypercalcaemia. There was no history of fractures or nephrolithiasis. DEXA scan showed normal bone mineral density (femur, spine and forearm). The gastrointestinal symptoms and fatigue were investigated with a full blood count, biochemical profile, coeliac screen, faecal calprotectin, short Synacthen test and CT thorax/abdomen/pelvis which were all normal. In a vitamin D replete state, the 24-hour urinary calcium: creatinine excretion ratio was 0.0043, pointing to a diagnosis of FHH and genetic sequencing analysis of FHH related mutations returned heterozygous for AP2S1 (Arg15His), confirming a diagnosis of FHH3.
Discussion
FHH is a rare (1 in 78000), autosomal dominant (AD) and PTH dependent cause of hypercalcaemia. It is classified into three types based on inactivating mutations of *CaSR*, *GNA11* and *APS2S1* resulting in FHH1, FHH2 and FHH3, respectively.[1] FHH3 is associated with variable learning disabilities and behavioural difficulties[2] and can be misdiagnosed as Asperger's syndrome or other neurodevelopmental disorders.
Conclusion
Consider FHH3 in young patients with cognitive dysfunction and hypercalcaemia.

Table 1 Summary of investigations

PTH	2.70 pmol/l
Serum adjusted calcium	2.67 mmol/l
Serum creatinine	76 umol/l
24-hour urine calcium	4.0 mmol
24-hour urine creatinine	16.7 mmol/l
Serum vitamin D	64.4 nmol/l

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CC3

Hypercalcemia caused by Advanced Chronic liver disease without Malignancy: A rare entity

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Background
Hypercalcemia in patients with advanced chronic liver disease (CLD) without hepatic neoplasia is a rarely reported and poorly understood entity. CLD is usually associated with hypocalcaemia because of hypoalbuminemia. Hypercalcemia on the other hand is extremely rare and needs meticulous ruling out of other causes.
Case Report
A 55-year-old male who was admitted with jaundice, weight loss and hypercalcaemia. He had a calcium that peaked at 3.34 with a suppressed PTH (<0.4). Labs revealed worsening liver enzymes. Total bilirubin peaked around 9 days, at 149umol/l, before starting to trend down. He had extensive evaluation of hypercalcemia. He had an urgent CTCAP to look for malignancy which found new diagnosis of liver cirrhosis with multi nodular liver and features of portal hypertension. Focal hepatic abnormality was difficult to exclude with the background of cirrhosis. He went onto have an MRI on which there were no discrete focal liver lesions although there was decompensation with ascites not seen on the first scan few days prior. His vitamin D was low, ruling out parathyroid adenoma or vitamin D toxicity. AFP and ACE levels were normal, as was TSH and T4, ruling out malignancy and hyperthyroidism as etiology. Normal renal function ruled out renal etiology for hypercalcemia. There was no evidence of granulomatous disease. He had raised IgG 21.2 but normal immunoglobulins. Serum electrophoresis and urine BJP were negative. No paraprotein detected, no urinary free light chains. After extensive work-up, no cause was found and he was treated with IV fluids and given an IV infusion of bisphosphonate.
Discussion
Hypercalcemia caused by advanced chronic liver disease in the absence of malignancy is a rare condition. It is a diagnosis of exclusion and responds well to bisphosphonate treatment, leading to resolution of hypercalcemia and prevention of further debility.

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CC4

Kennedy's Disease: An uncommon cause of androgen insensitivity and motor neuropathy

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Kennedy's Disease (KD) or Spinal and Bulbar Muscle Atrophy is a rare X-linked recessive condition due to CAG repeat in the androgen receptor (*AR*) gene. KD affects males with unaffected female carriers. Reported prevalence in male populations is highly variable; recent data suggests 2.5 in 100,000 with region specific higher prevalence. KD manifests as androgen insensitivity (AI) with features including gynaecomastia and motor signs such as early tremor, facial and bulbar muscle dysfunction, and slowly progressive proximal limb weakness. We present a 16 year old male with marked gynaecomastia. He had normal birth, met milestones and developed normally with no other relevant personal history. He was eugonadal and euthyroid. Most notable observation was marked upper limb tremor but no other motor symptoms. Testosterone 54 nmol/l with correspondingly high LH (13.0 IU/l), and normal oestradiol (182 pmol/l). Other pituitary

hormones normal, including prolactin (267 mIU/l). Beta-HCG, US testes, MRI adrenals/pituitary normal. Several male relatives were previously diagnosed with motor neuron disease (MND) with unaffected females, suggesting X-linked inheritance. Given this family history (FH), in combination with AI and tremor, he was referred to neurology and genetics. Initial analysis of the *AR* gene was negative for abnormalities, but specific KD abnormality testing confirmed diagnosis. Patient's priority was excision of gynaecomastia to good effect. KD is often misdiagnosed as MND due to features of progressive motor neuropathy in some patients. We should be mindful that KD is likely underdiagnosed due to rarity and limited awareness so actual prevalence could be underestimated. Gynaecomastia and tremor may be the sole early manifestations. Genetic testing for KD should be considered in men with AI with a relevant FH or with tremor or motor neuropathy. Specific analysis for KD genetic abnormalities should be requested as initial *AR* gene analysis may be normal.

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CC5

Transformation of a non-functional to a functional neuroendocrine tumour

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Case
A 69 year old man was diagnosed with poorly differentiated pancreatic adenocarcinoma with liver metastases in November 2017 and received FOLFIRINOX chemotherapy followed by Gemcitabine. This stabilised his disease and chemotherapy was stopped in March 2020. In April 2021 he presented with a 3-4 month history of tiredness; intermittent confusion, especially in the early morning; the discovery that food resolved his symptoms, albeit temporarily; and accompanying significant weight gain. A blood glucose monitor was supplied which demonstrated that his capillary blood glucose would drop as low as 1.5 mmol/l when the symptoms occurred. Biochemical assessment was consistent with insulin hypersecretion (glucose 2.0 mmol/l, insulin 109miU/l (4.4-26), C-peptide 3068 pmol/l (298-2350)). He was started on dexamethasone, diazoxide and given a Freestyle Libre 2 flash glucose monitor. Differential diagnoses included a new insulinoma in addition to his pancreatic adenocarcinoma, non-islet cell tumour hypoglycaemia or transformation of an original non-functional neuroendocrine tumour (NET) into a functional NET. Interestingly he did not have any symptoms of insulin hypersecretion at original presentation in 2017. The original histology was reviewed with immunostaining and reclassified as a WHO grade 2 NET, strongly positive for synaptophysin and CD56. Octreotide scan showed an intensely avid pancreatic lesion with extensive avid liver metastases, which were also visualised on MRI, and confirmed the diagnosis of NET. Treatment options are currently limited and will be palliative.
Discussion
It is highly unusual for NETs to transform from non-functional to functional however this transformation, especially into insulinoma, has previously been described. A possibility is that he has developed intra-tumour heterogeneity or clonal evolution as a consequence of the chemotherapy, with only some areas of tumour mass hypersecreting insulin. The flash glucose monitor has significantly improved his quality of life, allowing early detection of hypoglycaemia and prevention of hospital admission, however his general prognosis is guarded.

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CC6

Monozygotic twins with hypothyroidism responding to T3 / T4 combination: a role for Nuclear Factor-kappa B (NF-κB)?

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Introduction
There are patients who remain symptomatic with hypothyroidism despite apparent adequate replacement on levothyroxine (LT4) therapy. We present an observation where monozygotic twins responded only to combination therapy with liothyroinine (LT3), and were found to have a genetic variation which may have clinical significance in thyroid metabolism.
Case report
A 47-year-old female with polyglandular auto-immune syndrome (APS1) presented with lethargy and cognitive dysfunction on LT4 despite good compliance. FT4 12 pmol/l (9-25); TSH 121miU/l (0.3-5.0). Further LT4 dose increase gave her unpleasant combination of fatigue and palpitations. Symptoms responded promptly and reproducibly to thyroid extract containing LT4 38mcg/LT3 9mcg bought online. Thyroid function stabilised: FT3 5.6pmol/l; FT4 17pmol/l; TSH 0.1miU/l. Her monozygotic twin-sister had hypothyroidism, coeliac disease and elevated ANA of unknown aetiology. She also remained symptomatic on conventional LT4 but improved on combined LT4/LT3 extract. Thyroid function stabilised: FT4 8.2pmol/l; TSH 3.6miU/l. Whole-Genome-Sequencing (WGS) revealed heterozygous mutation in NFκB1 in both twins, and their mother.
Discussion
NFκB is a family of transcription factors that among its functions is the activation of D2 in the hypothalamus. Most T3 is produced locally in the brain by D2, expressed in tancytes lining the 3rd ventricle. In-vivo studies showed that NFκB-mediated activation of D2 can locally increase T3 levels. Conversely, inhibition of p65 subunit of NFκB abolishes the increased D2 in tancytes. Therefore, mutation of NFκB gene might be of relevance in T4/T3 metabolism and action. Interestingly, this variation may impair a functionally significant part of the gene involved in recognition of self in auto-immunity.
Conclusion
This is the first observation of an association between a familial NFκB1 variant and twins with APS1. There was symptomatic response to combination LT4/LT3 therapy only. Possibly, this genetic region is important in auto-immunity and might provide an explanation for the differing responses to thyroid replacement.

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CC7

COVID-19 AstraZeneca Vaccination Induced Subacute Thyroiditis

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A 50 year old Asian lady developed neck pain and sore throat 10 days after first dose of AstraZeneca COVID-19 vaccination. Her dentist thought she had tonsillitis. She then presented to hospital a few days later with dyspnoea, palpitations, tremor and neck pain. She was apyrexial but clinically thyrotoxic with sinus tachycardia. Thyroid gland had normal size with tenderness without bruit or lymphadenopathy. Her Free T4 was >100 pmol/l (11.2 - 20.2), TSH $<$ 0.01mIU/l, ESR: 58 mm/hr (0-30 mm/hr) and CRP: 23 mg/l (0-4.9 mg/l), with normal full blood count. Thyroid peroxidase antibodies were 32 IU/ml (0-50 IU/ml) and TSH receptor Antibodies was 1.7 IU/l (0-2.9). Thyroid Ultrasound scan 3 weeks later showed subtle heterogeneity and hypoechogenicity with appearance suggesting thyroiditis. Thyroid uptake five weeks after presentation showed relatively reduced tracer uptake in upper left lobe with thyroid to background ratio 2.4 (0.5-3.5) . There was no previous medical history, recent viral infections, family history of thyroid or autoimmune conditions, allergies. She was not on any medication and was not pregnant. She was started on Carbimazole which was stopped 12 days later (T4: 35.6 pmol/l). She was asymptomatic a week later.
Discussion
This is the first reported case of AstraZeneca COVID-19 vaccine induced thyroiditis. It is of public and medical importance that we present any cases of such side effects as this will keep clinicians aware of this. There has been 7 cases of vaccine induced thyroiditis in literature of which only one is due to COVID-19 vaccine (Pfizer). Proposed mechanisms include T -cell mediated vaccine antigen presentation or autoimmune /inflammatory syndrome induced by adjuvants. This also raises the question if giving the 2nd vaccination is appropriate in this patient.
Conclusion
COVID-19 AstraZeneca induced subacute thyroiditis had a rapid recovery but long term sequelae and development of post-thyroiditis hypothyroidism is still unknown.

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CC8

Atraumatic chylothorax due to Graves' disease

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Case presentation
A 40-year-old Caribbean woman presented with sudden onset palpitations. She described 3 months of progressive shortness of breath, non-productive cough and 7kg weight loss. She denied chest pain, fevers or night sweats, but reported increased stool frequency, gritty eyes, and occasional visual blurring. She appeared cachectic and had a fine tremor, left eye proptosis and a visible pulsatile goitre. She was afebrile, tachypnoeic, hypoxic, hypotensive with fast atrial fibrillation (HR 240-260bpm). After unsuccessful DC cardioversion, she was admitted to ITU for rate control and high flow oxygen.
Initial investigations
Admission blood tests showed a free T4 of 82.1 pmol/l with supressed TSH. Chest and neck imaging showed a heterogeneously enlarged thyroid gland without substernal extension, extensive ground-glass opacification, mediastinal lymphadenopathy and small bilateral pleural effusions, but no discrete masses. Pulmonary angiography was unremarkable. Thyroid ultrasound was suggestive of thyroiditis.
Progress
Graves' disease was confirmed (TRAb 25.39units/L). Propylthiouracil (PTU) and dexamethasone were given with good initial response, however the addition of cholestyramine was later required to maintain biochemical euthyroidism. The arrhythmia, initially refractory to treatment, eventually settled with propranol. During her ITU admission, she developed an enlarging left pleural effusion which required chest drain insertion; 500ml of milky transudate was drained (normal LDH, cytology and immunophenotyping). Chylothorax was confirmed biochemically: triglycerides 4.58 mmol/l, cholesterol 0.6 mmol/l. Serum ACE and mycobacterial investigations were negative. There was no histopathological evidence of malignant or granulomatous disease following endobronchial ultrasound. PET-CT on day 25 showed no avidity and near-complete resolution of mediastinal lymphadenopathy and pleural effusion following treatment of Graves' disease. She was discharged on PTU, propranolol, dexamethasone and cholestyramine, with plans for radioiodine therapy as definitive treatment for Graves' disease.
Conclusion
Atraumatic chylothorax is rarely described in Graves' disease. In this case, chylothorax likely occurred due to thoracic duct obstruction by enlarged mediastinal lymph nodes.

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CC9

A Puzzling Set of Thyroid Function Tests: Thyroid storm or Secondary Hypothyroidism?

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We report the case of a previously healthy, 40 years old obese male, who was admitted in emergency with complaints of chest pain, shortness of breath and loose stools. His physical examination was relatively unremarkable except for sinus tachycardia and restlessness. He had no history of ischemic heart disease. He was admitted under cardiologists and had various investigations (echocardiogram, stress test and coronary angiogram), all normal. Due to the presentation, thyroid function tests (TFTs) were also checked, and surprisingly, showed picture of secondary hypothyroidism with a very low TSH and very low FT4 & FT3. He had no personal and family history of thyroid disease or endocrine disorder and he was not on any antithyroid medications. Endocrine opinion was sought and pituitary investigations were requested, with planned follow-up in the endocrine outpatient clinic. On discharge day, he revealed to the pharmacist that he had been taking over the counter Thyro-T2 fat burner, weight losing medications. On further scrutiny it was found that fat burners contain 3, 5 Diiodo-L-Thyronine (T2), a thyroid hormone metabolite. There have been very few case reports in the literature of severe hyperthyroidism induced by Thyro-T2 abuse. T2 is not routinely measured by assays and the biochemical picture could be confusing. A literature review and discussion follows the case.

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CC10

Alemtuzumab mediated alternating states of thyroid dysfunction

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A 29 year old woman with multiple sclerosis and no history of thyroid dysfunction was referred to endocrinology with T3 thyrotoxicosis (TSH <0.01 mU/l, fT4 20.7 pmol/l, T3 2.9 nmol/l). She had received monoclonal alemtuzumab therapy 9 months prior. This hyperthyroid phase was short lived and in the absence of anti-thyroid medication developed symptomatic hypothyroidism within 2 months of referral (TSH 52.9 mU/l, T4 <5 pmol/l, T3 0.8 nmol/l). Thyroid receptor antibodies were raised (34 U/l) although thyroid peroxidase antibodies were within normal reference ranges (4.4 U/ml). Levothyroxine 100 mcg/day was initiated, but was downtitrated due to rising fT4 levels over the subsequent 6 months. Following the eventual discontinuation of levothyroxine, the patient was admitted acutely with symptomatic thyrotoxicosis (TSH <0.01 mU/l, fT4 34.9 pmol/l, T3 >9.2 nmol/l) with tachycardia (HR 160), anxiety, tremor and weight loss (>10 kg). High dose carbimazole therapy (60 mg/day) was initiated and the patient currently awaits radioactive iodine therapy for definitive treatment. Alemtuzumab is a humanised anti-$CD52^+$ IgG1 monoclonal antibody utilised in the treatment of relapsing-remitting multiple sclerosis. It acts by targeting the $CD52^+$ epitope on $CD4^+$ and $CD8^+$ T lymphocytes and B-cells, which results in their antibody- and complement-mediated depletion, subsequent repopulation and immune reconstitution. Up to one third of individuals receiving alemtuzumab experience thyroid dysfunction where fluctuations in thyroid activity are mediated via the coexistence and balance of thyroid receptor antibodies with stimulating and blocking functions. We report the case of a patient with relapsing-remitting multiple sclerosis who presented with three distinct phases of thyroid dysfunction following alemtuzumab. Surveillance of thyroid function is imperative in individuals receiving this therapy, and clinicians should be aware that thyroid dysfunction may alternate rapidly between hyperthyroid, euthyroid and hypothyroid states and severity.

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Poster Presentations

Adrenal and Cardiovascular

P1

Plasma steroid profiles in patients hospitalised with COVID-19 - an ISARIC/WHO CCP-UK cohort study

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Background
Secretion and metabolism of glucocorticoids and sex steroids is disrupted in critical illness, and may be further disrupted in COVID-19. The host receptor (ACE-2) is expressed in endocrine tissues including adrenal cortex and gonad, and its occupancy may dysregulate the renin-angiotensin system. We hypothesise that severe COVID-19 results in glucocorticoid and sex hormone deficiency, and aldosterone excess.
Methods
Plasma was obtained from 279 adults admitted to UK hospitals with COVID-19 between March and June 2020, at recruitment to the ISARIC/WHO CCP-UK prospective cohort study. 67% were male, median (interquartile range (IQR)) age was 63.0 (52.0-73.5) years, and time from symptom onset was 11.0 (6.0-16.5) days. These represented a spectrum of disease severity as per the WHO Ordinal Scale, with 19.7% in-hospital mortality. 22 steroid hormones, precursors and metabolites were quantified by LCMS/MS. Data are median (IQR).
Results
Compared with patients not requiring supplemental oxygen, those with fatal disease had higher cortisol concentrations (793.2 (552.7-957.9) vs. 465.9 (338.4-580.8) nmol/l, $P < 0.001$) and cortisol:cortisone ratios (16.7 (12.2-23.7) vs. 8.6 (6.6-12.8), $P < 0.01$), and (in males) lower testosterone concentrations (1.1 (0.6-2.1) vs. 6.8 (4.8-10.5) nmol/l, $P < 0.001$). Testosterone correlated inversely with IL-6 ($r = -0.62$, $P < 0.01$) and estrone ($r = -0.3$, $P < 0.01$) in males, while estradiol was below detectable threshold (*46 pmol/l*) in 266/279 patients. Aldosterone levels were raised in those receiving invasive mechanical ventilation (586.0 (125.0-885.2) vs 136.1 (75.0-357.6) pmol/l, $P < 0.01$). Findings remained significant after adjustment for confounders.
Conclusions
Amongst patients hospitalised with COVID-19, steroid responses are similar to other causes of critical illness, including elevated glucocorticoids and reduced male testosterone. The efficacy of glucocorticoid treatment is therefore unlikely related to any COVID-induced hypocortisolism. Re-evaluation of these hormone axes is important to determine if abnormalities persist beyond resolution of infection in people with 'long COVID'.

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P2

A QIP to improve quality of care in adrenal insufficiency and steroid dependent patients

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Aim
A QIP to improve early recognition and treatment of adrenal crisis (AC) in adults. Issuance of new NHS emergency steroid cards (SEC) in accordance with National Patient Safety Alert (NPSA) August 2020.
Background
National Reporting and Learning System found that two deaths and six incidents (severe harm) were associated with shortfalls in managing adrenal insufficiency (AI) over 4 Years. A resulting NPSA advised the care organisations to identify those at risks and issue them with a Steroid Emergency Card (SEC). Members of endocrine team led the Trust's response to the NPSA.
Methodology
Retrospectively, all patients admitted in 2019-2020 with diagnosis of adrenal insufficiency were identified and their clinical records were analysed. 76 out of 110 cases either had a diagnosis of adrenal insufficiency or were on long term steroids. These 76 cases were reviewed for appropriate management of AC, use of sick day rules (SDR) and involvement of endocrine team.
Results
24 patients were in addisonian crisis; 22(92%) were managed appropriately according to national guidelines while 2 were not (8%). The 52 patients who were not in AC were audited for compliance with SDR. SDR were followed in 33(63%) patients but not in 19 cases (37%). The main intercurrent illness responsible for AC was gastrointestinal (29%); followed by other infections (24%). Only 13 out of 24 AC patients were referred for inpatient endocrine review; 11 were not.
Improvements
1-A Trust-wide guideline developed based on existing SFE publications. 2-Issuance of NPSA letters and SECs to clinicians/clinical areas that most likely deal with AI. 3- The AI patients admitted in 2019-2020 were issued with SEC. 4-Poster/Screen saver developed for awareness about AI patients and SEC. 5- AI alerts to be incorporated in e-noting and ePMA (electronic prescribing). 6-Trust wide educational activities to improve compliance with AI management.

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P3

Improving outcomes from SSTS: Redefining Cortisol Cut-Offs

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Background
Short Synacthen Tests (SSTs) are integral to the diagnosis of Adrenal Insufficiency (AI). A 30-minute stimulated cortisol value is assessed against local assay dependent thresholds to ascertain or exclude the diagnosis. A diagnosis of AI is a life changing event requiring the initiation of life long glucocorticoid replacement therapy for survival. Glucocorticoid replacement is associated with long term morbidity and mortality, including an increased risk of diabetes, cardiovascular disease and osteoporosis. It is essential therefore that the diagnosis of AI is secure, and a lifetime of replacement not commenced inappropriately.
Methods
SSTs performed at North West London Pathology were isolated from 60,178 cortisol tests performed between May 2016 and February 2020. Patient electronic medical records were exhaustively reviewed longitudinally to assess whether a diagnosis of AI was correctly or incorrectly applied, based on expert assessment.
Results
SST data was isolated for 670 patients. Receiver Operator Curve analysis identified that an SST cut-off of 370 nmol/l at 30 minutes achieved a sensitivity and specificity of 97.4% and 93.4% respectively. A 60-minute cut-off of 420 nmol/l produced a 97.4% sensitivity and 93.1% specificity. A total of 628 patients passed their SSTs: 140 (22.3%) patients passed at 60 minutes but would have failed at 30 minutes, according to biochemical criteria. Only 2 of these patients were later prescribed glucocorticoids. In one patient, there was unrelated pituitary tumour regrowth, and the other later discontinued their replacement therapy.

Conclusions
SST thresholds for Abbott cortisol assays can be lowered to to 420 nmol/l at 60 minutes and 370 nmol/l at 30 minutes, and both timepoints should be routinely performed. The above recommendations should reduce the number of patients who are inappropriately labelled with a diagnosis of AI, thereby avoiding the associated deleterious effects of inappropriate glucocorticoid replacement therapy.

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P4

The saline infusion test, but not the captopril challenge test, is associated with intra-test hypertension and hypokalaemia in patients being investigated for primary aldosteronism

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Background
Primary aldosteronism (PA) is a common, curable and high-risk subset of hypertension, mandating detection. In all but the most severe cases, learned society guidelines recommend confirmatory testing. Whilst a variety of confirmatory tests exist, data describing their safety are limited. Concerns centre around the potential of some tests to precipitate hypokalaemia or a hypertensive emergency in a patient with PA on sub-optimal anti-hypertensive medication. In this study, we evaluated the intra-test effect on blood pressure and potassium of the two most widely used confirmatory tests for PA, the saline infusion test (SIT) and the captopril challenge test (CCT).
Methods
Retrospective analysis of patients being investigated for PA and who underwent either SIT or CCT between 2014 and 2021 at two tertiary centres in London. Identical protocols were used. Blood pressure was measured hourly from the start of each test. Serum potassium was measured at the start and end of each test.
Results
96 SITs and 71 CCTs were performed in 159 patients (final diagnosis of PA in 115; 72.3%). The SIT was associated with a fall in serum potassium (mean change -0.18 mmol/l, $P < 0.01$) and rise in systolic blood pressure (median change +3 mmHg, $P < 0.01$). No episodes of hypertensive emergency were observed although one SIT was terminated due to hypertension. No alteration in either serum potassium or blood pressure was seen with the CCT.
Conclusions
The SIT, but not the CCT, was associated with a statistically significant decrease in serum potassium and increase in systolic blood pressure. Whilst this suggests that the CCT might be a more appropriate confirmatory test than the SIT in patients with problematic hypokalaemia or hypertension control (assuming equivalency of diagnostic performance), the absolute change in systolic blood pressure was small and test discontinuation was rarely required.

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P5

SIMBA as a complement to small group teaching in undergraduate medical curriculum: A pilot study

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Introduction
Small-group teaching (SGT) has been widely adopted in medical education to promote problem-based learning and enhance the process of deep learning. Simulation via Instant Messaging - Birmingham Advance (SIMBA) is a simulation-based learning approach using WhatsApp and Zoom to increase participants' confidence in managing various clinical scenarios.
Aim
To investigate whether SIMBA provided similar knowledge and experiences as compared to SGT.
Methods
Prior to SGT, two SIMBA sessions were conducted on corresponding topics — adrenal and reproductive endocrinology — for Year 2 medical students. Each session involved simulations of real-life cases via WhatsApp, followed by a discussion with a specialist doctor over Zoom. Attendees' attitudes and knowledge were assessed using likert scales and multiple-choice questions (MCQs), respectively, in post-SIMBA and post-SGT surveys. Data were analysed for knowledge, effectiveness, and acceptance quantitatively. Responses collected from open-ended questions were reviewed and combined in a thematic analysis to identify common themes.
Results
43 SIMBA attendees' and 42 SGT attendees' responses completed the surveys. Knowledge acquisition by SIMBA was better than SGT (86.7% vs 80%, $P = 0.047$). Attendees strongly agreed/agreed that SIMBA was more engaging (100% vs 84.8%), gave more in-depth knowledge (100% vs 87.9%), better prepared for the topic (97.7% vs 57.6%), promoted new knowledge (97.7% vs 87.9%), stimulated interest in Endocrinology (90.7% vs 75.8%), and created a friendly environment for questions (97.7% vs 81.8%). Thematic analysis showed individualised, structured and engaging sessions as strengths for SIMBA over SGT.
Conclusions
SIMBA is effective in increasing the knowledge and better accepted by undergraduate medical students compared to SGT. Further large-scale studies are needed to investigate if SIMBA can replace or be an adjunct to the traditional SGTs in Endocrinology and other specialties.

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P6

The effect of plasma potassium on hospital length of stay in unselected acute admissions

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Introduction
Hypo-&hyperkalaemia are common laboratory abnormalities, complicating up to 10% of all hospital admissions and contributing to mortality. Ideally, patients with mild deviations can be treated as outpatients, and only those patients with objectively severe or life-threatening levels are hospitalized. Once admitted, there are few data as to whether the degree of electrolyte disturbance consumes greater resource(s). We analysed the admission and discharge data, for acute admissions, with reference to the admission potassium value.
Methods
Clinical data for all unscheduled admissions were retrieved from the electronic health record (EHR). We used the CogStack ecosystem to access structured fields in the EHR. We analysed a 12-month cohort of all patients who had an A&E discharge summary created between 1st Jan 2017 and 1st Jan 2018 (dates of admission min 21st December 2016 – 1st Jan 2018). For each admission, the laboratory U&Es were obtained, and first potassium identified. Cox proportional hazard models evaluated the independent effect of potassium on likelihood of discharge, with eGFR, age and sex as covariates, treating potassium as categorical data ('Hypokalaemia' <3.5 mmol/l and 'hyperkalaemia' ≥ 5.0mmol/l) and continuously using linear spline terms (boundary knots at 3.5 and 5.0 mmol/l).
Results
In 12-months, there were 138,307 visits by 98,357 unique patients in the Emergency department. Laboratory potassium was measured in 36,631 attendances (not including haemolysed samples). Hypokalaemia was found on the initial sample in $n = 2095$ (5.7%), hyperkalaemia in $n = 1581$ (4.3%) and eukalaemia in $n = 32,955$ (90.0%). The eGFR was missing in $n = 3310$, of whom $n = 2763$ (83%) had potassium 3.5 to 5 mmol/l. In the categorical multivariable model, hypo- (HR : 0.644, 95% CI 0.613 - 0.676 $P = <0.0001$) and hyperkalaemia (HR 0.812, 95% CI: 0.765 -

0.862 $P < 0.0001$) remained independent predictors after adjusting for eGFR (HR 1.009 (95% CI 1.008 - 1.009; $P < 0.0001$) and age (HR 0.990, 95% CI 0.989-0.990; $P = < 0.0001$). The spline model demonstrated an n shaped relationship between admission potassium and hazard of discharge against time, the likelihood of discharge crossing unity between 4.0-5.0 mmol/l.

Conclusion

Both hypo-&hyperkalaemia are independently associated with prolonged length of stay for acutely hospitalised patients, even at less extreme levels of dyskalaemia.

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P7

Simulation via Instant Messaging – Birmingham Advance (SIMBA): Impact of online simulation-based learning on doctors' confidence in managing cases during the COVID-19 pandemic

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Background

SIMBA is a simulation-based learning platform designed to increase clinicians' confidence in managing various clinical scenarios. The restriction of face-to-face learning during the COVID-19 pandemic led to switching Simulation via Instant Messaging – Birmingham Advance (SIMBA) to entirely virtual sessions.

Objective

To explore SIMBA's effectiveness to sustain medical education in endocrinology during the pandemic.

Methods

We included six sessions on different subspecialties in endocrinology (adrenal, thyroid, pituitary, diabetes, metabolic bone, and gonadal) conducted from May 2020 to June 2021. We analysed participants' pre- and post-simulation surveys studying change in confidence on simulated case post-session and proportion change in core competencies recommended by the Accreditation Council for Graduate Medical Education (Patient Care, Knowledge, Communication Skills, Professionalism, Practice-Based Learning, Systems-Based Practice).

Results

279 participants were included in the analysis. Participants' approach to simulated cases significantly improved following SIMBA: [overall ($n = 279$) ($P < 0.001$); adrenal ($n = 33$) ($P < 0.001$), thyroid ($n = 37$) ($P < 0.001$), pituitary 2.0 ($n = 79$) ($P < 0.001$), diabetes 2.0 ($n = 46$) ($P < 0.001$), metabolic bone ($n = 44$) ($P < 0.001$), gonadal ($n = 40$) ($P < 0.001$)]. SIMBA improved participants' clinical competencies in patient care [56.6% ($n = 158/279$)], professionalism [40.0% ($n = 92/279$)], patient management [86.4% ($n = 241/279$)], systems-based practice [46.2% ($n = 129/279$)], practice-based learning [70.3% ($n = 196/279$)], and communication skills [23.7% ($n = 66/279$)].

Conclusions

SIMBA is an effective model to improve clinicians' confidence in approaching various endocrine conditions, thereby maintaining medical education throughout the pandemic. Future sessions with a hybrid model of face to face and virtual learning will be experimented to provide the best possible learning experience to medical students and healthcare professionals.

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Comparative steroid profiling in large animals

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Large animals are increasingly used a models for endocrine research. Unlike rodents they are cortisol-dominant and thus more similar to humans. In this study we use two novel analytical methods to compare the steroid profile of pigs, sheep and humans; **1.** Simultaneous quantification of primary glucocorticoids, glucocorticoid precursors and mineralocorticoids in plasma (>20 steroids); **2.**Quantification of glucocorticoids metabolites (>10 steroids) in plasma. Steroids were extracted from plasma (100μL) from healthy adult female pigs($n = 12$), sheep($n = 12$) and humans($n = 6$) by automated supported liquid extraction and analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). We have shown that components of the glucocorticoid/mineralocorticoid synthesis pathways can be simultaneously quantified and that glucocortocoid metabolites, normally only measured in urine, are present at high concentrations in plasma. Application of these methods to clinical samples could offer valuable insight into endocrine disease pathophysiology. We demonstrated that pigs and sheep have similar glucocorticoid/mineralocorticoid profiles to humans but subtle differences, particularly in glucocorticoid metabolism, should be considered when using these animals in disease models.

Table 1 Plasma concentrations of primary glucocorticoids cortisol and corticosterone (B), glucocorticoid precursor 17-hydroxyprogesterone (17OH-P), glucocorticoid metabolites cortisone (E), 11-dehydrocorticosterone (A), 5α-tetrahydrocortisol (5α-THF), 5β-tetrahydrocortisol (5β-THF) and 20β-dihydrocortisol (20β-DHF) and mineralocorticoids 11-deoxycorticosterone (DOC) and aldosterone.

	Human	Pig	Sheep
Primary Glucocorticoids	Cortisol **210.2** ± **37.86**[a]	Cortisol **167.8** ± **15.41**[a]	Cortisol **141.8** ± **10.29**[b]
	B **6.65** ± **1.71**	B **5.34** ± **0.57**	B **4.01** ± **0.39**
Glucocorticoid precursors	17OH-P **1.08** ± **0.23**[a]	17OH-P **0.36** ± **0.10**[b]	17OH-P **0.13** ± **0.34**[b]
Glucocorticoid Metabolites	E **34.54** ± **2.70**[a]	E **26.19** ± **2.46**[b]	E **14.36** ± **0.6419**[c]
	A **1.64** ± **0.23**	A **1.11** ± **0.11**	A **1.09** ± **0.12**
	5α-THF **10.02** ± **1.49**[a]	5α-THF **0.64** ± **0.05**[b]	5α-THF **1.72** ± **0.60**[b]
	5β-THF **61.35** ± **19.49**[a]	5β-THF **11.70** ± **1.45**[b]	5β-THF **70.03** ± **16.34**[a]
	20β-DHF **3.57** ± **0.56**[a]	20β-DHF **2.34** ± **0.28**[a]	20β-DHF **11.73** ± **0.94**[b]
Mineralocorticoids	DOC **0.07** ± **0.02**	DOC **0.08** ± **0.02**	DOC **0.18** ± **0.04**
	Aldosterone **0.09** ± **0.01**	Aldosterone **0.14** ± **0.06**	Aldosterone **0.10** ± **0.01**

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Cortisol measurement post steroids (Dexamethasone) treatment for COVID-19

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Introduction
The RECOVERY trial[2] reported patients with Covid-19 receiving requiring invasive mechanical ventilation or oxygen that the use of dexamethasone (6 mg for 10 days) resulted in lower 28-day mortality. Adrenal insufficiency (AI) from hypothalamic-pituitary-adrenal (HPA) axis suppression[3] is a serious, potentially life-threatening side effect of glucocorticoids treatment.
Objective
We aimed to investigate the effects of Covid dexamethasone protocols on adrenal function.
Methodology
We collected data from patients admitted with a diagnosis of Covid-19 treated with dexamethasone or hydrocortisone by searching electronic patient records from November 2020 to March 2021 at our institution. Adrenal function was screened by 09:00 am cortisol, at least 48 hours off of steroids. Cortisol levels > 300 nmol/l excluded adrenal insufficiency. Levels between 100-300 nmol/l underwent further assessment. Concentration < 100 nmol started on hydrocortisones replacement.
Results
79 patients were alive at the time of initial data collection. 51/79 patients had 7-10 days 6 mg dexamethasone whilst 28/79 had additional ARDS regimen of dexamethasone. 8 of this group died, and data available for 60 patients. 18/60 had suboptimal cortisol level (<300nmol/l) and 5/60 had cortisol <100 nmol 48 hours after stopping dexamethasone, 4 of these having had ARDS regimen of prolonged dexamethasone. 10 patients recovered their axis prior to confirmatory testing within 1-4 weeks. Confirmatory testing undertaken SST (Short Synacthen test) on 6/18 patients. 5 had satisfactory results, 1 of them unable to attend yet.
Summary
These data demonstrate minimal risk of adrenal insufficiency after treating with Recovery doses of dexamethasone 6 mg. Almost 50% of patients on ARDS regimen on ICU had early evidence adrenal insufficiency- rate of recovery unclear because of deaths in this cohort. This cohort may need steroid cover for invasive procures such as tracheostomy, but this currently remains unclear. These data also suggest that Covid-19 itself does not cause adrenal insufficiency which is reassuring.

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Method of venesection and location of peripheral sample alter adrenal venous sampling results and interpretation in primary aldosteronism

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Introduction
Adrenal venous sampling (AVS) is the criterion standard method of lateralisation in primary aldosteronism (PA). Despite this pivotal role, there is limited consensus and significant variability between centres related to many of the technical aspects of AVS. In this study, we sought to address whether variations in two different technical aspects of AVS altered parameters and interpretation, namely: 1. Peripheral sample site 2. Method of adrenal vein (AV) venesection
Methods
Retrospective single centre analysis of 147 PA patients who underwent ACTH-stimulated AVS between 2018 and 2021. Peripheral samples were obtained from the infra-renal inferior vena cava (IVC) and the iliac vein. Two samples were obtained from each AV: one under gravity (sample 1), the other under gentle negative pressure (sample 2). All samples were analysed for aldosterone (A) and cortisol (C) by immunoassay.
Results
Both aldosterone and cortisol concentrations were significantly higher in IVC than iliac vein samples. The selectivity index (AV_C/PV_C) was lower when the IVC was used as the peripheral sample and resulted in up to 5% of AV samples being classified as unsuccessfully cannulated compared to the iliac vein sample. In the left AV, aldosterone, cortisol and the A/C ratio were all significantly higher in sample 2 than sample 1. In the right AV, cortisol was significantly higher in sample 1 than sample 2. The overall lateralisation index (dominant $AV_{A/C}$/non-dominant $AV_{A/C}$) was not significantly different between the two samples; however, in 12% of cases there was a difference in lateralisation result depending on the sample used.
Conclusions
Both the location of peripheral sample and method of AV venesection have significant impact on ACTH-stimulated AVS results. The iliac vein appears to be a better choice of peripheral sample than the IVC, whilst the optimal method of AV venesection remains to be determined.

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P11

SGPL1 regulates expression of electron transport chain components to modulate cellular metabolism in the adrenal gland

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Introduction
Sphingosine-1-phosphate lyase (SGPL1) catalyses the final step in sphingolipid metabolism, irreversibly degrading the lipid signalling molecule sphingosine-1-phosphate (S1P). The relative abundance of S1P compared to its precursors sphingosine and ceramide finely tunes signal transduction for a wide range of cellular pathways including proliferation, apoptosis, migration and calcium handling. Loss-of-function mutations in SGPL1 cause a spectrum of disorders, including steroid-resistant nephrotic syndrome, primary adrenal insufficiency, ichthyosis and more. In each case, it is unclear how altered SGPL1 activity causes the phenotypes.
Methods
We generated isogenic SGPL1-knockout and stable SGPL1-overexpressing H295R adrenocortical cells to better analyse the role of SGPL1 in the adrenal gland. To investigate the effect of these perturbations on cell signalling and function we conducted MTT, circle scratch and seahorse XF assays, plus RNAseq, with western blotting and qPCR validation.
Results
We noticed a marked increase in proliferation in the overexpressing cells and a concordant decrease in proliferation in knockout cells. Similarly, overexpressing cells migrated faster while knockout cells were slower. We then sought transcriptome changes accompanying these phenotypic differences. Gene-set enrichment analysis of RNAseq data revealed a highly significant enrichment of genes associated with oxidative phosphorylation in the overexpressing cells, and a downregulation of genes involved in steroidogenesis in the knockout. Seahorse analysis revealed SGPL1 overexpressing H295R cells had increased basal and maximal respiration. SGPL1 knockout cells had markedly reduced non-mitochondrial oxygen consumption, which led us to believe there may be a difference in glycolysis in these cells. Surprisingly, we found the greatest differences in the overexpressing cells, which showed increased basal and maximal glycolysis, while the knockouts had a slightly reduced maximal glycolytic capacity.
Conclusions
SGPL1 expression correlates with growth and migration rates in H295R cells, with knockout reducing steroidogenic capacity and overexpression increasing metabolism.

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A crisis waiting to happen; long-term steroid use in a cohort of neuromuscular patients - what do they know?

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Aim
To assess whether patients on glucocorticoids understand how to manage their medication in the event of intercurrent illness.
Background
Studies have shown that, after as little as two weeks of glucocorticoid treatment, 10% of patients have adrenal suppression and it can take one year or longer for adrenal function to recover. With 7 out of 1000 people in the general population prescribed glucocorticoids, there is a large group at risk of adrenal crises and there were 78 reported incidents associated with glucorticoid prescribing in the last 4

years in England. Consequently, there is a national drive to improve safety of glucocorticoid prescribing. Neurology is one speciality in which glucocorticoids are frequently prescribed and often for extended periods of time.
Methods
Patients who attended the Oxford Muscle clinic during the past year and prescribed glucocorticoids were identified (Duchenne muscular dystrophy $n = 11$ and idiopathic inflammatory myopathy $n = 9$). Standardised telephone interviews were conducted to assess patient and family understanding of how to manage glucocorticoids in the event of an intercurrent illness.
Results
Despite improvements over the last 12 months, $<20\%$ of patients had documentation in their medical record that "sick day" rules were specifically discussed. Seventy per cent were uncertain or unaware of what to do in the event of an intercurrent illness and 60% did not know to seek medical advice if they were unable to take their glucocorticoids. Only half reported carrying a steroid card.
Conclusions
Improvements are needed to increase patients' and healthcare professionals' understanding of the potential risks associated with glucocorticoids. To mitigate against this, a programme of increased education and training of patients, families, and clinical staff has been undertaken and written information is now provided to every patient and their GP.

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Bilateral Adrenal Haemorrhage due to vaccine induced thrombosis and thrombocytopaenia following Covid-19 Vaccine

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Case history
A 62-year-old lady with no significant past medical history presented early February 2021 with a week history of epigastric pain, tiredness and poor oral intake, 5 days following her first dose of AstraZeneca Covid-19 vaccine. She was cardiovascularly stable but generalised abdominal tenderness was noted. There was no history of hypertension, hypokalaemia or symptoms consistent with phaeochromocytoma.
Investigations
Admission bloods revealed significant thrombocytopenia. CT scan revealed hepatic vein thrombosis and bilateral adrenal haemorrhage with no evidence of underlying adrenal masses. Adrenal insufficiency was confirmed on short Synacthenâ test. An underlying autoimmune process was excluded with normal lupus and vasculitis screens. Metastatic or tuberculous infiltration were excluded including CT-PET scan.
Treatment
The patient was managed by multi-disciplinary approach involving haematologist, endocrinologist and gastroenterologist and commenced on heparin and intravenous hydrocortisone. She was discharged on direct oral anticoagulant and oral steroids. Following case reports of vaccine induced thrombosis and thrombocytopaenia (VIIT) associated with Covid-19 vaccine, the temporal relationship between this patient's onset of symptoms and her first dose of AstraZeneca vaccine was noted by her haematologist. The case was reported to the MHRA.
Conclusion
Bilateral adrenal haemorrhage associated with thrombosis in this case was likely due to VIIT. Unusual sequelae of Covid-19 vaccine are increasingly being recognised, with VIIT particularly associated with AstraZenca Covid-19 vaccine, typically presenting 5 to 28 days after first dose. Awareness of such complications is of paramount importance as the vaccination rollout continues globally. To our knowledge, this is this first case of VIIT due to Covid-19 vaccine causing bilateral adrenal haemorrhage resulting in adrenal failure. Endocrine follow up of this case will determine if the adrenal insufficiency is temporary or permanent.

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P14

COVID-19 and Adrenal Insufficiency: A retrospective Study at a District General Hospital

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Introduction
Covid -19 can cause serious or severe illness in anyone but those with chronic health conditions are at greater risk. Adrenal insufficiency (AI) is assumed to be associated with an increased Covid-19 infection risk, which could trigger an adrenal crisis. We conducted a retrospective study at district general hospital to assess the incidence of COVID-19 in Adrenal insufficiency patients.
Method and material
Retrospective review of 43 patients who were under the follow up of our endocrine team with primary and secondary adrenal insufficiency was conducted using standardised questionnaire over the telephone. We collected data on COVID-19 symptoms and complications.
Results
Of 43 patients, Covid-19 PCR was positive in 9(21%) patients and negative in 34 (79%) between 1 March 2020 and 30 April 2021. Among the positive patients, 8/9 (88.8%) were symptomatic, and 1/9 (11.11%) was asymptomatic; P value $<$ 0.001. Most of patient were above 60, 4/9 (44.44%); P value <0.001. 4/8(50%) patients required hospital admission for oxygen support, but none of them had an adrenal crises; P value <0.001. 1/9 patients required ITU admission (11%).
Conclusions
We concluded that there was overall low risk of contracting covid-19 infection in our adrenal insufficiency patients (21%) but that it is higher than the baseline rate in the general population (6%). There did not appear to be any increased incidence of adrenal crisis in our small DGH sample.

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Giant bilateral adrenal mylelolipoma in a patient with congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive disorder characterized by insufficient production of cortisol and high androgens. Myelolipoma is a benign neoplasm of adrenal gland composing mature adipose tissue and scattered islands of hematopoietic elements. We report a case of rare association of giant bilateral adrenal mylelolipoma in a congenital adrenal hyperplasia patient who was non-compliant with medication.
Case report
A 45-year-old male with congenital adrenal hyperplasia (21-hydroxylase deficiency) diagnosed at birth presented with dyspnoea and severe abdominal discomfort from gross abdominal distension. No hypo-adrenal crises reported despite non-compliance. Past history included hypertension; no other family members have CAH. Computed tomography of abdomen showed hypo-enhancing fat containing large bilateral adrenal masses (Right 26.5x15.1 cm; Left 21.2 cm x 16.1 cm)) occupying most of the abdomen. Investigations: 17-OH-progesterone 172.48 nmol/l (1.8-6.65), Androstenedione 52.38 nmol/l (2.1-10.48) , DHEAS 1.28 µmol/l (1.2-8.98), Testosterone 12.2 nmol/l (8.6-29), Plasma Renin level 230.58, Plasma Aldosterone 941 pmol/l (117-580).
Progress
Abdominal discomfort and dyspnoea resolved following open bilateral adrenalectomy, right adrenal weighed 5.8kg; left weighed 5.4kg. Histology revealed mature adipose tissue with scattered islands of haematopoietic tissue consistent with myelolipoma. Commenced on Prednisolone and Fludrocortisone and compliance reiterated.
Discussion
Most myelolipomas are unilateral, small and asymptomatic. Giant bilateral myelolipomas are rare especially in the context of CAH. Literature review reveals over 30 patients with this association. Whether non-compliance to CAH treatment has a role in aetiology of giant myelolipomas is not fully established. Cases of giant bilateral myelolipomas as initial presentation of CAH have been reported, thereby indicating non-compliance leading to chronic corticotropin stimulation as a potential risk factor.
Learning point
1. Please consider CAH as a differential diagnosis in incidental bilateral adrenal masses. 2. Non-compliance to CAH treatment can potentially lead to abnormally huge bilateral adrenal masses necessitating bilateral adrenalectomy.

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P16

Implications of UK adrenalectomy guidelines for remote and rural patients in the Highlands of Scotland: An audit of adrenalectomy practice in a single UK Centre

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Introduction
National audits suggest significant variation in experience of individual surgeons performing adrenalectomies. A 2016 cross specialty consensus statement recommended that adrenal surgeons perform a minimum of six adrenalectomies per year given improved outcomes with higher volume surgeons. Patients in the Scottish Highlands requiring adrenalectomy are referred to a single Consultant Urologist with a specialist interest in retroperitoneal surgery based in Raigmore Hospital, Inverness. We sought to audit our adrenalectomy practice.
Methods
A list of adult patients having undergone adrenalectomy was obtained. Raw data on demographics, indication for and details of surgery, complications and pathology was collected from Scottish Care Information store and case records. Descriptive statistics were performed.
Results
40 adrenalectomies were performed between 2004 and 2019, with a mean of 5.4 per year over the last five years. Indications included non-functioning incidental lesions (27.5%), hypercortisolism (20%), primary hyperaldosteronism (20%), phaeochromocytoma (17.5%) and malignancy (15%). 80% were performed laparoscopically, 15% were planned open procedures and 5% were converted to open intraoperatively. 25% had postoperative complications, of which 5% were grade I (temporary LFT derangement and urinary retention) and 20% were grade II (blood transfusions, hypertension, acute kidney injury and infections). No patients had grade III-V complications. Mean length of stay was 4.1 days after laparoscopic procedures and 10 days after open procedures. The 30-day mortality rate was 0%.
Conclusion
Whilst not meeting the 6 adrenalectomy threshold for a high volume surgeon, our results were reassuring. Length of stay was comparable to high volume surgeons in national audits. Urologists who perform a high volume of laparoscopic retroperitoneal procedures have valuable experience and may have comparable outcomes to endocrine surgeons who perform adrenal surgery. There are strong arguments for centralisation of adrenalectomies to higher volume surgeons, but this decision could have a significant impact on patients from remote and rural communities.

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P17

The 4E (Engage, Educate, Equip and Empower): A framework for supporting the approach in the prevention, early recognition and effective management of adrenal crisis in adults

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Introduction
Patients with adrenal insufficiency (AI), continue to face many challenges including: dealing with symptoms and associated disorders; managing medication regimens; prevention and management of complications, and effective engagement and interactions with healthcare providers. In patients with AI, adrenal crisis (AC) continues to lead to unnecessary deaths. We illustrate how University Hospitals Birmingham NHS Foundation Trust used the 4E framework (***Engage, Educate, Equip and Empower***) as a strategy in implementing the National Patient Safety Alert on steroid emergency card (SEC) to support the prevention, early recognition and management of AC in adults.
The 4E Framework
- ***Engage.*** A working group was established consisting of: consultant Endocrinologist; endocrine nurse; emergency and critical care clinicians; pharmacists, and members on non-clinical team (Patient Safety, Communications and IT services). To understand patients' experience and expectations, a series of patient engagement sessions were also facilitated.
- ***Educate.*** A series of webinar sessions and speciality specific education sessions were facilitated on: AI; safe prescribing and monitoring of glucocorticoid treatment, and prevention and management of AC. An online on-demand module on AI was also developed.
- ***Equip.*** Clinicians were provided with tools including: a comprehensive guideline on the management of AI and AC; simple management algorithms; access to steroid emergency cards, and direct access to the Endocrinology helpline. Patients were equipped with SEC, hydrocortisone injection kit as well as means of accessing expert support and advice through our helpline.
- ***Empower.*** Well-engaged, well-informed and well-equipped patients are likely to be empowered to facilitate effective self-management of their condition. Similarly, clinicians are likely to be empowered to provide timely and appropriate live saving interventions.

Conclusion
AC is a life-threatening emergency that contributes to the excess mortality in patients with AI. The 4E framework (Engage, Educate, Equip and Empower) provides a systematic and effective system to support the prevention, early recognition and effective management of AC in adults.

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P18

Do we need to reset the threshold of screening for Autonomous Cortisol Secretion?

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Autonomous cortisol secretion (ACS), a term that refers to biochemical evidence of excess cortisol, but without the overt Cushing's syndrome in people with adrenal adenomas. Prevalence of adrenal tumours is 5-10%. Up to 50% of benign adenomas present with some degree of cortisol excess. There is little guidance for investigating and managing these patients leading to different standards of care. Cortisol secretion here is in wide range although post dexamethasone suppression test (ODST) cortisol of 50 nmol/l has been accepted widely below which ACS could be ruled out. There is emerging evidence to support that any amount of excess cortisol could be associated with increased risk of comorbidities, cardiovascular events, mortality and bone fractures compared to non-functioning adrenal tumours. We looked at 113 patients over the past 5 years who had screening for cortisol excess. We categorised them into 3 groups of cortisol values post ODST: group1: 40-49mmol/l (32patients), group 2: 50-138mmol/l (65 patients) and group 3: $>$138mmol/l (16 patients). The mean age of each group was 65.47, 66.11 and 63.34 respectively. 81% in group1, 75% in group 2 and 39% in group 3 had hypertension. Type 2 diabetes and pre-diabetes were similar across the groups (35.7%, 44.6% and 33.3%) respectively. overweight/-obesity was noted in 62.5%, 70.8% and 55.5% in three groups respectively. The majority had no data on Bone density. Of the ones reported, 9% in group 1 , 22% in group 2 and 27% in group 3 had decreased bone density. 28% in group1, 17% in group 2 and 33% in group 3 had dyslipidemia. We found that prevalence of comorbidities were comparable across all the three groups. More research is needed in this area. Individualised care, proactive approach in screening for comorbidities and a dedicated pathway is highly recommended to risk stratify these patents.

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P19

Prednisolone versus Hydrocortisone in Adrenal Insufficiency: A positive and negative control cross-sectional study

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Background
Management of adrenal insufficiency (AI) with glucocorticoid replacement is associated with increased mortality and morbidity. There is growing evidence that this is because of excess, non-physiological steroid exposure. Low dose prednisolone (2-4 mg) is a once-daily alternative to standard hydrocortisone regimens that more closely mimics the circadian rhythm and may translate to better outcomes. There is however a paucity of studies comparing the two treatments.
Methods
Twenty healthy volunteers (HV), 20 AI patients on prednisolone, 18 AI patients on hydrocortisone and 5 patients on anti-inflammatory doses of steroids (including IV methyl-prednisolone) were recruited to this study. All groups had

anthropometric, bone turnover, glycaemic, immune cell and cardiovascular risk markers assessed at a single timepoint. Patient groups had blood samples collected 2 hours after steroid treatment was administered.
Results
Mean hydrocortisone dose was 29.0 mg compared to 3.3 mg of prednisolone. Hydrocortisone patients had larger waist-hip ratios than HVs (0.9 vs 0.83; $P < 0.05$). No other differences in anthropometric markers were noted. Urinary NTX was significantly elevated in the anti-inflammatory group compared to the prednisolone and hydrocortisone groups. Triglycerides were markedly elevated in the hydrocortisone patients compared to HVs (1.28 mmol/l vs 0.86 mmol/l; $P < 0.05$). WBC was significantly elevated in the hydrocortisone and anti-inflammatory groups compared to the healthy volunteers, but not in the prednisolone group. All treatment groups demonstrated a raised neutrophil count compared to the healthy volunteers. Fructosamine was significantly higher than the HVs in the hydrocortisone group but HOMA-B was significantly lower.
Conclusions
There are currently no clear differences between prednisolone and hydrocortisone in the management of AI. There are some indications that hydrocortisone may be worse for cardiovascular risk, and glycaemic outcomes, but the data for the latter is discordant. All treatment groups showed a neutrophilia compared to HVs, suggesting that there remain relative excess glucocorticoid exposure.
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Adrenal Incidentaloma Pathway - A four-year experience at a teaching hospital

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Background /Methods
Adrenal incidentalomas pose a significant burden to endocrinology services in assessing the clinical significance of these lesions. Following vetting of the incidentaloma referrals, the patients at our centre are initially seen in a nurse-led clinic for biochemical investigations and to ensure completion of radiology assessment using a structured proforma. This step facilitates efficient patient flow and quicker decision making. The clinical outcomes of the patients evaluated though this pathway are summarised below.
Results
329 patients were seen in our endocrine unit between February 2017 and February 2021. 65.4 % (215) were females and 34.6% (114) males. The mean age was 63.8 $\pm$ 12 years.
Discussion
The widespread use of cross-sectional imaging has led to an increasing number of adrenal incidentaloma referrals to endocrinology. We have assessed 329 patients with this pathway in the last four years and continue to receive an average of 10 referrals per month. Our pathway simplifies the logistics of organizing multiple tests and reduces the number of medical appointments required, leading to quicker appointments. This pathway helps to streamline the patient journey and reduce the cost of medical appointments.

Adenoma Laterality		
Left	190	57.8%
Right	81	24.6%
Bilateral	58	17.6%

Radiology Outcomes		
Benign	273	83%
Indeterminate	52	15.8%
Metastases	4	1.2%

Diagnosis		
Benign NFA	289	87.8%
Phaeochromocytoma	4	1.2%
Autonomous adenoma	4	1.2%
Adrenal cancer	1	0.3%
Metastases	3	0.9%
Awaiting confirmation	28	8.5%

1 mg Overnight Dexamethasone Suppression Test		
Cortisol (nmol/l)	Patients	Percentage
>138	13	4%
51-138	90	27.4%
<=50	226	68.7%

Pathway Outcomes		
Discharged	268	81.5%
Medical clinic	40	12.2%
Surgical clinic	12	3.6%
Deceased	5	1.5%
Declined	3	0.9%
Relocated	1	0.3%

Surgical Outcomes *		
Phaeochromocytoma /Paraganglioma	8	40%
Adrenal cancer	3	15%
Adenoma	3	15%
Metastasis	2	10%
Cushing's	2	10%
Conns	1	5%
Ectopic ACTH bilateral adrenalectomy	1	5%

*Includes patients who were not classified as incidentaloma at detection

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P21

A review of management of adrenal incidentalomas at a District General Hospital and development of a local clinical management pathway

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Aim
This is a retrospective study of imaging with adrenal incidentalomas at our DGH to assess clinical practice. Their management was followed and compared with the European Society of Endocrinology (ESE) Clinical Practice Guidelines 2016 for management of adrenal incidentalomas. The aim was to improve clinical service by developing a local management pathway.
Materials and Methods
Data was collected for two years from 2018 to 2019 which included all images with an incidental adrenal adenoma. Out of 191 patient's scans, 168 were selected as appropriate, and their clinical records were reviewed.
Results
30% of the reports did not mention the size of the adenoma and among the 47 dedicated adrenal scans, 27% did not have a Hounsfield Unit (HU). Only 36% of all scans were referred to endocrinology for investigation hence it was possible to ascertain that only 2.38% were functional, but the functionality of 71% adenomas was unknown. 29% had repeat imaging done. 22 scans showed bilateral adenomas, and only half of them were referred for further work up. We were also

able to determine the characteristics of the 4 functional adenomas. These findings further confirmed that radiologically benign adenomas can be functional.
Conclusion
This audit identified the need to develop a local management pathway for adrenal incidentalomas at our hospital. We liaised with the urologists and the radiologist to create a pathway, which involved investigations as recommended by the ESE, a reporting guide for the radiology department, and the criteria for referral to the local or tertiary surgical team. This pathway was presented at the department clinical governance meeting, and subsequently was approved at the Medicine Divisional Governance Group meeting. The pathway is now available for reference on the hospital intranet.

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P22

Searching for a new PAL

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Primary adrenal lymphoma is an extremely rare type of lymphoma. There have been only about 200 cases described in the literature so far. About a half of patients can present with adrenal insufficiency. We report a case of a 70- year-old previously fit and well patient referred to Endocrinology services after a CT scan of her adrenal showed bilateral adrenal masses right measuring 6 cm and left measuring 9 cm. CT was performed as she complained of 9 kilograms weight loss in last three months. She denied any other symptoms. Later on, she did complain of some night sweats. Clinically, she had no sinister signs. She had a new hyponatremia 127 mmol/l (135-145), Lactate dehydrogenase of 1009 U/l (0-479) and B2- microglobulin of 3.4 mg/l (1.1-2.5) Blood metadrenalines, urine steroid profile, and 17 OH progesterone was normal. 9 am cortisol was 568 nm/l (140-620) ruling out adrenal insufficiency. She underwent a CT guided biopsy. Histology was consistent with a diagnosis of Diffuse Large B cell Lymphoma. 70 % of PAL's are Diffuse Large B cell Lymphomas. The prognosis of Primary Adrenal lymphoma remains very poor. Chemotherapy remains the mainstay of treatment. Little is known about the chemotherapy regimen, the rate of relapse, and the role of adrenalectomy. Adrenal lumps can be a sign of pathology relating to other body systems such as a haematological malignancy in this case. Haematological malignancy pathways need to be revisited. Adding LDH as a tumour marker can be of value and can help redirect early referral to the right speciality.

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P23

Feminizing adrenal tumours (FAT): Rare tumours of the adrenal gland

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Functioning adrenal masses are often a diagnostic challenge and can present with unusual symptoms. We describe a case of a 37-year-old male with a background of ulcerative colitis, who presented with gynecomastia in the breast clinic. His serumbiochemistry showed persistently elevated Oestradiol and prolactin, with low testosterone and FSH. On physical examination, he had marked breast tenderness, bilateral gynecomastia and no signs of steroid excess. He reported a decline in his libido but no erectile dysfunction. After excluding common causes of gynecomastia, further investigations were performed to investigate the cause of raised Oestradiol. Differential diagnoses considered included exogenous source, testicular tumours, feminising adrenal tumours (FATs), or aromatase excess syndrome. Subsequently, CTadrenal showed a well-defined enhancing tumour, arising from the left adrenal gland measuring 5cm in the maximum axial dimension. The PET FDG confirmed a hypermetabolic tumour on the left adrenal with no distant metastases. The patient underwent urgent laparoscopic surgery with an excellent surgical and biochemical outcome.

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P134

In vitro splicing assay proves the pathogenicity of intronic variants in MRAP

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Familial glucocorticoid deficiency (FGD) is characterised by isolated glucocorticoid deficiency with retention of normal mineralocorticoid production. FGD causing mutations in the MC2R accessory protein, *MRAP*, often occur at the canonical donor splice-site of intron 3, presumed to result in skipping of the first coding exon with unknown consequences at the protein level. DNA from three patients (0 - 6 months) with high ACTH and/or low cortisol levels underwent whole exome sequencing. The proband in family 1 (P1) presented at 13 months and had a hyperpigmented sibling who died in neonatal period due to adrenal failure. Patient 2 (P2) had a family history of adrenal insufficiency and was hyperpigmented at birth and patient 3 (P3) had diffuse hyperpigmentation in the early neonatal period and low cortisol on formal testing at 16m. Variants were confirmed using Sanger sequencing and predicted splice-site mutations were investigated using an *in vitro*splicing assay. Homozygous mutations in *MRAP* were identified in all three cases. Previously described, c.106+1delG (P1) and c.106+2dupT (P2) at the canonical donor splice-site of intron 3, were identified, with the former predicted to destroy the splice site and the latter to weaken it. These mutations *in vitro*resulted in the complete skipping of exon 3 with unknown consequence to the protein (p.?). A novel homozygous mutation in intron 4, c.206+5G>T was identified in P3 but was not predicted to alter splicing. However, *in vitro*, this mutation negates the canonical donor splice site and creates two different alternative sites, both resulting in frameshifts and predicted early termination of the protein (p.Val44fs*50, p.Asn70fs*92). Splice prediction protocols, though largely effective for variants within 2bp of exon/intron boundaries may not predict the true outcome of more distant base change(s), highlighting the necessity of functional assays to assign pathogenicity to them.

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P135

Undetectably low blood aldosterone concentrations are prevalent in COVID-19 patients but poorly quantified by chemiluminescent immunoassay

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Background
SARS-CoV-2 targets membrane-bound angiotensin-converting enzyme 2 (ACE2) to achieve cellular entry. Resultant loss of ACE2 function may lead to unregulated activation of the renin-angiotensin-aldosterone system (RAAS), contributing to the pathogenesis of hypertension and triggering a proinflammatory cascade. However, evidence to support this is conflicting, with either no change or an increase in the concentration of circulating aldosterone reported in patients with COVID-19.
Patients & Methods
Blood aldosterone concentrations from 126 steroid-naive patients, collected within three days of the patient's first positive SARS-CoV-2 PCR test, were analysed by liquid chromatography tandem mass-spectrometry (LC-MSMS). Cortisol was determined by immunoassay (Siemen's Centaur®).
Results
In contrast to previous reports, aldosterone was undetectable by LC-MSMS in more than half of the patients studied. Given this discrepancy, aldosterone measurement was repeated in a commonly used clinical immunoassay (Liaison Diasorin®). The immunoassay over-estimated aldosterone compared to the LC-MSMS assay, suggesting assay interference as a possible explanation of this discordance. Solvent extraction prior to immunoassay improved the agreement between methods and reduced random noise (Pearson R^2 0.96 c.f. 0.60) consistent with a water-soluble interference in the direct immunoassay. The magnitude of this interference did not obviously correlate with markers of kidney or liver function. As previously observed, blood cortisol concentrations were often increased and provided prognostic information in terms of overall 28-day mortality in this patient group with 44% of patients with serum cortisol >744nmol/l dying compared to 11% of patients in the low cortisol group ($P = 0.005$ log-rank test for difference in survival curves). Raised cortisol concentration may contribute to the paradoxical suppression of RAAS prevalent in this patient group due to cross-talk at the mineralocorticoid receptor;

however no obvious negative correlation between circulating cortisol and aldosterone was apparent.
Conclusions
This study does not support the hypothesis that SARS-CoV-2 infection leads to aldosterone excess
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P136

Glucocorticoid receptor activation regulates cardiomyocyte cell cycle in neonates

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In neonates, cardiomyocytes exit the cell cycle thus establishing cardiomyocyte number for life. Further growth is through hypertrophy. Factors that advance the timing of the switch from hyperplastic to hypertrophic growth may increase risk of cardiac disease in adulthood. Early life administration of glucocorticoids is known to increase risk of cardiovascular disease. We hypothesized that dexamethasone, a synthetic glucocorticoid, causes precocious cell cycle exit of neonatal mouse cardiomyocytes. The Fluorescent Ubiquination-based Cell Cycle Indicator (Fucci2a) system reports on cell cycle *in vivo*: mCherry-hCdt1 (red) and mVenus-hGem (green) are differentially degraded through the cell cycle, labelling cells in the G1/G0 and S/G2/M phases, respectively. R26Fucci2aRTg/Tg dams were crossed with rat cardiac troponin T promoter (Tnnt2)-Cre+ males to drive Cre expression in cardiomyocytes of TNT.R26Fucci2a fetuses. Neonates were treated with dexamethasone (500ug/kg, i.p.) at postnatal day (P)1, P3 or P6. After 24 hours, neonatal hearts were collagenase digested and the number of mCherry vs mVenus positive cells was quantified by flow cytometry. Nucleation was assessed by Draq5 staining. Data are mean±SD. The proportion of mCherry+ cardiomyocytes (G1/G0) was high at all ages in vehicle treated mice and was further elevated in dexamethasone-treated neonates compared to vehicle (87.2±3.3% vs 94.1±1.3% P2, 62.4±6.1% vs 84.4±9%.0 P4, 77.0±4.4% vs 88.3±4.6% P7). The proportion of mVenus+ cardiomyocytes (S/G2/M) in vehicle-treated mice was highest at P4 (5.4±2.9%) treated mice compared to P2 (1.8±0.99%) and P7 (2.1±0.55%). Dexamethasone reduced the proportion of mVenus+ cardiomyocyte population to negligible levels at all ages (0.12±0.11% P2, 0.18±0.11% P4, 0.006±0.011% P7) and reduced the proportion of binucleated cardiomyocytes at P4 and P7. These data suggest that dexamethasone treatment in early life may cause early cell cycle exit in cardiomyocytes, with a lifelong associated reduction in cardiomyocyte number.
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P137

Classic and 11-oxygenated androgens in serum and saliva across adulthood and the menstrual cycle – a mass spectrometry-based cross-sectional study

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Background
The gonads are the major source of classic androgens during reproductive years. Additionally, the adrenal gland produces precursors for both classic and 11-oxygenated androgen biosynthesis, with androgen activation predominantly occurring in peripheral target tissues of androgen action. We used liquid chromatography-tandem mass spectrometry to profile classic and 11-oxygenated androgens in serum and saliva across the adult age range and assessed diurnal as well as menstrual cycle-dependent variation.
Methods
We collected morning serum samples from 294 healthy volunteers (126 men, 22-95 years; 168 women, 21-91 years, 91 post- and 77 premenopausal, 16 on combined oral contraceptives, COCP). Morning saliva was collected by 83 healthy volunteers (51w, 32m); 26 volunteers (13w, 13m) also collected a 7-timepoint diurnal saliva profile and 12 women collected diurnal profiles during both follicular and luteal phase as well as morning saliva on 7 consecutive days during the follicular and luteal phase, respectively. Samples were profiled by liquid chromatography-tandem mass spectrometry (serum: 25 steroids; saliva: 6 steroids).
Results
In serum, classic androgen pathway steroids (DHEA, DHEAS, androstenedione, testosterone, dihydrotestosterone) decreased with age in both men and women. By contrast, serum 11-hydroxyandrostenedione and 11-ketotestosterone remained constant with age. Of note, in both sexes 11-ketoandrostenedione decreased with age and 11-hydroxytestosterone increased, in keeping with altered peripheral metabolism due to an age-dependent increase in HSD11B1 activity. Women on COCP had lower androstenedione, testosterone and 11-ketotestosterone concentrations. In saliva, classic and 11-oxygenated androgens showed a clear diurnal pattern in men and in the follicular phase in women, but only 11-oxygenated androgens showed luteal phase diurnal variation. Classic androgens were higher in the luteal phase while 11-oxygenated androgens remained unchanged across the menstrual cycle.
Conclusions
11-oxygenated androgens form a stable pool during adulthood while classic androgens decline with age and are subject to menstrual cycle-dependent variation.
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P138

Impact of COVID-19 on patients with primary adrenal insufficiency: a cross-sectional study

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Background
Primary adrenal insufficiency (PAI) predisposes patients to infections, which can precipitate life-threatening adrenal crises. PAI patients are thought to be particularly vulnerable to COVID-19; however, little is known about its true impact on this group.
Aim
To assess morbidity and health promotion attitudes during the COVID-19 pandemic amongst a large cohort of PAI patients.
Methods
In May 2020 COVID-19 information, including advice on strict social distancing and sick-day rules, was distributed to all PAI patients under a large secondary and tertiary centre. A semi-structured telephone questionnaire was used to survey these patients through January-April 2021. Data were analysed using Mann-Whitney and Fisher tests.
Results
Of 256 contacted patients, 162 responded (82 with Addison's disease, AD; 80 with congenital adrenal hyperplasia, CAH). AD patients were significantly older (median 51 vs. 39 years) with more comorbidities (Charlson comorbidity index ≥ 2 in 47.6% vs. 10.0%), including autoimmune disorders (42.7% vs. 10.0%) (all $P < 0.05$). 47 patients (29.0%) had suspected/confirmed COVID-19, the second most common cause of sick-day dosing during the pandemic. 15 patients (9.3%) had confirmed COVID-19, a prevalence similar to the general population. 17 patients reported 18 adrenal crises, and COVID-19 was the leading precipitant (4 cases). CAH patients had a higher risk of suspected/confirmed COVID-19 than AD patients (68.1% vs. 31.9%), were less likely to have had/be planning to have the COVID-19 vaccine (80.0% vs. 96.3%), and were less likely to have undergone hydrocortisone self-injection training (80.0% vs. 91.5%) or wear medical jewellery (36.3% vs. 64.6%) (all $P < 0.05$).
Conclusions
PAI patients provided with COVID-19 guidance suffered similar infection rates to the general population. However, COVID-19 was a principal trigger for adrenal crises and sick-day dosing. Despite carrying a higher risk of COVID-19 than AD patients, CAH patients showed less engagement with health promotion strategies.
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P139

The ULTRADIAN consortium - Ambulatory *in vivo* micro dialysis in primary adrenal insufficiency, preliminary data

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Patients on long term glucocorticoid replacement therapy have higher rates of morbidity and mortality. One causative factor may be non-physiological cortisol replacement. We have developed as part of the ULTRADIAN consortium (https://www.uib.no/en/ultradian) the U-RHYTHM, an ambulatory bio-sampling device that can collect clinical samples using *in-vivo* microdialysis every 20 minutes over the 24hour day whilst individuals continue with their normal everyday activities. We sampled 46 patients with a confirmed diagnosis of primary adrenal insufficiency (Addison's) on hydrocortisone ($n = 31$), cortisone acetate ($n = 9$), Plenadren ($n = 5$) and continuous subcutaneous pump treatment ($n = 1$). Here we present examples of the individual dynamic cortisol and cortisone profiles in these patients compared to the data from $n = 223$ healthy volunteers using a toolkit of mathematical techniques that extract information from fluctuating hormone levels. We identified significant deviations in the timing, magnitude of glucocorticoid dynamics, and a range of detectable adrenal steroids in all Addisons patients. The observed variability was present regardless of glucocorticoid replacement type, further reinforcing that current treatment options do not mimic normal physiology. This knowledge will allow for the development of replacement therapies that more closely mimic normal physiology and may be personalised according to age, sex, body mass index, chronotype.

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P140

Should the 1 mg -overnight dexamethasone suppression test be repeated in patients with benign adrenal incidentalomas and no overt hormone excess?

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Background
Benign adrenal incidentalomas (AI) are found in 3-5% of adults. All patients should undergo a 1 mg -overnight dexamethasone suppression test (1 mg -DST) to exclude cortisol excess (non-functioning adrenal tumours, NFAT; serum cortisol ≤ 50 nmol/l) or diagnose possible mild autonomous cortisol secretion (MACS; serum cortisol > 50 nmol/l). Current guidelines discourage repeating hormonal work-up in patients with benign AI. However, data underpinning this recommendation are scarce.
Aim
To determine the proportion of AI patients who develop incident changes in 1 mg -DST results.
Methods
Retrospective single-centre study including benign AI cases with no clinical evidence of steroid excess and at least one 1 mg -DST repeated during follow-up. Patients treated with glucocorticoids or strong CYP3A4 inducers were excluded. Mann Whitney and Fisher tests were used for statistical analysis.
Results
177 patients were included (median follow-up 21 months [range 2-44]). At baseline, 99 patients were classified as NFAT; 22 (22%) developed an abnormal 1 mg -DST during follow-up. Patients converting from NFAT to MACS had higher 1 mg -DST results at baseline (median cortisol 42 nmol/l [IQR 37-46] vs. 33 nmol/l [26-40], $P < 0.001$), lower DHEAS at baseline (median 1.4 µmol/l [0.8-2.1] vs. 2.2 [1.0-4.3], $P = 0.046$), and lower DHEAS during follow-up than patients who remained classified as NFAT. At baseline, 78 patients were classified as MACS; 14 (18%) developed a normal 1 mg -DST during follow-up. Patients converting from MACS to NFAT had smaller adrenal tumours (median diameter 20 mm [12-26] vs. 28 [22-34]), higher baseline ACTH (median 18.8 ng/l [12.5-23.5] vs. 5.3 [2.5-10.9], $P < 0.001$), higher baseline DHEAS (median 2.9 µmol/l [1.9-3.2] vs. 1.0 [0.6-1.9], $P = 0.010$), and higher ACTH and DHEAS during follow-up than patients with persistently abnormal 1 mg -DST.
Conclusions
20% of patients with benign AI changed their functional status during follow-up. 1 mg -DST repetition may therefore be warranted and tumour size, 1 mg -DST, ACTH, and DHEAS results can guide this decision.

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P141

Auditing Adrenal Vein Sampling for Primary Aldosteronism to highlight existing challenges

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Introduction
Clinical Practice Guidelines[1] advocate adrenal vein sampling (AVS) to distinguish between unilateral and bilateral primary aldosteronism (PA). Cannulating the right adrenal vein is difficult, and there is a lack of standardisation in sampling procedure and interpretation[2]. We audited our local service to identify improvements.
Methods
All AVS procedures performed between January 2018-December 2020 ($n = 31$) were reviewed. Data on screening using aldosterone:renin ratios (ARR), saline infusion confirmatory testing, imaging, AVS results and treatment decisions were reviewed against local and literature criteria[1-2].
Results
Elevated ARR (> 30pmol/mU) was the indication for AVS in 19 patients. 9/19 had persistent hypokalaemia (< 3.5 mmol/l). A positive (> 280pmol/l), intermediate (191–280pmol/l) and negative (< 140pmol/l) aldosterone result post-saline infusion was observed in 47.4, 15.8 and 5.3% of patients, respectively. 31.6% had no confirmatory testing data. One patient declined AVS, and the remainder had sequential sampling for cortisol and aldosterone without ACTH stimulation. 25 PA-AVS procedures were performed (6/19 patients had repeat sampling). A selectivity index of $>3{:}1$, $>2{:}1$, and $< 2{:}1$ defined successful, probable and failed catheterisation[2]; 40% PA-AVS procedures were successful, 40% probably successful and 20% failed. A lateralisation index of $>2{:}1$ was considered significant[2] with contralateral suppression providing additional assurance. Successful catheterisation and concordance between biochemistry, imaging and treatment decisions was achieved in 27.8% of PA-AVS patients. PET-CT Metomidate was a useful adjunct for treatment decisions in 27.8% patients with either failed or unclear AVS results. Otherwise, treatment decisions were based on imaging/clinical factors alone. Treatment involved adrenalectomy in 57.9% of patients (3 right, 8 left) and medical management in the remaining 42.1% (2 may be surgical candidates).
Conclusions
Difficulties in catheterisation and complexities in interpreting results limit the utility of AVS in reliably informing PA treatment decisions. Improvements in biochemical reporting may help. Emerging tests like Metomidate scans and steroid profiling warrant further investigation[3].

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P142

Clinical prediction scores in primary aldosteronism reliably identify a subset of patients with bilateral disease avoiding the need for adrenal venous sampling

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Introduction
Primary aldosteronism (PA) is both the most common form of secondary hypertension and a high-risk subset associated with increased cardiovascular, cerebrovascular and renal morbidity compared to essential hypertension. Unilateral PA is amenable to surgery, biochemical cure and reversal of this excess risk; whilst bilateral disease is best treated through mechanism-directed medical therapy. Currently, PA subtype classification relies on adrenal venous sampling (AVS); an expensive, invasive, and technically demanding procedure to which access is limited. Several clinical scores have been developed to predict PA subtype using standard clinical investigations. These systems were predominantly developed to predict unilateral PA and have not been widely tested outside their original cohorts. In this study, we evaluated the performance of six such systems in predicting bilateral disease with the aim of identifying patients in whom AVS could be avoided.
Methods
Retrospective analysis, in a single tertiary referral centre, of 230 adult PA patients with subtype confirmed via AVS (bilateral) or postoperative biochemical cure (unilateral). Predicted lateralisation was calculated from six published scoring systems and compared to confirmed subtype.
Results
119 (51.7%) of patients had bilateral disease. Four scoring systems achieved specificity for bilateral disease exceeding 95%.
Conclusions
Three clinical scores correctly identified a quarter of bilateral PA patients with a low probability (< 5%) of misclassifying those with unilateral disease. Such scores, the simplest comprising only two components, offer significant promise in patient selection and avoiding AVS in those with a very low likelihood of unilateral disease.

Score:	Components:	Specificity *[95% CI]*	Sensitivity *[95% CI]*
Kamemura 2017	CT, K, Gender, ARR	1 *[0.97, 1]*	0.03 *[0.01, 0.08]*
Kobayashi 2018	CT, K, Gender, ARR, PAC	0.97 *[0.92, 0.99]*	0.25 *[0.17, 0.33]*
Küpers 2012	CT, K, eGFR	0.98 *[0.94, 1]*	0.24 *[0.16, 0.32]*
Umakoshi 2018	CT, K	0.96 *[0.91, 0.99]*	0.27 *[0.19, 0.36]*

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P143

An unusual presentation of bilateral adrenal haemorrhage/ infarction and adrenal insufficiency associated with Astrazeneca COVID-19 vaccine

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Bilateral adrenal haemorrhage is an uncommon but life-threatening condition which may result from trauma, sepsis, coagulopathy, underlying tumour or autoimmune conditions. We present a 62-year-old female with a history of well controlled hypertension and asthma who was admitted with sudden onset epigastric pain and suspected cholecystitis. She received her first dose of Astrazeneca (AZ) Covid-19 vaccine seven days prior to onset of symptoms. Her systolic blood pressure was more than 200mmHg initially, which normalized on day three of admission and amlodipine was discontinued. There were no clinical features of Cushing's syndrome, phaeochromocytoma or skin hyperpigmentation. Investigations revealed normal full blood count. Abdominal ultrasound and subsequent MRCP identified no pathology. CT abdomen revealed bilateral adrenal oedema suggestive of haemorrhage/infarction. Vasculitis and autoantibody screen was normal. Both 9am and random cortisol were < 100nmol/l, consistent with adrenal insufficiency. Given that her symptoms had resolved, she was discharged on oral steroid replacement with urgent endocrine outpatient follow-up. A short synacthen test after holding fluticasone inhaler (four weeks later) confirmed adrenal insufficiency with a peak cortisol of 59nmol/l (>500). Significantly elevated basal ACTH, raised renin activity and undetectable aldosterone, adrenal androgens, 17-hydroxyprogesterone, plasma metadrenaline and 3-methoxytyramine confirmed primary adrenal failure. Plasma normetadrenaline was normal. Interval CT adrenal at three months showed resolution of adrenal haemorrhage and patient is stable on glucocorticoid and mineralocorticoid replacement. Spontaneous bilateral adrenal haemorrhage is rare and secondary causes must be excluded. We postulate that this may be a rare complication of the AZ Covid-19 vaccine, which has been associated with thromboembolic phenomena. Up to 12 cases of adrenal infarction, haemorrhage and thrombosis linked to AZ vaccine have been reported to UK's yellow card scheme over the last six months. Clinicians should have high index of suspicion to diagnose such a rare but potentially life-threatening complication.

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P144

An analysis of full blood count parameters in a cohort of patients with classical congenital adrenal hyperplasia

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Background
Hyperandrogenism in congenital adrenal hyperplasia (CAH) is associated with virilisation in female patients and subfertility in both male and female patients. However, little is known regarding the association of hyperandrogenaemia with polycythaemia. We evaluate the association between the adrenal hormone profile and haematocrit (HCT)/haemoglobin (Hb) in a cohort of patients with classical CAH.
Methods
Single centre retrospective analysis of paired samples for full blood count and adrenal hormones from 38 patients with classical CAH taken at routine clinic follow up appointments between 2018 and 2021. Seven patients were excluded (3 receiving exogenous testosterone, 4 missing samples). One individual suspected of having primary polycythaemia was also excluded, leaving 30 for analysis (12M, 18F; age 18-62 years).
Results
Median values for males and females respectively were: Hb 152g/l, 143g/l; HCT 0.465, 0.429; total testosterone 11.6nmol/l, 1.4nmol/l; 17-hydroxyprogesterone (17OHP) 81.15nmol/l, 51.2nmol/l; androstenedione 14.3nmol/l, 6.9nmol/l. One male and one female had HCT above the reference range (0.52 and 0.48 for males and females, respectively). In males, there was no relationship between testosterone and Hb/HCT, but there was a positive correlation between androstenedione and HCT ($rho = 0.68$, $P < 0.05$). There was also an association between 17-hydroxyprogesterone (17OHP) and HCT ($rho = 0.73$, $P < 0.01$). No significant correlations were found between testosterone, androstenedione or 17OHP and Hb or HCT in women. HCT/Hb were not associated with smoking status or urea.
Conclusions
We have found an association between adrenal androgens and HCT in male patients with CAH but not in females. Male patients with androgen excess may be more difficult to identify clinically than female patients, who typically develop symptoms. This preliminary data suggests a need for further, larger studies, examining the association between CAH, erythrocytosis and potential morbidity.

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P145

A case of immunoglobulin interference in an Adrenocorticotropic hormone immunoassay

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A 56-year-old woman presented with progressive swelling of her face and fatigability. Investigating for Cushing's, her 24-hour Urine Free Cortisol was negative at 43 and

70nmol/24hr (Reference interval or R.I. < 146 nmol/24hr) with overnight dexamethasone suppression test showing full suppression of cortisol to 34nmol/l. Her short synacthen test was normal at 30-minute cortisol of 753nmol/l (R.I. > 420); on Zumenon. Other pituitary function tests were unremarkable but plasma ACTH was > 1000ng/l on 3 occasions (Siemens® Immulite assay; R.I. 7.1-56.3ng/l) and did not suppress with dexamethasone. Given the discordance between the ACTH and cortisol results the ACTH sample was reanalyzed using a different method (Roche®). The results were strikingly different with values of 8 and < 3ng/l (R.I. < 50 ng/l) pre and post dexamethasone compared to 1214 and 1075ng/l using the Siemens assay. ACTH recovery following polyethylene glycol (PEG) precipitation (Smith et al J Clin Endocrinol Metab. 2002;87(12):5410–5415) was low (< 1%) compared to two control patients with plasma [ACTH] of 1044 and 377ng/l (66.5% and 67.7% PEG recoveries). These findings are consistent with immunoglobulin interference affecting the Immulite assay. Notably the apparent ACTH concentration increased following 1:1 dilution of sample with saline (164% compared to 96 and 85% in control samples) which is typical, although not diagnostic of a 'macro-hormone' interference (Imunoglobulin:ACTH complex). Gel filtration chromatography of patient's plasma confirmed the presence of a high molecular mass ACTH immunoreactive species co-eluting with the immunoglobulin fraction, that was absent from a control plasma. Given the reliance on ACTH assays to provide a differential diagnosis of Cushing's syndrome, awareness of this type of assay interference and use of relatively simple laboratory methods investigations such as method comparison and PEG precipitation to confirm, will prevent misdiagnosis and unnecessary investigations.

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P146

Co-syntropin stimulation test (CST) usage for the assessment of adrenal insufficiency (AI) - is less more?

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Aim
In light of recent publications - could a lower cortisol cut off value of ~350 nmol/l be used to safely rule out adrenal insufficiency (AI) compared to current local guideline cutoff value of either a baseline or 9am cortisol of 420 nmol/l? If so could this potentially help reduce the number of Co-syntropin stimulation tests (CST) performed?
Background
Current local guidelines recommend a cortisol cut value of 420 nmol/l to rule out adrenal insufficiency. If values are lower than this cut off then a CST is recommended if adrenal insufficiency is suspected. A recent retrospective study ($n = 393$) has shown that using a baseline cortisol level of > 354 nmol/l as a cut off is 100% sensitive in ruling out AI whilst other studies have even suggested a lower cut off.
Methods
Retrospective review of medical records of all CSTs performed as a day case over a period of 12 months.
Results
Based on logistic regression on the data from 106 patients, we have NOT identified a lower safe cut off. The statistically lowest cortisol value with 100% specificity of ruling out adrenal insufficiency was 325nmol/l (error range of 325 to 357 nmol/l).
Limitations
All tests were done as outpatients and therefore should not be applied to the inpatient setting. No distinction was made between primary and secondary adrenal insufficiency in our review.
Conclusions
Our data supports published data giving local validity to a cortisol cut off of ~350 nmol/l in outpatients for ruling out adrenal insufficiency.

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P147

Autonomous cortisol secretion (ACS) in other overt functioning adrenal adenoma: two case reports

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Incidentally discovered adrenal masses on abdominal imaging for unrelated reasons have a prevalence of 1-7%. A great majority of these are non-functioning adenomas, but 5-30% are associated with autonomous cortisol secretion (ACS), which is mainly subclinical, and 1-5% with phaeochromocytoma or Conn's syndrome. Here we report two cases of overt functioning adrenal adenoma with coexisting ACS. We could not find any other reports of such cases in the literature.
Case 1
A 38-year lady presenting with pain abdomen, hot flushes and palpitations. Her blood pressure was 133/88 mmHg. CT abdomen showed a well-circumscribed large left adrenal solid mass (74x63x62mm) with cystic components. Her 24hr-urine metadrenaline (5.25 micromol/24h (NR:0-1.2)) and normetadrenaline (140 micro-mol/24hr (NR:0-3.3)) were high; genetic test was negative. Her cortisol was not suppressed on overnight dexamethasone suppression test (360nmol/l), and low-dose dexamethasone suppression test (315nmol/l)); her aldosterone-renin ratio was normal. Of note, she did not have diabetes, or Cushingoid features. She had left adrenalectomy with peri- and post-operative steroid support. Histopathology confirmed phaeochro-mocytoma with low proliferation index. She failed the short-synacthen test at two weeks (30-min cortisol: 295nmol/l), but passed it two months later.
Case 2
A 55-year man with hypertension and hypokalaemia with a high aldosterone-renin ratio (530 pmol/l, < 0.2 nmol/l/hr) – off Ramipril and normal potassium – suggesting Conn's syndrome. His 24-hour urine cortisol was high (244 nmol/24hr), and serum cortisol (82 nmol/l) was not suppressed on low-dose dexamethasone suppression test; 24hr-urine metanephrines were normal. He had no Cushingoid features or diabetes. CT abdomen showed a 2.5 cm left adrenal adenoma (< 10HF units) and normal right adrenal. He is awaiting surgery. These two very rare cases show the need for looking for autonomous cortisol secretion in other overt functioning adrenal adenoma as the former would need peri- and postoperative stress glucocorticoid support.

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P148

Service Evaluation of Cortisol Testing for Adrenal Insufficiency in NHS GG&C Clyde Sector

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Introduction
Short Synacthen Tests (SSTs) are the gold standard for diagnosis of Adrenal Insufficiency. An early morning cortisol may be an acceptable alternative. We wished to establish current local practice in testing and what lessons could be learned. Clyde uses the Architect Cortisol Assay – adequate response taken as post-Synacthen cortisol of ≥430nmol/l.
Methods
We aimed to gather data on ≥100 SSTs and this took 11 weeks (20/05/19 - 04/08/19). We performed a retrospective analysis on these cases.
Results
- A serum cortisol level alone was measured in 122 patients, 23 had a cortisol level followed by a SST and 78 had a SST only.
- Five patients were newly diagnosed with Adrenal Insufficiency.
- 80 patients had a cortisol level < 430nmol/l but no further action was taken.
- Eight patients with a cortisol level ≥ 430nmol/l proceeded to SST.
- 79% (56) of random cortisol levels taken 10:00-03:59 were < 430nmol/l, compared to 51% (39) of early morning samples taken 04:00-09:59.
- 12 patients had cortisol testing without withholding corticosteroid treatment.
- All patients with a pre-Synacthen cortisol of ≥336nmol/l mounted a satisfactory response to Synacthen.

Conclusions
Random cortisol levels are frequently used in our hospitals to test for Adrenal Insufficiency. Our results reveal wide variation in use and interpretation. This may be due to a variety of factors including unfamiliarity, the variety of guidelines and assays staff have used in other institutions, and clinical judgement. A random cortisol is easier to perform than SSTs; we suspect that the tests were performed at a lower threshold of suspicion which may affect interpretation.
Based on these results we would recommend:
1. Avoid checking random cortisol levels outwith 04:00-10:00 (unless suspicious of acute adrenal crisis).
2. Withhold exogenous corticosteroid before testing.

3. For inpatients : check early morning cortisol and if < 336nmol/l proceed to SST. For outpatients : proceed straight to SST.

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P149

Atheromatous unilateral renal artery stenosis presenting as pheochromocytoma mimic

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A 63 year old man was admitted with headache, nausea, vomiting and BP of 247/155 mmHg. He had a 4 month history of headache. Past medical history of depression, back pain and 40 pack year smoking history. There was no history of chest pain, palpitation or neurological disturbance. ECG: sinus rhythm, Rate 110, LVH. Cholesterol 6.1 mmol/l. Creatinine 118umol/l. CT head unremarkable. He was commenced on amlodipine. Tramadol and pregabalin were stopped due to possible serotonin syndrome. Sertraline continued in view of ongoing depression. He was alpha-blocked with doxazosin and subsequently beta-blocked with propranolol. Due to severe and labile blood pressure, inpatient MRI adrenals and MRA renal arteries performed. This showed proximal stenosis/thrombosis of the left renal artery with patent accessory artery to left superior pole. Atheromatous disease of the aorta and some atrophy of the left kidney. Normal appearance of adrenal glands. He was discharged on day 7 after stabilisation of blood pressure. Plasma metanephrines (taken within 24 hours of admission): Normetanephrine 1779 pmol/l (0- 1180), metanephrine 282pmol/l (0-510). Aldosterone 764pmol/l and renin 17.1nmol/l/h. In renal artery stenosis, excess renin is secreted by ischaemic kidney. Repeat OPD plasma metanephrines after stopping sertraline for 2 weeks within normal range (normetanephrine 859 pmol/l). Vascular MDT: For medical management with atorvastatin and clopidogrel. Average BP 123/79 mmHg on outpatient 48 hour monitoring. Renal function stable. Follow up with renal physicians for medical optimisation.

Conclusions

2014 Endocrine society guidelines recommend CT as initial imaging for suspected pheochromocytoma. Renovascular hypertension is a common cause of secondary hypertension. In patients presenting with severe hypertensive crisis, inpatient MRA renal arteries/MRI adrenals may be a more appropriate form of imaging. This patient had significant risk factors for atherosclerotic disease. Polypharmacy may have contributed to patient's initial presentation.

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P150

Crescendo renal failure: an unusual presentation of Addison's disease

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The non-specific symptoms of Addison's disease may be attributed to other conditions with consequent delay in diagnosis. We describe such a case of novel presentation. A 61 year old female presented with a one-day history of vomiting, abdominal pain and 15kg weight loss over 6 months. PMH: hypertension of 15 years duration, chronic kidney disease (CKD3) for 7 years and hysterectomy for endometrial carcinoma 8 years earlier. Examination: dehydrated, sinus tachycardia 110 bpm, blood pressure supine 60/unrecordable mmHg. Investigations. Sodium 124 mmol/l, potassium 7.4 mmol/l, urea 35 mmol/l, creatinine 713 mmol/l, eGFR 5 ml/min (CKD 5), pH 7.2 and bicarbonate 14 mmol/l. Initial diagnosis was septic shock with acute on chronic renal failure. CT imaging, in view of previous malignancy, confirmed metastatic infiltration of adrenal glands. A cortisol level of 136 nmol/l supported a diagnosis of Addisonian crisis (confirmed by ACTH 1573.0 ng/l and Short Synacthen test cortisol: 0min 234, 30min 345, 60min 250 nmol/l). Previous records revealed admissions 8, 6 and 3 weeks previously with worsening hypotension and deteriorating renal function despite treatment with amlodipine, atenolol and doxazosin being stopped on the second admission. Treatment with IV hydrocortisone followed by oral hydrocortisone and fludrocortisone resulted in rapid clinical and biochemical improvement with renal function returning to baseline CKD 3. She died of metastatic disease 3 months later. Whilst anorexia, vomiting, weight loss, skin pigmentation and similar biochemical abnormalities occur in Addison's disease and renal failure, hypotension and dehydration are uncommon in the latter. That the progressive renal failure in this case was due to dehydration and hypotension consequent to progressive loss of adrenal function was confirmed by its reversal on treatment with hydrocortisone and fludrocortisone. We advocate assay of cortisol in cases of hypotension even when aetiology is apparently defined.

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P151

Iatrogenic Cushing's syndrome due to betamethasone nasal drops

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Introduction

Iatrogenic Cushing's syndrome (ICS) can be caused by virtually all forms of steroid treatment with or without suppression of hypothalamic–pituitary–adrenal (HPA) axis. Here we report betamethasone nasal drops used as treatment post septorhinoplasty as a cause of iatrogenic Cushing's syndrome.

Case

A 36 years old female with background history of depression presented to endocrinology clinic for evaluation of progressive weight gain. She gained total of 12 kg over the course of 3 months following septorhinoplasty. During this period, she had been using betamethasone nasal drops, 3 drops each nostril 3 times daily. Physical examination revealed a cushingoid face, stretch marks and skin bruises without any evidence of proximal myopathy. Further work-up revealed low levels of basal adrenocorticotropic hormone (ACTH) of 7.1 ng/l, low DHEA Sulphate of 0.4 umol/l [NR 1.9 to 9.4] and very low morning cortisol of 63 nmol/l confirming the clinical diagnosis of iatrogenic Cushing syndrome. She was advised to stop her betamethasone nasal drops and was provided with prescription of tapering dose of oral prednisolone to avoid abrupt withdrawal of glucocorticoids that may evoke an adrenal crisis. Two months later, her HPA axis fully recovered with pre-prednisolone morning cortisol of 283 nmol/l and normal ACTH of 24.9 ng/l. She continued to lose weight and remained well during follow up without any need for further glucocorticoid therapy.

Conclusions

Any form of exogenous corticosteroids can result in Cushing's syndrome if taken for prolonged periods. Betamethasone is an enantiomer of dexamethasone, so 1ml of these drops (the daily dose the patient took) would be the equivalent of 1 mg of dexamethasone. This case illustrates the ability of nasal corticosteroid drops to cause florid Cushing's syndrome and prescribing clinicians should be made aware.

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P152

The diagnostic and management conundrum of an unusual case of hypertension in pregnancy

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The four major hypertensive disorders in pregnancy are preeclampsia/eclampsia/HELLP syndrome, gestational hypertension, chronic hypertension and pre-eclampsia superimposed on chronic hypertension. The prevalence of hypertension in pregnancy has been reported to be around 6%. The commonest aetiology was found to be gestational hypertension which made up 40% of all cases. To our knowledge, secondary causes of hypertension in pregnancy has never been well described. We present a 20 year old gravid

patient who initially presented with an incidentally raised blood pressure of 147/79mmHg at 13 weeks of gestation. She had a previous miscarriage the year before at 16 weeks and her blood pressure readings during said gestation had been normal. She was coincidentally found to have hypokalemia with a reading of 2.3 mmol/l and metabolic alkalosis with a pH of 7.514 and a bicarbonate level of 34.1 mmol/l. She was admitted to the ward and required multiple IV potassium replacements and high dose oral potassium supplements before her potassium levels reached a stable level. During her admission her blood pressure remained elevated and had been difficult to control, with the highest reading at 164/116mmHg. She was started on oral methyldopa and required multiple dose titrations. Her plasma aldosterone level was found elevated at 4030pmol/l and her renin level was at the low end of normal with a reading of 1.4nmol/l. Radiological investigation revealed an 8mm adenoma at her left adrenal. A provisional diagnosis of hyperaldosteronism was made and she was subsequently started on Eprenolone and her methyldopa was switched to labetalol. Her hypokalemia and hypertension thereafter remained well controlled. As she was currently in her second trimester of her pregnancy, it was elected that further interventions were to be carried out post partum. This case highlights the rare occurrence of primary hyperaldoseteronism in pregnancy and the complexity in managing such cases.

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P153

Successful spontaneous pregnancy after transphenoidal surgery and bilateral adrenalectomy for Cushing's disease: A case report

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Introduction
Cushing's syndrome can impair the gonadotrophic axis in women of child bearing age if left untreated. Furthermore undergoing endoscopic transphenoidal surgery can render patients hypogonadal, thereby reducing the chances of spontaneous conception. In such cases, pregnancy is usually achieved by assisted contraceptive techniques. We present a case of spontaneous pregnancy following transphenoidal surgery and bilateral adrenalectomy.
Case
A 28 year old lady was referred to the joint antenatal endocrine clinic at 13 weeks gestation. She was initially diagnosed with Cushing's disease three years prior and underwent transphenoidal resection of a 5mm right sided pituitary tumour. Biochemically she went into remission for approximately 12 months however she suffered a recurrence of Cushing's syndrome and subsequently underwent laparoscopic bilateral adrenalectomy. Post operatively there was evidence of complete cure with unrecordable cortisol levels. She was maintained on a daily dose of hydrocortisone, fludrocortisone and levothyroxine. Following her operation she experienced somewhat irregular but heavy periods and spontaneously became pregnant 15 months thereafter. Through the course of her pregnancy, her dose of hydrocortisone, fludrocortisone levothyroxine were increased. She did suffer mild adrenal crises at eight weeks and 34 weeks gestation. She developed Gestational diabetes at 26 weeks and was managed with metformin and insulin. From the obstetric point of view, there were no major concerns regarding foetal growth. At 37 weeks gestation she underwent induction, receiving Betamethasone prior, to aid foetal lung maturation. She delivered a healthy male infant via caesarean section and was managed with intrapartum intravenous hydrocortisone.
Conclusions
The patient reverted to her original medication post partum and no complications were experienced during the intra and postpartum period. The patient was unable to breastfeed following delivery due to lack of milk expression. Our case adds to the limited number of patients who have achieved spontaneous pregnancy following transphenoidal surgery for pituitary disease.

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P154

Retrospective analysis of the screening for primary hyperaldosteronism (PHA) - are we doing enough beyond screening?

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Background
Primary hyperaldosteronism (PHA) is characterised by inappropriately high aldosterone production, most commonly caused by unilateral/bilateral adrenal adenoma or bilateral adrenal hyperplasia. It usually manifest as hypertension and/or hypokalaemia. There is emerging evidence to support the prevalence of PHA in more than 10% in hypertensive patients but only a minority will have a confirmed diagnosis and receive specific treatment.
Aim
To process map our patients suspected to have PHA on the initial screening test.
Methods
Retrospective analysis of 149 patients, who underwent screening for suspected PHA.
Results
149 patients (48% male and 52% females) with youngest aged 17 and the oldest aged 89 years. 53% were screened for secondary hypertension; 38% for adrenal lesions. 80% had hypertension; 66% had details on antihypertensive; 39% were using single agent; 27% double agents; and 34% were using ≥ 3 agents. 98% had serum potassium available and 22% were hypokalaemic ($K+ < 4$ mmol/l). 40% had specific adrenal imaging: 61% had unilateral disease; 17% had bilateral disease; 20% had normal adrenals; and in 2% details were not available. 27% patients had aldosterone ≥ 400 pmol/l with Aldosterone Renin Ratio (ARR) of ≥ 30 consistent with PHA and 4% patients had aldosterone in the range of ≥ 250 pmol/l - 399 pmol/l with ARR of ≥ 30 where PHA could not be excluded. Only 26% of them proceeded to have saline infusion test for biochemical confirmation, 9% had adrenal venous sampling (AVS) and none underwent 11C-Metomidate PET CT.
Conclusions
Currently only minority of eligible patients proceed to confirmatory tests, AVS and 11C-Metomidate PET CT. Difficulties in biochemical interpretation with interfering medications, technical difficulty with AVS, lack of access to specialised services contribute towards treatment inertia in these patients. Discussing these patients in the adrenal MDT and having a dedicated pathway helps patient selection for appropriate treatment.

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P155

Adrenal insufficiency secondary to primary adrenal lymphoma

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Primary adrenal lymphoma is a rare cause of adrenal insufficiency, accounting for only approximately 1% of non-Hodgkin lymphoma cases. Most common subtype of PAL is diffuse large B cell lymphoma. A 71-year-old gentleman with the past history of hypertension, type 2 DM and the incidental finding of adrenal hyperplasia, presented with the general ill health with lethargy, weight loss and reduced appetite. He has the past history of hypertension, type 2 DM and the incidental finding of adrenal hyperplasia. Examinations were unremarkable apart from the signs of dehydration and postural hypotension. Initial investigations showed normocytic anaemia of Hb 70g/l, hyponatraemia with Na level of 128 mmol/l. A short synthacth test revealed adrenal insufficiency. CT scan showed bilateral adrenal haemorrhages on a background of pre-existing adrenal hyperplasia. Given the engulfing nature of the left-sided haematoma underlying lymphoma cannot be excluded. Treatment with glucocorticoid and mineralocorticoid hormone replacement therapy was started. A subsequent FDG/PET showed intensely hypermetabolic disease in both adrenal glands further soft tissue disease in the retroperitoneum and mesentery. Appearances are in keeping with an aggressive lymphoma for proliferative disorder. CT guided left adrenal mass biopsy was done which revealed high grade diffuse B-cell Non-Hodgkin lymphoma (DLBCL). R-CHOP chemotherapy was planned by consulting haematology.

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Bone and Calcium

P24

Hyperparathyroid service evaluation at the Royal Cornwall Hospital Trust from 2013 to 2021

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Introduction
Primary hyperparathyroidism affects 0.3% of the general population[1]. 90% are due to single parathyroid adenoma[1]. Surgical treatment is the only definitive cure[2]. Improvements in imaging permit radiologists to better identify parathyroid adenomas[1], enabling more targeted surgery[1], thus shortening general anaesthesia, as well as lowering post-operative complication rates. Neck ultrasound (US) and parathyroid scintigraphy (MIBI) are commonly used together for adenoma detection.[1,2] The aim of our quality improvement project was to evaluate the parathyroid service at the Royal Cornwall Hospital Trust (RCHT). We identified what imaging (US/MIBI/both) was performed, adenoma detection rate, surgical intervention and overall patient outcome.
Methods
We performed CRIS data search of patients undergoing MIBI from March 2013 to March 2021, assembling a log of all parathyroidectomies, relevant histopathological records and examining biochemistry records (PTH and calcium) pre- and post-surgery.
Results
201 parathyroid surgeries were performed over 9 years. Of 201 patients, six underwent US only, 44 underwent MIBI only, and 151 benefitted from both US and MIBI. 82 patients undergoing both US and MIBI had a concordant imaging result whilst 5 had discordant results. The remainder demonstrated an adenoma on either US (19) or MIBI (40) only. Three patients were excluded as they only had planar SPECT imaging. A combination of USS and MIBI had the highest true positive rate (87%) vs MIBI only (76%), USS only (59%). Over nine years, 422 MIBI were performed for 201 surgeries. The success rate of patients undergoing surgery was 93%. Furthermore, 64 patients who were diagnosed with primary hyperparathyroidism were aged fifty or younger. 11 patients were screened for MEN1, two of whom with subsequently confirmed diagnosis.
Conclusion
Over 75% of patients undergo US and MIBI. Discordancy was low between US and MIBI (3.3%), although less than 50% of patients who had MIBI proceeded to surgery.

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P25

Seasonal variations in circulating vitamin D appear gender dependent and may highlight a novel health inequality

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Vitamin D is a pleotropic hormone with important actions in a wide variety of cell types. Whilst its role in the endocrine control of calcium metabolism via the active circulating metabolite 1,25- dihydroxy cholecalciferol is widely appreciated, other actions in a range of cells and tissues depend on activation of circulating 25-hydroxy vitamin D by intracrine mechanisms and paracrine actions which may be locally controlled. Of particular interest are the roles of vitamin D pertaining to innate immunity, the antimicrobial response and inflammation which are the focus of considerable study and debate. Dietary sources of vitamin D are generally inadequate and most vitamin D is produced by ultraviolet B exposure of the skin which at temperate latitudes is restricted to the summer months. We aimed to study the seasonal variation of vitamin D in our local adult population (>18y) in Preston Lancashire UK by examining vitamin D requests in our laboratory database. Twelve months of anonymised requests from primary care were retrieved from December 2018 to November 2019 and stratified by month and gender. Vitamin D was requested considerably more frequently in women than men. There was a noticeable seasonal variation in both sexes with the highest values in late summer (July to September) and the lowest values in winter (January to March). Except in July and August values were higher in women. Vitamin D deficiency was more common in men than women and more pronounced in the winter months. These observations suggest a hitherto unrecognised gender related health inequality and lend further support to the use of seasonally adjusted ranges when assessing vitamin D status.

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P26

Pre-antiresorptive therapy dental screening (PADS): a successful intervention against medication related osteonecrosis of the jaws (MRONJ)

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Introduction
MRONJ is defined as exposed bone in the maxillofacial region that persists after eight weeks in patients treated with antiresorptive or anti-angiogenic drugs, without previous radiotherapy. The estimated United Kingdom incidence of MRONJ in osteoporosis patients is 0.01-0.1% (1). MRONJ can cause severe disfigurement, speech and feeding difficulties. We aim to investigate MRONJ incidence and utility of dental screening in patients receiving Zoledronate or Denosumab within the NHS Lanarkshire osteoporosis service.
Methodology
440 patients referred for PADS (2012-2018) were identified for retrospective data collection using electronic health and dental records and analysed using IBM SPSS 26.
Results
78.6% of patients had no delays in therapy commencement ($n = 346$). The median time from therapy decision to treatment administration following PADS was 110 days (23-1069 days). Delays were due to dental non-attendance 4.3% ($n = 19$), dental treatment completion (7.0% $n = 31$) and secondary care referrals (2.7 % $n = 12$). In 7.4 % ($n = 32$) of patients, antiresorptive therapy was not started due to non-attendance for dental treatment. During the follow-up period, two patients developed MRONJ. One patient was excluded as they had concurrent radiotherapy for tonsillar cancer. The incidence of MRONJ is therefore 0.002% (1 in 440) over a period of 7 years. 22.5% of the cohort were not registered with a dentist, triggering a public dental service referral. In this subset, 130 dental extractions, 52 periodontal treatments and 112 dentures manufactures were carried out.
Conclusions
NHS Lanarkshire has a high deprivation level(2) and despite 99.4% of adults being registered with an NHS dentist(3), dental treatment need is high which increases MRONJ risk. Our introduction of PADS did not delay antiresorptive treatment for most patients and triggered 294 dental treatments in patients not registered with a dentist. In conclusion, PADS has improved oral health and achieved a lower incidence of MRONJ than the national average.

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P27

An Audit into the Diagnosis and management of primary hyperparathyroidism

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Background
Primary Hyperparathyroidism is a leading cause of hypercalcaemia and is frequently asymptomatic. Due to its long-term complications, early diagnosis and management is essential. NICE published guidelines on diagnosis and management of Primary Hyperparathyroidism in May 2019. The aim of this audit was to compare our existing practices against NICE guidance.
Methods
We conducted retrospective data collection by identifying patients diagnosed with Primary Hyperparathyroidism in the Endocrinology Outpatients at Darent Valley Hospital between January 2018 and June 2019. The patients' symptoms, calcium levels, PTH levels, diagnostic tests and management were compiled into tabulated format and the relevant areas were analysed against NICE guidance to determine compliance.
Results
A total of 44 patients were identified as diagnosed with Primary Hyperparathyroidism in Endocrinology Outpatients. Of the 44 patients, renal function was checked in all 44, DEXA scan was done in 28, and renal tract ultrasound was done in 25. The compliance percentage of these practices was 100 %, 64 % and 57 % respectively. Urinary calcium excretion measurement to exclude FHH was done in 22 patients (50 %). 28 patients met the criteria for surgical referral and 23 of these were referred for surgery. 16 patients did not meet the criteria for surgery but 2 of these were referred for surgery.

Conclusion
The compliance against NICE recommendations was variable, which was expected as the audit was done to review practices prior to the guidelines. Renal function testing, symptoms review and surgical referrals were in accordance with guidelines. Urinary calcium measurement, renal imaging and DEXA scan should be incorporated into current practices.
Action Plan
FHH should be excluded in patients with suspected Primary Hyperparathyroidism by measuring urinary calcium excretion. Patients with confirmed Primary Hyperparathyroidism should have renal imaging and DEXA scans.
References
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P28

Case Report: Asymptomatic hypercalcaemia in a patient with TB re-activation

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Background
Vitamin D is important for calcium homeostasis. In granulomatous diseases including tuberculosis (TB), hypercalcaemia may be seen. Suspected mechanisms include elevated vitamin D sensitivity and increased extrarenal synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] by alveolar macrophages within granulomas. Prevalence of hypercalcaemia in TB patients vary worldwide, yet is rare in the UK. We present a case of hypercalcaemia in a patient with TB reactivation.
Case Report
Twenty-one-year-old female of African origin presented with dyspnoea, cough and weight loss. She moved to UK at the age of three. Fourteen years ago she was treated for latent TB. Chest x-ray and CT chest indicated TB reactivation while sputum culture confirmed Mycobacterium tuberculosis. She was commenced on quadruple anti-TB therapy. Additionally MRI Spine revealed impending cord compression at mid-thoracic vertebral level due to spinal TB. One month later, blood tests showed parathyroid hormone (PTH)-independent hypercalcaemia (Adjusted Calcium 2.77mmol/l, PTH $<$0.6pmol/l, 25OHD_3 115 nmol/l). We requested multiple 1,25$(OH)_2$D levels, but faced issues processing the samples. Other causes of hypercalcaemia including malignancy were excluded after thorough biochemical and radiological investigations. It was concluded that hypercalcaemia was secondary to TB. Of note, patient developed acute kidney injury (AKI). Renal biopsy confirmed drug-induced interstitial nephritis likely due to Levofloxacin and was treated with prednisolone. Despite resolution of AKI, hypercalcaemia persisted. After one month of anti-TB and prednisolone treatment, calcium levels (2.53mmol/l) normalised.
Conclusion
Granulomatous-induced hypercalcaemia can pose a diagnostic challenge and a high index of suspicion enables early detection and treatment. As well as treating the underlying cause, glucocorticoid therapy is vital to reduce intestinal calcium absorption and inhibit synthesis of 1,25(OH)2D. We wish to highlight the importance of having a high clinical suspicion for granulomatous-induced hypercalcaemia, since prevalence is rare in the UK.
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P29

Comparison of local cinacalcet prescribing trends with NICE guidelines

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Introduction
Cinacalcet is an allosteric modulator of the calcium sensing receptor which lowers parathyroid hormone (PTH) secretion. However, it is expensive and there is limited evidence of benefit in reducing complications of primary hyperparathyroidism (PHPT). In 2019 the National Institute for Health and Care Excellence (NICE) guidelines suggested that cinacalcet could be considered in individuals with PHPT if surgery has been unsuccessful or is unsuitable and if adjCa^{2+} is $\geq$2.85mmol/l with symptoms or $\geq$3.0mmol/l without symptoms.
Aims
We sought to; i) compare local cinacalcet prescribing practice to NICE guidelines and ii) perform a cost analysis of cinacalcet prescribing.
Methods
We identified all individuals prescribed cinacalcet from 2015 to 2020 from our pharmacy prescribing database and undertook an electronic case note review after excluding those prescribed cinacalcet from the renal clinic. Those starting cinacalcet prior to 2011 were excluded due to incomplete electronic records.
Results
19 patients (6 male, 13 female) were identified that were prescribed cinacalcet from the endocrinology clinic between 2015 and 2020. All had PHPT. Cinacalcet was used as bridging therapy to surgery in 3 patients, with the remainder not suitable for surgery; indeed 5 patients were deceased at the time of audit. Mean age at initiation was 72 years with a mean starting adjCa^2 of 2.91mmol/l. The mean duration of treatment was 3.3 years and mean treatment dose was 64 mg/day (range 15-240 mg/day). 36.8% (7/19) became hypocalcaemic and 47.4% (9/19) achieved an adjCa^{2+} in the lower half of the local reference range (i.e. $<$ 2.41mmol/l) suggesting possible overtreatment. Only 52.6% (10/19) of these patients met 2019 NICE criteria, with a potential cost saving of £31,133.59 over 5 years.
Discussion
This audit highlights the importance of analysing local prescribing trends and ensuring compliance with national guidelines which could lead to significant cost savings and reduced side effects such as hypocalcaemia.
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P30

Pregnancy and Lactation Associated Osteoporosis (PLO)- Case Report

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The partum period can be seen as a transient condition of "menopause" due to the physiological decline to a baseline of the high estrogens found during pregnancy, and bone metabolism is likely to alter. Moreover, high calcium requirements for fetal growth and during breastfeeding are covered in the maternal metabolism from enhanced intestinal absorption in a Calcitriol dependent pathway, and maternal bone reabsorption under control of parathyroid hormone (PTH) parathyroid-related protein (PTHrP) reportedly increased during lactation. We report a 34-years-old primiparous woman showing clinical vertebral fragility fractures that occurred shortly after childbirth while breastfeeding. Two months postpartum - in the context of lumbar pain, a spine MRI revealed recent compression fractures of T8-L2 and a 3 cm decrease of her height. She was on a restricted protein diet, with Thyroxine treatment with a gradual increase during pregnancy stopped 4 months after delivery, she received a 20 weeks period of low molecular weight heparin during pregnancy, and she had a positive history of family low bone density - with her mother on bisphosphonate treatment and her maternal grandmother - hip fracture. Secondary causes of osteoporosis were excluded, and increased bone turnover markers (betacrosslaps, alkaline phosphatase) and low bone density with a Z score of -3.6 SD in the lumbar spine and -2.1 SD total femur was found at determination. She was advised for weaning and supplement her calcium vitamin D intake. After 6 months from the first bone density test and 10 months after delivery, at her first visit to our clinic, the bone mass continues to decrease (4%), and turnover markers turned in the normal range. We proposed treatment 18 months of teriparatide - with Risendronate as possible, consolidating therapy with bisphosphonates because of his shortest persistent period.
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P31

Recombinant PTH 1-84 (Natpar) treatment in a case of refractory hypocalcaemia secondary to surgical hypoparathyroidism and malabsorption post-gastric bypass

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We report the case of a 63-year-old lady with refractory hypocalcaemia due to surgical hypoparathyroidism, decompensated by malabsorption following gastric bypass, successfully treated with recombinant human parathyroid hormone 1-84 (rhPTH), Natpar. She initially presented with medullary thyroid cancer aged 33 and was found to have MEN2A. She underwent thyroidectomy and developed post-surgical hypoparathyroidism. She was managed for over 20 years with

alfacalcidol and oral calcium supplementation. In 2015, aged 57, she underwent Roux-en-Y gastric bypass surgery. Following this, she developed malabsorption and persistent, severe symptomatic hypocalcaemia (<1.5mmol/l). She struggled to tolerate oral calcium supplements finding calcium carbonate effervescent the most tolerable. She required long duration IV calcium infusions 3 times per week, in hospital, to maintain a calcium level >1.9mmol/l, which resulted in a negative impact on her quality of life. In 2018, Teriparatide was trialled (off-licence) but failed to maintain adequate calcium levels and the patient continued to require multiple calcium infusions per week. Additionally, she subsequently developed a portacath infection, which was removed and PICC line inserted. In 2021, she commenced Natpar 50 mg/day alongside IM ergocalciferol 300,000 units every 3 months. Within 4 weeks of treatment, her IV calcium dose was reduced and over subsequent weeks, the frequency of infusions was also reduced. After increasing Natpar to 75 mg/day, she no longer required IV calcium, maintaining calcium levels >2.0mmol/l with only transient symptoms of hypocalcaemia. She is now maintained on the maximum dose (100 mg/day) and remains on IM ergocalciferol, with plans to gradually reduce the alfacalcidol dose if serum calcium remains stable. This case demonstrates the challenges of managing hypoparathyroidism following gastric bypass surgery. Of note, chronic hypoparathyroidism is currently not a contraindication to Roux-en-Y gastric bypass. It also demonstrates the benefits of rhPTH replacement over conventional therapy in complex patients with chronic hypoparathyroidism and malabsorption.

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P32

Bendroflumethiazide-induced hypocalciuria in a patient with hypercalcaemia and unsuppressed parathyroid hormone levels

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Introduction
There are reports of patients having co-existing primary hyperparathyroidism and familial hypocalciuric hypercalcaemia (FHH). The combination of relative hypocalciuria, hypercalcaemia and slightly elevated serum parathyroid hormone (PTH) could indicate FHH. Medications such as, lithium and bendroflumethiazide can reduce renal excretion of calcium. We report a case highlighting the importance of being aware of drug-induced hypocalciuria during the investigation of hypercalcaemia.
Case
A 69-year-old woman had mild tiredness for several years. Routine test revealed hypercalcaemia. She had no other symptoms. Medical history included type 2 diabetes, hypertension, atrial fibrillation and psoriasis. Medication list consisted of amlodipine, metformin, atorvastatin, digoxin, losartan, bendroflumethiazide and warfarin. She had no previous calcium levels for comparison.
Investigations and management
Her serum calcium was 2.85 mmol/l with a slightly elevated PTH of 7.3 pmol/l. Serum phosphate, magnesium, vitamin-D, renal and liver function, angiotensin-converting enzyme and electrophoresis were normal. Full blood count and erythrocyte sedimentation rate was normal. Urine protein was normal. A 24-hour urinary calcium of 1.6 mmol/24h indicated relative hypocalciuria, suggesting possible FHH. Her calculated calcium-creatinine clearance ratio (CCCR) was also low (0.0009) with serum calcium of 3.04 mmol/l. A parathyroid ultrasound was negative, but a nuclear medicine scan demonstrated increased uptake in the right thyroid lobe. Kidney ultrasound scan was normal. Bone density scan revealed slightly low levels in the hip only. On stopping the bendroflumethiazide, her CCCR increased to 0.0163 and 0.0183 (serum calcium: 2.77 mmol/l and 2.89 mmol/l, respectively). Her 24-hour urinary calcium increased to 7.5 mmol/24h. A repeat serum calcium was 2.92 mmol/l, while serum PTH fell to 4.7 pmol/l. A subsequent 4-dimensional CT scan revealed two discreet nodules suggestive of parathyroid adenomas.
Conclusion
This case report emphasizes the importance of stopping bendroflumethiazide before assessing urinary calcium excretion during the investigation of hypercalcaemia.

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P33

Severe Hypercalcemia in a Patient with Milk Alkali Syndrome

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Introduction
Hypercalcemia has a broad differential, including primary hyperparathyroidism, non-parathyroid hormone-mediated hypercalcemia, including humoral hypercalcemia of malignancy, or medication mediated. We report a case of severe hypercalcemia attributable to milk-alkali syndrome due to excessive calcium carbonate use.
Case
A 71 year-old female with a history of hypertension presented after a fall without loss of consciousness. She endorsed episodes of confusion for several days but denied any constitutional symptoms. Vitals were stable and physical exam was significant for dry mucous membranes. Labs were notable for calcium of 17.6 mg/dl, creatinine of 1.8 mg/dl (baseline 1 mg/dl), and bicarbonate of 33 mmol/l. The patient received fluids, calcitonin, and pamidronate, with normalization of her calcium level. She underwent a malignancy workup that revealed an appropriately suppressed parathyroid hormone (PTH) level, normal PTH-related peptide, serum and urine protein electrophoresis, and 1,25 hydroxyvitamin D. Malignancy workup with imaging of chest, abdomen and pelvis was unremarkable. Upon further investigation, the patient revealed that she had been taking 6 tablets of Tums, calcium citrate, and a glass of milk every day for two weeks. Her hypercalcemia was attributed to being medication-induced. The patient was discharged with recommendation to limit her calcium consumption with close outpatient follow-up.
Discussion
Milk alkali syndrome consists of a triad of hypercalcemia, alkalosis with varying degrees of renal dysfunction caused by the ingestion of large amounts of calcium and absorbable alkali. It is an often overlooked cause of hypercalcemia. Due to the availability of calcium carbonate over the counter (OTC), and lack of patient education on the ideal way of using the medication, the incidence of the milk-alkali syndrome is on the rise. It is crucial for physicians to inquire specifically about OTC drugs, medical foods, and supplements as they can lead to significant interactions and side effects.

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P34

Vitamin D deficiency and inflammation in IBD patients

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Introduction
Vitamin D is a potential immune modulator and low levels are common in inflammatory bowel disease (IBD) patients. The aim of the study was to determine the association between deficient vitamin D and inflammatory profile.
Methods
Intestinal (fecal calprotectin) and blood inflammatory profile [erythrocytes sedimentation rate (ESR), protein C reactive, fibrinogen], were performed to all patients. In addition, level of 25 hydroxy vitamin D was determined and patients were divided into deficient (25 hydroxy vitamin D <20 ng/ml), and sufficient group (25 hydroxy vitamin D >=20 ng/ml).
Results
62 patients IBD patients (median age 45 (IQR 24) years; mean age at diagnosis, 34.9 (± 14.1 SD) years and median duration of the disease, 6 (IQR 11) years) were included in this study. Mean 25 hydroxy vitamin D level was 20.9 ± 8 ng/ml SD. Deficient vitamin D level was seen in 43.5% of the patients. When compared between the two groups, protein C reactive was significantly higher in deficient group (2.14 (IQR 10.9) vs 0.8 (IQR 2.05) mg/dl, $P = 0.007$). Moreover, all inflammatory markers were higher in deficient vitamin D group, fibrinogen (309 (IQR 122) vs 299 (IQR 96) mg/dl, $P = 0.4$), (ESR 14 (IQR13) vs 9 (IQR14) mg/dl, $P = 0.6$), fecal calprotectin (100 (IQR 275) vs 30 (IQR115) mg/g, $P = 0.06$), although they did not reach statistically significance.
Conclusions
Our study showed that vitamin D deficiency is common in IBD patients. Higher inflammatory profile was found in deficient patients and vitamin D intervention studies are warranted in order to find if its correction will decrease inflammation.

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P156

Primary Cinacalcet therapy is safe and effective as alternative or bridging modality in Primary Hyperparathyroidism

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Purpose
To evaluate long-term safety and efficacy of cinacalcet in management of primary hyperparathyroidism (PHPT).
Material/Methods
We retrospectively studied all patients on cinacalcet for primary hyperparathyroidism over 3 year's period. Data was collected and analyzed for indication, daily maintenance dose, tolerability, biochemical effect at 3, 6 and 12 months, effect on bone mineral density and renal stone disease. This study excluded those who were on cinacalcet for other indications.
Results
Over 3-years period, 66 patients received cinacalcet with mean age of 76.97 $\pm$ 10.37 and females (74%). All patients met criteria for surgical treatment. 40% declined surgery due to co-morbidities and 23% due to negative localization. 20 % chose medical treatment despite specialist involvement and clear counseling. Ten patients (15 %) have been on treatment for pre-operative control due to delayed parathyroid surgery during COVID-19 pandemic. Cinacalcet was generally well tolerated with only one patient (1.5 %) discontinued treatment because of side effects. Biochemical control which was defined as maintained eucalcaemia, reduced level of PTH and normalised serum phosphate was achieved with average total daily dose 60 mg (range 30-180 mg). At second year of treatment, there was trend of improvement in bone mineral density and resolution or none worsening on pretreatment renal stone disease.
Conclusions
Overall, the study demonstrated good safety profile and biochemical efficacy of cinacalcet as primary therapy for PHPT, in predominantly elderly population with multiple co-morbidities. Interestingly there was no unfavorable long-term effect on renal and bone complications with trend towards improvement after three years of cinacalcet treatment. Cinacalcet was effective in preoperative control of significant hypercalcaemia.
Recommendation
Larger study to confirm our observation (Planned for East Yorkshire and Humber region), which if have proof positive then Cinacalcet could be considered as first line treatment modality in older patients with PHPT, and as safe bridging therapy for parathyroid surgery.

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P157

A case of familial hyperparathyroidism with an uncommon mutation

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A 29 year-old nursing student, was incidentally detected to have high serum calcium 3.43 mmol/l (2.2-2.6) whilst being treated for community acquired pneumonia. She had no symptoms of hypercalcaemia. Her uncle had been operated for primary hyperparathyroidism (PHPT) although only limited details were available. PTH of 28 pmol/l (1.6-7.2) confirmed the diagnosis of PHPT. She had vitamin D deficiency, normal liver and renal function. She was offered parathyroidectomy and preoperative neck ultrasound and radio-nuclide scan (MIBI with SPECT) were concordant for right lower parathyroid adenoma. In view of the young age, genetic tests were arranged. Analysis of all the coding regions and exon/intron boundaries of the MEN1 gene by Sanger sequencing did not reveal any pathogenic mutation. Further dosage analysis of the AIP, CDKN1B and MEN1 genes by multiplex ligation dependent probe amplification did not detect partial or whole gene deletion. During elective parathyroidectomy intraoperative PTH dropped to $<$ 50% and histology confirmed parathyroid adenoma. Over the next 4 years, she maintained normocalcaemia and normal PTH. 5 years later and 12 months after the last normal serum calcium value she presented with hypercalcaemia (3.15 mmol/l) and PTH 31.16 pmol/l confirming recurrence of PHPT. Localisation scans were concordant for left lower parathyroid adenoma. Extended genetic testing confirmed partial gene deletion of CDC73 gene which is linked to autosomal dominantly inherited PHPT, hyperparathyroidism-jaw tumour syndrome and renal lesions (cysts, renal hamartomas and rarely Wilm's tumour). After local and regional discussion, left unilateral neck exploration is planned after providing the patient with a full explanation of the decision and possibility of further neck surgery. This patient raises several interesting features about genetic testing in a patient with PHPT, complex decision making about surgical approach, CDC73 related manifestations and implications for family and off-springs.

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P158

Immobilization induced hypercalcemia

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Introduction
Immobilization hypercalcemia is uncommon condition associated with limited movements following brain and spinal cord lesions. Immobilization results in stimulation of osteoclastic bone resorption hypercalciuria and hypercalcemia.
Case report
57 year female, Background of Breast Cancer (Treated with Skin sparing mastectomy and adjuvant radiotherapy) admitted following large subdural hematoma leading to craniotomy and evacuation of hematoma. Postoperative period was complicated with pneumonia and Gastric ulcer perforation requiring laparotomy. She had prolonged Hospital stay, initially in ITU and then Neurorehabilitation unit. Six weeks following admission, she was noted to have raised Corrected calcium (2.77 mmol/l) with suppressed PTH (0.8 pmol/l). Phosphate was normal with slightly elevated alkaline phosphatase. Hypercalcemia was acute and noted following 6 weeks of immobility. Bone profile was normal on admission. Calcium levels continued to rise to reach the level of 3.03 mmol/l. She had extensive investigations in the form of imaging and tumor markers and no evidence of occult malignancy or recurrence of breast cancer was found. Vitamin D levels were adequate. Urine calcium excretion was raised (12.13 mmol/24 hour). Thyroid and adrenal functions were normal. She was not on any drugs to cause hypercalcemia. Multiple myeloma was excluded with serum and urine electrophoresis and bone marrow biopsy (No evidence of plasma cell myeloma Multiple myeloma). Diagnosis of hypercalcemia due to immobility was established and she was treated with fluid replacement and Zoledronic acid infusion. Calcium level normalized 2 days later and remained normal when mobilization commenced the following week. The patient has been followed up and there has been no evidence of recurrence of hypercalcemia.
Discussion
Albright described immobilization-associated hypercalcemia in 1941. Hypercalcemia immobilization should be accounted for in patients with immobilization and hypercalcemia. It requires extensive evaluation to rule out other more likely hypercalcemia causes. The patients with sepsis or with reduced Glomerular filtration rate are at increased risk.

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P159

Hypercalcaemia as an isolated manifestation of Sarcoid Myositis: A rare case report

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Background, case-history
Hypercalcaemia secondary to parathyroid hormone (PTH) independent mechanisms is well known, with differentials including Sarcoidosis. We describe a case of Sarcoid Myositis presenting with symptomatic hypercalcaemia (adjusted serum calcium levels of 3.12 mmol/l) but no muscle weakness in a 39-year-old lady with a background of Type 1 Diabetes Mellitus, Hyperthyroidism, and Rheumatoid Arthritis.
Investigations
Laboratory investigations comprised of suppressed PTH, vastly elevated Calcitriol (1,25-dihydroxy vitamin D) level (314pmol/l, normal 55-139pmol/l) along with normal CT scan thorax, abdomen, and pelvis. Serum calcium was refractory to fluid resuscitation and intravenous pamidronate, thus other rare differentials were considered. Full biochemical and immunological investigations revealed serum ACE levels above the detectable range ($>$148 U/l) suggestive of sarcoidosis. As chest findings and CT scan reports were unremarkable, an extrapulmonary cause of sarcoidosis was considered. Subsequently, an FDG PET CT scan showed increased muscular uptake in gluteal muscles suggestive of inflammatory myositis; heightening the suspicion of rarely reported, and often asymptomatic, Sarcoid myositis.

Results, treatment
Biopsy from the inflamed site, localized from MRI, showed prominent granulomatous inflammation typical of sarcoid myositis. Our patient was commenced on a reducing dose of steroids, which normalised adjusted serum calcium. Disease-modifying therapy included Rituximab, targeting B cells numerous within granulomas.
Conclusions
points for discussion: Granulomatous causes, especially in PTH independent cases of hypercalcaemia should be considered as a part of differential diagnosis at initial presentation and relevant laboratory workups should be incorporated in the investigative protocols. Sarcoidosis accounts for calcitriol-mediated hypercalcaemia in 49% of cases, other causes include haematological malignancy (17%) and infection (8%). Therefore, in cases of hypercalcaemia of unknown origin, calcitriol levels can help form a focused differential diagnosis. The manifestation of sarcoidosis with myositis only is rare, cases are usually accompanied by other manifestations with myopathy often being chronic and asymptomatic in 86% of patients.

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P160

An interesting case of Turner syndrome and Parathyroid Carcinoma with recurrent mild asymptomatic hypercalcemia

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Introduction
Primary parathyroid carcinoma accounts for less than 1% of the parathyroid gland tumours and almost always presents as primary hyperparathyroidism. Very few Turner syndrome patients have been reported so far to present with primary hyperparathyroidism secondary to parathyroid adenoma. We report a case of parathyroid carcinoma in a 59 years old lady with Turner syndrome who is presenting with recurrent mild hypercalcemia.
Case presentation
A 59 years old lady with Turner syndrome under the dedicated Endocrine Service for her long term surveillance. She firstly presented in 2008 with elevated calcium of 3.00 mmol/l and PTH just above the upper border of normal. Sestamibi and ultrasound parathyroid identified parathyroid adenoma in the inferior pole of the left lobe of the thyroid and given persistent hypercalcaemia she underwent parathyroidectomy. Histology revealed parathyroid adenocarcinoma and patient then underwent elective left hemithyroidectomy. Her calcium profile and PTH remained stable for 11 years but in 2019 she was found presenting with recurrent hypercalcemia with corrected calcium of 2.64 mmol/l, phosphate 1.12 mmol/l, PTH 3.0 pmol/l and vitamin D 75 mmol/l against a normal kidney functions and bone density scan. She was further investigated with US parathyroid and CT parathyroid that did not demonstrate any parathyroid adenoma. Her urinary calcium output was 7.2 mmol/24 hour with a calcium creatinine clearance ratio of 0.04. She was further discussed in parathyroid MDT and monitoring of calcium with surveillance scan was suggested. Patient remains completely asymptomatic from her hypercalcemia.
Conclusions
This is a unique case of Turner syndrome with mild hypercalcemia on the background of hemithyroidectomy for parathyroid carcinoma who remains currently asymptomatic. She continues to have biochemical and radiological monitoring.

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P161

Autoimmune Polyglandular syndrome presenting with multiple Endocrinopathies

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Background
Autoimmune polyglandular syndrome type 1 (APS-1) is an autoimmune inherited disorder, a potentially underdiagnosed clinical entity, caused by mutations in the autoimmune regulatory gene that can present with varying symptomatology as it affects various organs, posing both a diagnostic and management hurdle. We report a case to highlight this complexity.
Case report
Case details involves a female who first presented in childhood with rash, eye redness, photophobia and tenderness following MMR vaccination in childhood, treated as a mild viral inflammatory process. Months later she developed lethargy, chronic diarrhoea, abdominal discomfort which necessitated parenteral feeding. She had evidence of multiple electrolyte imbalances involving sodium, potassium and calcium first thought to be due to persisting diarrhoea. Testing confirmed a diagnosis of symptomatic hypocalcaemia secondary to hypoparathyroidism (Low Calcium, Low parathyroid hormone, Normal Vitamin D) with evidence of adrenal insufficiency low 9:00am Cortisol, suboptimal response to short synacthen test). In her late teens, she presented with amenorrhoea of 6 months duration and hot flushes. Hormone profile confirmed premature ovarian failure (FSH -166IU/l, LH-165IU/l and Oestrogen 105 pmol/l) treated with combined hormone replacement therapy. Genetic testing revealed Chromosome 13 deletion in younger brother (milder disease expression with only alopecia and hypoparathyroidism) and both parents (asymptomatic carriers). Other non-endocrine pathologies present in this case include Alopecia, Autoimmune keratitis, Palindromic rheumatism, Nephrocalcinosis, and Thrombocythemia.
Conclusions
APS-1 is rare and presents with enormous variability. It typically presents with a triad of hypoparathyroidism, Addison disease, and chronic mucocutaneous candidiasis, not a feature in our case. Management involves collaboration with several specialities as a result.

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Undiagnosed probable genetic primary hyperparathyroidism presenting with brown tumors and deafness

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A 25 year old Afghan male presented with a 4 day history of worsening left-sided loin pain. He had a past history of deafness since birth, speech problems and development delay. Bilateral renal calculi and widespread multiple well defined lytic lesions (likely brown tumours) were seen on CT-KUB. The corrected calcium was 3.21 mmols/l, PTH 80 pmol/l, Vitamin D 25 nmol/l, phosphate 0.49 mmols/l, ALP 960 IU/l and fractional calcium excretion was 0.16. His skull X Ray/OPG, done due to prominent skull and jaw deformities, revealed early pepperpot skull appearances with bilateral ossicular abnormalities along with brown tumours throughout the jaw and maxilla. Audiology revealed mixed conductive and sensorineural hearing loss. An ultrasound revealed a large necrotic mass below the lower pole of the left lobe of thyroid, measuring 3.9 x 2.7 x 3 cm; Sestamibi scanning showed concordant results, suggesting a left-sided parathyroid adenoma. Other investigations revealed a GGT of 12 U/l; and normal TSH, FSH, LH, IGF-1, prolactin, cortisol and 24-hour urinary metanephrines (done to ascertain MEN/known syndrome associations.) Pedigree charting revealed a family history of renal calculi and deafness affecting grandparents, both parents, maternal uncle and sibling. There was an extensive history of consanguinity. Extended genetic testing done including AP2S1, CASR, CDC73, CDKN1B and MEN1 genes and exons 5, 7, 8, 10, 11, 13, 14, 15, 16 of the RET gene, GCM2 and GATA3: all were negative. A left hemi-thyroidectomy and left parathyroidectomy was done due to uncertain diagnostics. Histology was consistent with a parathyroid adenoma. Although genetic testing was negative and a literature search revealed no similar case, we still remain concerned that our patient has genetic hyperparathyroidism due to an as yet unidentified mutation.

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P163

Symptomatic primary hyperparathyroidism in the first trimester of unplanned pregnancy

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Primary hyperparathyroidism (PHP) is the most common aetiology for hypercalcaemia. Its prevalence in pregnancy is reported to be between 0.15% and 1.4%[i][ii]. It presents a threat to the health of both mother (hyperemesis, nephrolithiasis) and foetus (foetal death, congenital malformations, neonatal severe hypocalcaemia induced tetany)[iii][iv]. However, there is a lack of clear

guidance on management of primary hyperparathyroidism in pregnancy. We describe the case of a 26 year old female patient who presented with severe hypercalcaemia secondary to primary hyperparathyroidism and underwent successful parathyroid adenectomy under local anaesthesia. Our case report highlights the following relevant learning points:

1. The prevalence of primary hyperparathyroidism is reported to be low at < 1.4%.
2. There is a perceived risk of general anaesthesia to the pregnancy in the first trimester, pushing general consensus to delaying surgery to second trimester when possible
3. Imaging such as parathyroid USS and SPECT CT + Sestamibi scan Tc99m can help localise the culpable adenoma with minimal radiation to the mother and patient
4. If the patient presents with severe or symptomatic hypercalcaemia, minimally invasive surgery under local anaesthetic would be the treatment of choice regardless of the gestational age of the pregnancy.

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P164

Resolution of primary hyperparathyroidism following parathyroid adenoma infarction on treatment with cinacalcet

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Spontaneous resolution of primary hyperparathyroidism following infarction for parathyroid adenomas is rare with infarction on treatment with cinacalcet being even rarer. A 53 year old female who presented to primary care with malaise was found to have biochemical evidence of primary hyperparathyroidism with adjusted calcium 3.31 mmol/l and parathyroid hormone 28.8 pmol/l. Previous medical history was unremarkable. Following discussion with endocrinology, treatment with cinacalcet 30 mg od was commenced and 2 weeks later adjusted calcium was 2.84 mmol/l and parathyroid hormone 19.5 pmol/l. At endocrine review 1 month later she was asymptomatic with no abnormal physical signs. Surgical intervention was agreed as the appropriate form of management after parathyroid imaging (US/SPECT CT/MIBI scan). Imaging confirmed the presence of an adenoma inferior to the right lobe of thyroid. A plan to continue treatment with cinacalcet pending surgery was unfortunately impacted by the Covid-19 crisis. At review 4 months later she was found to have stopped cinacalcet for 3 months and adjusted calcium was 3.25 mmol/l and parathyroid hormone 26.5 pmol/l. Treatment with cinacalcet 30 mg od was re-started. One month later she experienced pain and swelling anteriorly on the right side of her neck and paraesthesia of her fingers. Investigations confirmed adjusted calcium 2.22 pmol/l and parathyroid hormone 2.6 pmol/l by which time she was asymptomatic. Repeat imaging could not identify the previous adenoma. Eight months later adjusted calcium and parathyroid hormone remained normal at 2.47 mmol/l and 6.8 pmol/l respectively. Whilst cinacalcet has been demonstrated to decrease the size of parathyroid adenomas and to cause aptosis of parathyroid cells there have only been two previous reports of resolution of hyperparathyroidism following infarction. Whether cinacalcet was causative is speculative. We also speculate whether infarction is more common and under recognised.

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P165

Hypercalcemia secondary to Hypervitaminosis D caused by over the counter consumption of vitamin D

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Introduction
Vitamin D toxicity (VDT) is quite an uncommon condition which results from misperception between dosage regimens of vitamin D supplementation. VDT is diagnosed when Serum 25-hydroxyvitamin D levels are higher than 375 nmol/l (150 ng/ml). Vitamin D supplementation is easily accessible as over-counter medication and online. This report describes a patient who presented with severe hypercalcemia and acute kidney injury (AKI). Further assessment revealed that patient was taking mega dose of vitamin D over a period of at least 12 months.
Case Summary
A fit and healthy 71 years old male attended emergency department with symptoms of polyuria, polydipsia, constipation, lethargy, and weight loss. Initial Investigations revealed raised calcium (3.30 mmol/l), raised creatinine (465umol/l) and Urea (17.6 mmol/l) and low eGFR (10 ml/min/1.73m^2). Work-up for the underlying causes of hypercalcemia showed: suppressed PTH (0.8pmol/l), negative myeloma screen and normal TSH (3.8mU/l). CT Thorax, Abdomen and Pelvis showed no evidence of malignancy. Further history revealed that he was taking 50,000 units/day of vitamin D (cholecalciferol) for more than 12 months. Vitamin D levels were checked, and it was more than 375nmol/l. He was treated with stopping vitamin D supplements, hydration, and steroids. Calcium levels dropped to 2.69 mmol/l although vitamin D level remains high at 375nmol/l. Patient was also started on calcitonin as his calcium levels kept fluctuating to higher levels.
Conclusions
Hypercalcemia due to VDT is uncommon but well recorded. Self-administration of vitamin D in uncontrolled and mega doses can result in Vitamin D Toxicity and related complications due to hypercalcemia. Looking for uncommon causes of hypercalcemia, in this case VDT, is advisable on top of taking good medication history for any complementary supplements. Increasing public awareness on the maximum daily requirement of vitamin D is highly recommended and is a good preventative practice.

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P166

Systematic review of cardiovascular morbidity and mortality associated with primary hyperparathyroidism; does early surgical intervention improve the outcome?

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Introduction
Primary hyperparathyroidism is associated with numerous cardiovascular complications including hypertension, left ventricular hypertrophy and calcification of cardiac valves. However NICE have not included cardiovascular complications as an indication of parathyroidectomy. This literature review will be focused on benefits of parathyroidectomy on cardiovascular complications of primary hyperparathyroidism.
Methodology
Literature search done through use of search engines google scholar, PubMed, Cochrane database, Medline and EmBase using PRISMA model. Initial database search revealed 79 studies. After applying exclusion and inclusion criterion, 43 studies were finalized for systemic review.
Results
Amongst the cardiovascular complication of 1PHPT hypertension and LVH are most investigated in literature ad evidence is relatively strong for hypertension and LVH compared to other cardiovascular complications. Evidence is relatively weak for coronary artery disease, serum lipid profile, endothelial vasodilatory dysfunction, calcification of cardiac valves, occurrence of cardiovascular events and cardiovascular mortality.
Conclusions
Although evidence of benefits of parathyroidectomy for HTN and LVH is relatively strong, lack of well-designed multicentre randomized control trial seems to be the main obstacle for inclusion of this as part of parathyroidectomy criterion. However, there is a rationale on basis of evidence available to include Hypertension and LVH as possible indications. Consideration should be given for inclusion of echocardiogram at baseline and follow up of 1PHPT patients managed conservatively.

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Endocrine Cancer and Late Effects

P35

A Case of MEN-1 Syndrome presenting as Lung carcinoid tumour

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Multiple Endocrine Neoplasia Type 1(*MEN1*) syndrome is commonly associated with the three 'P's-pituitary, parathyroid and pancreatic lesions. However, increasingly, thoracic neuroendocrine tumours (NETs) are being recognised with the syndrome. We present a case of *MEN1* syndrome who primarily presented with a lung carcinoid tumour. A 31-year-old lady with without a significant past medical history presented with 2-month history of a persistent cough. Consequent chest x-ray and computed tomography (CT) scanning revealed a right middle lobe lung tumour, which was resected; histology revealed a typical carcinoid tumour (T2a N1 M0 R0). She did not have a family history of endocrine neoplasia. She subsequently underwent a whole body 68Ga-DOTATOC positive emission topography/CT scan, which showed three pancreatic NETs with magnetic resonance imaging detecting at least 2 of these sub centimetre intrapancreatic lesions (pancreatic head and uncinate process). She was commenced on monthly somatostatin analogue therapy. On biochemical screening, she had a raised serum adjusted calcium of 2.76 (2.2–2.60 mmol/l) and corresponding parathyroid hormone level of 8.2 (1.5–7.6 pmol/l) in keeping with primary hyperparathyroidism. Parathyroid imaging showed a focal 0.8 cm adenoma, and she is awaiting a subtotal parathyroidectomy. Her chromogranin A was 30 (0-91 mg/ml) and fasting gut hormones and basal pituitary profile were normal. Magnetic resonance imaging of her pituitary gland revealed a 0.4 cm cystic lesion. Genetic screening revealed a mutation in the *MEN1* gene. This case highlights an unusual presentation of *MEN1* syndrome with the initial symptoms being manifestations of a pulmonary NET. Previous studies have reported an estimated prevalence of thoracic NETs (thymic and pulmonary) of 2-8% with these being associated with premature mortality. It is therefore imperative that clinicians incorporate regular surveillance for thoracic NETs in their long-term management of *MEN1* patients.

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P36

The Impact of COVID-19 on Endocrine Treatments from a Neuroendocrine (NET) patient perspective: homecare and self-injection

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Introduction
The global impact of COVID-19 has been unprecedented. Specific recommendations for the management of neuroendocrine disorders in the pandemic were rapidly released by Endocrine experts. To comply with COVID rules, NET patients, due to attend the endocrine unit in March 2020 for Somatostatin analogue therapy, were rapidly identified. 25 vulnerable patients had urgent domiciliary administration arranged. Other patients were taught to self-inject. Postal surveys were sent to these patients with prepaid envelopes, 3 months after the implementation. Patient satisfaction; administration of injections; side effects and the desired place of treatment following the pandemic were assessed. The questions included multiple choice satisfaction ratings, yes or no answers and free text areas for patients to elaborate on their answers and experience.
Results
68 % of patients responded. Patients were satisfied with the information provided. All respondents had their injection given by a homecare or community nurse and 94% of respondents had no issues with the timeliness of injections delivered in the community. 14 out of 17 patients were either very satisfied or satisfied by their new treatment regime. Frequency of bowel related side effects was rare and the majority of patients had no new side effects. 75% of patients said they would rather continue home treatments during the uncertainty of the pandemic. These were justified by fears of the first wave and the convenience of home treatment. Some patients however still opted for hospital visits due to the familiarity of endocrine nurses and ability to see their doctor face to face.
Conclusion
This study has shown NET patients adapted quickly to the changes in delivery of Somatostatin analogues and provided a patient perspective on domiciliary treatment in the pandemic. Patients were satisfied and happy to receive treatment at home post pandemic. This could impact positively on efficiency in the Endocrine unit.

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P37

Parathyroid Tumour of Uncertain Malignant Potential (PTUMP): a rare case of hyperparathyroidism associated with transient hyperglycaemia

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A 60-year-old South African male, presented as an emergency with a 4 week history of lethargy, polyuria, increased thirst, constipation and weight loss. Blood tests revealed hypercalcemia with CCa-4.72 mmol/l, PTH-159.3pmol/l and 25 OH Vitamin D 22mmol/l. Intensive iv hydration was followed by IV Pamidronate 60 mg stat. Calcitonin (4 units/Kg tds) was started 48 hours later which resulted in a fall in the calcium to 2.66 by day 5. Cinacalcet 30 mg od was then introduced such that normocalcaemia was achieved by day 14. Interestingly admission CBG readings were in the range 10-18. The concurrent HbA1c was normal at 40mmol/mol. Amylase was normal. A basal bolus regimen of insulin was started. As the calcium lowered, so did his insulin requirement such that he was discharged on Metformin & Linagliptin. Intracellular hypercalcaemia decreases normal insulin-stimulated glucose transport, thereby increasing insulin requirements. A 4D-CTparathyroid with contrast demonstrated a heterogenous left parathyroid nodule close to subclavian with focal calcification raising suspicion of parathyroid carcinoma. He had an uneventful left parathyroidectomy and the initial histology report suggested a benign left parathyroid adenoma. Due to clinical concern, a second opinion from a regional head and neck centre was requested. The expert histopathologist characterised this as Parathyroid tumour of uncertain malignant potential PTUMP (otherwise known as atypical adenoma). This is a rare condition with incidence of 1-3% and requires close follow up. The histology sample has been sent to USA for further analysis. Eight weeks after surgery, calcium is normal at 2.25. The patient has stopped all anti diabetic medication. Blood glucose readings are within normal range. The HbA1c has fallen to 31. Atypical parathyroid adenomas represent a group of intermediate form of parathyroid neoplasms of uncertain malignant potential which show atypical histological features and lack evident signs of local invasion and/or metastasis.

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P38

A challenging case of hyponatraemia

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We would like to describe a case of resistant hyponatraemia. A 65-year-old Caucasian male presented to ED with a two-day history of blurred vision and transient numbness in his right hand. He was an ex-smoker with a past medical history of a transient ischaemic event in 2019 and a myocardial infarction in 2005. He admitted to a 10kg weight loss. He had no changes to his medications in the recent past which included lansoprazole, ramipril, mirtazapine, atenolol, clopidogrel, atorvastatin and isosorbide mononitrate. He used to drink eight to ten cups of tea a day and enjoyed soups. He was clinically euvolaemic with a serum sodium of 117mmol/l and urinary sodium of 83 on admission. After investigations, a diagnosis of syndrome of inappropriate of antidiuretic hormone (SIADH) was made. Mirtazapine, lansoprazole, ramipril and atenolol were stopped and he was commenced on fluid restriction. A CT chest, abdomen and pelvis was normal and his hyponatraemia persisted past the wash-out period after stopping medications. His sodium levels proved difficult to correct and he was maintained on a one litre fluid restriction four months on from diagnosis. He was intolerant to demeclocycline but had a good response to tolvaptan. A PET-CT three months after initial presentation confirmed an underlying small cell lung carcinoma (SCLC). Hyponatraemia is a common presentation on the medical take but not a common presentation for lung cancer. This case highlights the challenges of maintaining a patient on a long-term fluid restriction through patient education, considering the wash-out periods of possible offending drugs and undergoing further investigations if the clinical suspicion for malignancy is high. Hyponatraemia and the failure to normalise serum sodium both are independent negative prognostic factors in patients with malignancy. Our patient died of metastatic SCLS ten months after initial presentation having refused any chemotherapy.

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P167

Novel management of resistant hypoglycaemia in a patient with malignant Insulinoma

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An 82-year-old lady admitted after multiple episodes of collapse and her blood sugar levels were noted to be less than 2.0 mmol/l. A supervised controlled fasting test was performed and results were consistent with Insulinoma. Imaging revealed a mass in the tail of the pancreas with metastasis to the liver. Liver biopsy confirmed the diagnosis of a poorly differentiated neuroendocrine tumour. She continued to have hypoglycaemic episodes which were difficult to manage. Dietary modifications and intravenous glucose had no success. Treatment with diazoxide and later with lanreotide, bore no success. Case was discussed in the surgical MDT which concluded that surgery was not an option. Further discussion in endocrine MDT advised a modified corn-starch product – glycoside should be tried. Glycosade is a long acting carbohydrate which is used in the treatment of glycogen storage diseases as the carbohydrate is slowly released. Glycosade is not currently licenced for use in insulinomas but was considered in this case due to its long-acting benefits. Response was great to the point of her not requiring any further intravenous glucose or dietary modifications. Further oncology commenced her on chemotherapy using streptozocin and capecitabine. Everolimus, could not be used because of high proliferation index noted on histology. The glycosade regimen was spread out throughout the day to allow stabilisation of the patient's glucose levels. As an inpatient and even after discharge patient's blood glucose levels have maintained between 4-9 mmol/l

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P168

A case report of Parathyroid Carcinoma following a low-impact trauma

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Background
Parathyroid Carcinoma (PC) is a very rare endocrine malignancy. Unlike Parathyroid Adenoma (PA) and Parathyroid Hyperplasia which represents 80% and 15-20% cases of primary hyperparathyroidism (PHPT) respectively, PC only constitutes 1-2% of cases. Herein we present a clinical case of PC following a low-impact trauma.
Clinical case
A 50-year-old Bulgarian female presented with a pathological mid-shaft fracture of her right femur following a trivial trip over her shoe laces when walking in the street. Initial biochemical values are remarkable for adjusted serum calcium of 3.22 mmol/l, Alkaline phosphatase (ALP) of 280 IU/l, urea of 18.4 mmol/l and creatinine of 182 μmol/l. Further blood tests revealed a significant parathyroid hormone level of 1997 ng/l. A subsequent computerised tomography scan of chest, abdomen and pelvis discovered no focal parenchymal abnormality but expansile right sided rib metastases with widespread lytic lesions of the pelvic bones. An incompletely imaged density in the left supraclavicular fossa may represent a thyroid mass. An urgent ultrasound of the neck was followed which showed a very large (2.1x2.3x4.3cm) ectopic left inferior parathyroid gland with clearly defined margins. A bone biopsy obtained at the same time as her right femur intramedullary nail intervention was sent and revealed a brown tumour of hyperparathyroidism with no evidence of atypia or malignancy. She underwent left inferior parathyroidectomy from which tissue sample was obtained. Histological studies discovered PC with extensive adjacent lymphovascular invasion. Both local and external Multi-disciplinary team (MDT) discussions have agreed to proceed with left hemithyroidectomy and neck dissection to ensure complete removal of microscopic disease.
Conclusions
As PC is very rare and has many overlapping features with other common causes of PHPT, confirming the diagnosis pre-operatively is challenging. A thorough MDT involvement is also important in providing safe and effective care for the patient.

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P169

Simultaneous ADH and ACTH secretion by small cell lung cancer: a diagnostic challenge

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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs in 10-45% of patients and secretion of ectopic adrenocorticotrophic hormone (EAS) in 2.5% of patients with small cell lung cancer (SCLC). Simultaneous secretion of ADH and ACTH is rare with only 10 cases being reported. The varying biochemical data leads to misdiagnosis as this case demonstrates. A 67 year old male presented with a 2 week history of falls attributed to alcohol abuse. Physical signs were unremarkable. Investigations: sodium 111 mmol/l, serum osmolality 235 mmol/kg and urine osmolality 467 mmol/kg suggested a diagnosis of SIADH. CXR was normal and cortisol 382 nmol/l. Fluid restriction and demeclocycline 150 mg bd improved sodium to 128 mmol/l. At review 2 months later sodium remained unchanged at 128 mmol/l and demeclocycline was increased to 300 mg bd. CT imaging 1 month later confirmed a subcarinal mass and metastases throughout the abdomen. Referral for biopsy was made but 2 weeks later he presented with generalised oedema and leg weakness. Proximal myopathy was confirmed. Investigations: sodium 143 mmol/l, potassium 2.5 mmol/l, pH 7.43, bicarbonate 28.6 mmol/l, cortisol 3104 nmol/l and ACTH 209.1 ng/l. A diagnosis of primary hyperaldosteronism was made and the cortisol level attributed to stress. Referral to endocrinology resulted in diagnostic revision. In view of his poor physical state and extensive metastatic disease oncology opined that symptomatic treatment was appropriate. Metyrapone and spironolactone improved clinical and biochemical status transiently (potassium 4.3 mmol/l, cortisol 731 nmol/l) and he died 2 months later. Cases of SCLC secreting both ADH and ACTH tend to have more extensive disease at presentation and poorer prognosis. Hypercortisolaemia has been invoked as the cause of the latter due to enhanced tumour growth, high rate of metastases, hyperglycaemia, hypokalaemia and infection.

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P170

Pituitary metastasis from lung adenocarcinoma presenting with panhypopituitarism

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Background
Pituitary metastases are a rare occurrence, accounting for just 0.4% of intracranial metastatic tumours and are most often associated with breast and lung malignancies. The vast majority of lesions are asymptomatic and due to the predilection of metastasis to the posterior lobe of the pituitary gland, clinical presentation with anterior pituitary insufficiency is uncommon and rarely reported in literature.
Case summary
A 51-year old male with known epidermal growth factor receptor-positive lung adenocarcinoma was admitted with mild nausea and vomiting secondary to chemotherapy. Five days into admission he developed confusion and biochemistry revealed a new hyponatraemia with a low sodium level of 116 mmol/l. Urine osmolality was elevated and urinary sodium was significantly raised (104 mmol/l). Cortisol was low (119nmol/l) and subsequent short-synacthen test showed an inadequate adrenal response. ACTH was 16ng/l and T4 was low (10.3pmol/l) with a normal TSH. Completion of the pituitary profile demonstrated a low testosterone ($<$ 0.1nmol/l), with inappropriately normal gonadotrophin levels (LH 2.4iu/l, FSH 1.4iu/l) and a low IGF-1 (6.3mol/l). Prolactin was normal. Magnetic resonance imaging showed a pituitary lesion alongside extensive brain metastases. In the context of the biochemical and radiological findings the pituitary lesion was concluded to be of metastatic aetiology. Symptoms and hyponatraemia improved with corticosteroids and subsequent thyroid hormone replacement. The patient commenced second-line chemotherapy and will receive whole-brain irradiation.
Conclusions and Learning points
Most pituitary metastases are diagnosed in patients with known cancer and therefore any biochemical or clinical sign of pituitary gland pathology in this context should prompt further investigation. In this case the presence of an elevated urinary sodium ($>$ 100 mmol/l) was a clue to the underlying cause of the

hyponatraemia being caused by adrenal insufficiency and hypothyroidism rather than SIADH, a distinction that is crucial for appropriate management.

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Metabolism, Obesity and Diabetes

P39

Longitudinal clinical trajectory analysis of individuals before and after diagnosis of Type 2 Diabetes Mellitus (T2DM) indicates that vascular problems and asthma pre-date diabetes diagnosis by many years

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Introduction
Type 2 diabetes mellitus (T2DM) frequently associates with increasing multi-morbidity/treatment complexity. Some headway has been made to identify genetic and non-genetic risk factors for T2DM. However longitudinal clinical histories of individuals both before and after diagnosis of T2DM are likely to provide additional insight into both diabetes aetiology/further complex trajectory of multi-morbidity.
Methods
This study utilised diabetes patients/controls enrolled in the DARE (Diabetes Alliance for Research in England) study where pre- and post-T2DM diagnosis longitudinal data was available for trajectory analysis. Longitudinal data of 281 individuals (T2DM $n = 237$ vs matched non-T2DM controls $n = 44$) were extracted, checked for errors and logical inconsistencies and then subjected to Trajectory Analysis over a period of up to 70 years based on calculations of the proportions of most prominent clinical conditions for each year.
Results
For individuals who eventually had a diagnosis of T2DM made, a number of clinical phenotypes were seen to increase consistently in the years leading up to diagnosis of T2DM. Of these documented phenotypes, the most striking were diagnosed hypertension (more than in the control group) and asthma. This trajectory over time was much less dramatic in the matched control group. Immediately prior to T2DM diagnosis a greater indication of ischaemic heart disease proportions was observed. Post-T2DM diagnosis, the proportions of T2DM patients exhibiting hypertension and infection continued to climb rapidly before plateauing. Ischaemic heart disease continued to increase in this group as well as retinopathy, impaired renal function and heart failure.
Conclusion
These observations provide an intriguing and novel insight into the onset and natural progression of T2DM. They suggest an early phase of potentially-related disease activity well before any clinical diagnosis of diabetes is made. Further studies on a larger cohort of DARE patients are underway to explore the utility of establishing predictive risk scores.

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P40

A randomised controlled pilot trial of oral 11β-HSD1 inhibitor AZD4017 for wound healing in adults with type 2 diabetes mellitus

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Chronic wounds (e.g. diabetic foot ulcers) have a major impact on quality of life, yet treatments remain limited. Glucocorticoids impair wound healing; preclinical research suggests that blocking glucocorticoid activation by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) improves wound repair. This investigator-initiated double-blind, randomised, placebo-controlled parallel-group phase 2b pilot trial investigated efficacy, safety and feasibility of 11β-HSD1 inhibition for 35 days by oral AZD4017 (AZD) treatment in adults with type 2 diabetes ($n = 14$) compared to placebo (PCB, $n = 14$) in a single-centre secondary care setting. Computer-generated 1:1 randomisation was pharmacy-administered. From 300 screening invitations, 36 attended, 28 were randomised. There was no proof-of-concept that AZD inhibited 24 hour skin 11β-HSD1 activity at day 28 (primary outcome: adjusted difference AZD-PCB 90% CI (diffCI) = -3.4,5.5) but systemic 11β-HSD1 activity (median urinary [THF + alloTHF]/THE ratio) was 87% lower with AZD at day 35 (PCB 1.00, AZD 0.13, diffCI = -1.04,-0.69). Mean wound gap diameter (mm) following baseline 3 mm punch biopsy was 34% smaller at day 2 (PCB 1.51, AZD 0.98, diffCI = -0.95,-0.10) and 48% smaller after repeat wounding at day 30 (PCB 1.35, AZD 0.70, diffCI = -1.15,-0.16); results also suggested greater epidermal integrity but modestly impaired barrier function with AZD. AZD was well-tolerated with minimal side effects and comparable adverse events between treatments. Staff availability restricted recruitment (2.9/month); retention (27/28) and data completeness (95.3%) were excellent. These preliminary findings suggest that AZD may improve wound healing in patients with type 2 diabetes and warrant a fully-powered trial in patients with active ulcers. Trial Registry: www.isrctn.com/ISRCTN74621291.

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P41

Investigating 2-oleoylglycerol responsive neuronal pathways

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Dietary fat intake is an important source of energy and in excess can drive the development of obesity. Investigating how dietary fat intake alters neuronal activity in the brain and drives behavioural changes may help us understand the mechanisms behind high fat diet induced obesity. 2-oleoyglycerol (2-OG) is a naturally occurring unsaturated long chain fatty acid produced by fat digestion in the gut and a ligand of G protein-coupled receptor 119 (GPR119). Published data has shown that 2-OG increases glucagon-like peptide-1 (GLP-1) release in murine colonic crypt cultures and this effect is lost in crypts cultured from gpr119 knockout mice. Our data shows that 2-OG improves oral glucose tolerance in both lean and high fat diet induced obese mice possibly via incretins such as GLP-1. However, the neuronal responses and behavioural changes driven by intestinal 2-OG are still unclear. In addition to gut hormone signalling, the transduction of gastrointestinal luminal nutrient information to the brain is also mediated by the parasympathetic vagus nerve. The cell bodies of vagal afferent neurons reside within the nodose ganglia, which highly express GPR119. Our data shows that 2-OG increases intracellular calcium signalling in murine nodose ganglia neurons *in vitro*. The effects of oral administration of 2-OG or the synthetic GPR119 agonist AR231453 on neuronal activation were assessed by the immunostaining of c-Fos. The vagus nerve signals to specific regions of the brainstem, including the nucleus of the tractus solitarius (NTS). Oral administration of 2-OG to mice increased the number of c-Fos expressing cells in the NTS and the dorsal motor nucleus of the vagus (DMV). Because NTS and DMV are closely related to gastric motility and food preferences, we studied the effects of 2-OG on gastric emptying and food choice. Mapping 2-OG responsive gut-brain pathways may help to provide new therapeutic targets in obesity.

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P42

Chronic inflammation regulates androgen metabolism and exposure in Macrophages

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Active androgens exert immunomodulatory actions at sites of inflammation and lower levels are implicated in the increased incidence of rheumatoid arthritis (RA) in females. However, inflammatory regulation of intracrine androgen metabolism within cell populations at sites of inflammation remain poorly defined. In this study we characterised immune and stromal cell androgen metabolism in RA patients and assessed their functional significance. Using the online Accelerating Medicines Partnership (AMP) RA dataset, bulk RNA sequencing data from FACS-sorted synovial macrophages, fibroblasts, T cells and B cells were analysed. Expression of 132 steroid hormone receptor, transporter and enzyme genes were analysed in 35 RA patients (27 female, 8 male). Androgen metabolism and its functional effects was determined in RA synovial fluids and primary human macrophage cultures using LC-MS/MS, RT-qPCR and ELISA. Examination of RNA sequencing data from macrophages showed that 5 steroid metabolism genes were significantly (greater than 2-fold, $P < 0.05$) differentially expressed across inflammation severity (as measured by DAS28-CRP), more than in other cell types assessed. Androgen metabolism pathways showed the greatest relationship with inflammation, with androgen activating enzyme AKR1C3 reduced 4-fold ($P < 0.001$) in low inflammation compared to high inflammation RA. Analysis of synovial fluids from RA patients revealed quantifiable concentrations of the downstream substrates of AKR1C3, namely DHEA and androstenedione, with metabolite ratios suggesting enzyme dysregulation with inflammation. In primary human monocyte-derived macrophages, pro-inflammatory cytokines, including TNFα (10ng/ml) and IFNγ (20ng/ml), significantly downregulated AKR1C3 *in vitro*. Incubation of macrophages with the androgen precursor androstenedione (10nmol/l) and the active androgen dihydrotestosterone (10nmol/l) resulted in a marked suppression of the inflammatory cytokines TNFα and IL6, and upregulation of pro-resolution marker CD163. These data reveal novel inflammatory regulation of androgen metabolism in chronic inflammation in macrophages, identifying a putative key role of the androgen-activating enzyme AKR1C3 and demonstrating potent anti-inflammatory effects of androgens in macrophages.

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P43

5β-reductase is downregulated in patients with non-alcoholic fatty liver disease and hepatocellular carcinoma and controls metabolic and proliferative phenotype through LXR-dependent mechanisms

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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease ranging from simple intrahepatic lipid accumulation to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). 5β-reductase (AKR1D1) is a liver enzyme that catalyses a fundamental step in bile acid (BA) synthesis. Both BAs and BA intermediates are established as potent regulators of metabolic and proliferative phenotype. We have hypothesised that AKR1D1 plays a crucial regulatory role in NAFLD and HCC. Human liver biopsies were obtained from 34 obese patients. Genetic manipulation of AKR1D1 (siRNA/shRNA) was performed in human HepG2 cells. Effects on BA synthesis, nuclear receptor activation, insulin sensitivity, cell cycle and proliferation were determined by LC-MS, qPCR, western blotting, flow cytometry, luciferase reporter assays, and RNA-sequencing. Recombinant human AKR1D1 was expressed in BL-21 bacteria cells, purified, and screened to identify novel AKR1D1 pharmacological inhibitors. In liver biopsies, *AKR1D1* expression decreased with advancing steatosis, fibrosis, and inflammation. RNA-sequencing in AKR1D1-knockdown HepG2 cells identified dysregulated pathways impacting insulin signalling, DNA replication, cell cycle and proliferation. AKR1D1 knockdown decreased primary BA and increased AKR1D1-substrate (7α, hydroxy-cholestenone, 7α,12α, dihydroxy-cholestenone) concentrations, and increased insulin-stimulated AKT phosphorylation, consistent with enhanced insulin sensitivity. Additionally, AKR1D1 knockdown decreased cyclin-dependent kinase and increased cyclin-dependent kinase inhibitor expression, downstream resulting in cell cycle arrest at G1/S phase, impaired proliferation, and enhanced apoptosis. Complementing these findings, pharmacological inhibition of AKR1D1 using three novel AKR1D1 inhibitors (identified through a high-throughput drug screen of >300,000 compounds) impaired cell proliferation and proliferative gene expression. Luciferase assays revealed increased LXR activation following AKR1D1 knockdown, identifying the AKR1D1 substrates as novel endogenous LXR ligands. Pharmacological inhibition of LXR activation prevented the induction of metabolic and proliferative gene expression. In conclusion, AKR1D1 knockdown enhances insulin sensitivity, delays cell cycle, and inhibits proliferation through LXR-dependent mechanisms. Taken together, these data suggest a beneficial role of AKR1D1 inhibition in NAFLD and HCC.

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P44

11β-HSD1 determines the extent of muscle atrophy during an acute exacerbation of COPD

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Introduction
Muscle atrophy is a major clinical complication of acute exacerbations (AE) in chronic obstructive pulmonary disease (COPD). The enzyme 11 beta-hydroxysteroid dehydrogenase 1 (11β-HSD1) activates glucocorticoids (GCs) within muscle, is induced by inflammation, and has been shown to contribute towards GC-induced muscle wasting. In this study, we examined the role of 11β-HSD1 in this context using a murine model of COPD-AE in animals with transgenic global deletion of 11β-HSD1.
Methods
WT and 11β-HSD1/KO mice received two intra-tracheal (IT) instillations of elastase to induce stable emphysema (COPD), followed by a single bolus of IT-LPS to mimic AE, or vehicle. After 48 hours muscle, serum and lung tissues were collected. μCT scans were collected prior and following IT-LPS, to assess emphysema progression and muscle mass changes, respectively. Anabolic, catabolic and inflammatory gene and protein expression were examined by RT-qPCR and western blot. Serum corticosterone was determined by ELISA. *in vitro*myonuclear accretion in response to serum and GCs was determined in C2C12.
Results
Comparable emphysema progression was observed in both WT and 11β-HSD1/KO animals.Muscle wasting was exacerbated in 11β-HSD1/KO COPD-AE animals compared to WT controls characterised by reduced gastrocnemius muscle wet weights and total leg muscle by μCT. Catabolic pathways, including Atrogin-1 and MuRF-1 were elevated in 11β-HSD1/KO COPD-AE animals relative to WTs, whilst anabolic and anti-catabolic pathways such as p-S6 (S235/236) and p-FoxO1 (S256) were suppressed. Serum corticosterone levels were significantly higher in 11β-HSD1/KO COPD-AE animals relative to compared to WT, whilst C2C12 myotubes treated with 11β-HSD1/KO COPD-AE plasma or exogenous GCs had a reduced capacity for myonuclear accretion relative to WT counterparts.
Conclusions
These findings demonstrate 11β-HSD1 determines the extent of muscle wasting during acute exacerbation of COPD. Here, transgenic deletion of 11β-HSD1 drives dysregulation of circulating corticosteroids and muscle metabolism, favouring increased catabolic and decreased anabolic responses.

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P45

PARP1 mediated ADP-Ribosylation events during myoblast fusion contribute to murine skeletal muscle phenotype

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The nicotinamide adenine dinucleotide (NAD+) dependent Poly-(ADP-ribosyl)polymerase 1 (PARP1) generates the post-translational modification ADP-Ribosylation (ADPR). Molecular studies have identified potential for NAD+ consuming enzymes to influence metabolic function. Given that PARP1 determines cellular NAD+ concentrations and ADPR shifts target protein activity, we sought to identify the molecular actions of PARP1 within skeletal muscle. Analysis of C2C12 lysates demonstrate that PARP1 (often assumed as basally inactive) and ADPR proteins, are detectable and dynamic during differentiation days 0-5 ($P < 0.001$; $n = 6$). RNAseq of siPARP1 ($n = 4$)

versus scrambled control ($n = 5$) showed that knockdown of PARP1 significantly upregulated 115 and downregulated 150 genes. Gene ontological analysis of these gene-sets showed over-representation in siPARP1 cells of those pathways regulating cell differentiation, inducing actin binding, cytoskeletal structure, and NAD+ binding genes. To identify if dynamic peaks in PARP1 and ADPR protein levels have functional consequences over fully formed myotubes, C2C12 cells were treated with a single dose of the PARP1 inhibitor BYK204165 (10uM) at initiation of differentiation. Cells were left to align and fuse, with the media being replaced on differentiation day 2; final lysate collection was on day 5. Unbiased LC-MS analyses of these lysates detected 180 significantly differential proteins in PARP inhibitor treated cells ($n = 6$) when compared to vehicle controls ($n = 7$). Pathway over-representation analyses showed that PARP inhibition impacted biological processes governing muscle development (False Detection Rate 8.99-08), muscle contraction (FDR 9.47-08, myofiber assembly (FDR 8.06-05) and metabolism (FDR 2.93-06). Cell respirometry data support influence of PARP1 over myotube function. Our experiments show PARP1 mediated ADPR is critical to 'early phase' events surrounding myotube formation. Reducing PARP1 expression during these critical times significantly altered the orchestration of genes crucial to achieving skeletal muscle architecture and overall phenotype. These results have importance for studies seeking to leverage PARP inhibition or NAD+ availability towards human-health.

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P46

AKR1C1 knock-down does not alter cell proliferation or response to chemotherapeutic agents in human hepatoma models

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Hepatocellular carcinoma (HCC) is the 6th most common form of cancer and the 4th most common cause of cancer related death. AKR1C1 is a member of the aldo-keto reductase 1C (AKR1C) subfamily and has important roles in steroid hormone metabolism and in reducing lipid peroxides. AKR1C1 is ubiquitously expressed, with high levels of expression in the liver. Studies have identified differential expression in HCC with high levels of AKR1C1 expression associated with a worse HCC prognosis as well as poor response to sorafenib chemotherapy. Using human cell hepatoma models (HepG2 and Huh), we have undertaken a series of experiments to determine the impact of AKR1C1 siRNA and CRISPR knock down and pharmacological inhibition on cell proliferation, gene expression (using RNA-sequencing) and response to treatment with the chemotherapeutic agent, sorafenib. Significant knock down of AKR1C1 gene and protein expression was achieved with both the siRNA and CRISPR approaches. AKR1C1 knock down had no impact on cell viability or proliferation. As expected, sorafenib decreased cell proliferation. Neither gene silencing of AKR1C1 nor pharmacological inhibition using 5-PBSA altered the cellular response to sorafenib treatment. Furthermore, RNA-sequencing analysis demonstrated only a very small number of differentially expressed genes when comparing AKR1C1 siRNA treated cells and scrambled controls. In conclusion, AKR1C1 knock down had a minimal impact on the proliferative phenotype in human hepatoma cell lines and failed to regulate the response to sorafenib treatment. These data would suggest that AKR1C1 in isolation has little direct impact to modulate the development and progression of HCC.

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P47

Leicestershire wide steroid safety programme 2019-21 and effectiveness of electronic alert on prescription software in a tertiary centre

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Background
Omission of steroids and unsafe steroid prescription in Adrenal insufficiency (AI) patients during intercurrent illness or surgery is unfortunately common, and can lead to adrenal crisis and potentially death. Anna Mitchell *et al*, New Castle-upon-Tyne have demonstrated potential use of electronic automation with steroid alerts to minimise human error for ensuring patient safety.
Objectives
1. Similar use of artificial intelligence was introduced in range of steroid safety measures in primary and secondary care settings with principle of 'education at the point of care'.
2. To evaluate efficacy of electronic steroid alert in University Hospitals of Leicester's (UHL) prescription software (EPMA).

Methodology & Results
Steroid safety measures undertaken are as below:
1. UHL emergency guideline for AI introduced in 2019.
1. EPMA alert is placed in prescribing software. 50 patients on hydrocortisone pre/- and post alert introduction (January 2019 and January 2020) were assessed with electronic and case note records to see the effectiveness of such an alert. Doubling of steroid doses and parenteral hydrocortisone for hypotensive patients improved from 28% to 68%.
1. Electronic alert placed on UHL's patient handover software 'Nervecentre', which is used in Emergency department as well as on wards.
1. Primary care: Similar electronic alert was introduced in 2019 in primary care patient management software: 'System one' and 'EMISS':
1. NPSA mandatory steroid guidance and new NHS steroid cards introduced in all clinical areas of primary/secondary care from May 11th 2021.

Conclusion
1. Electronic automation of point of care is potentially useful/life-saving and minimises human error in preventing omission of steroids.
2. Although the safe steroid prescription behavior improved significantly, to ensure alerts are acted upon, awareness needs to be brought about amongst clinicians and pharmacists by means of Trust communications, induction programs and mandatory training.

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P48

The neuroophthalmological manifestations of obesity

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Introduction
Obesity is associated with a plethora of metabolic and physiological side effects. Excess adiposity is associated with raised intracranial pressure (ICP) in obesity, where raised ICP sequalae include headache and visual decline in humans. We aimed to assess the effects of diet induced obesity (DIO) on ICP and related neuroophthalmological outcomes of headache behavior and retinal anatomy in rats.
Methods
Female Sprague-Dawley rats received high fat diet (60% fat) or matched control diet (10% fat) for 15-17 weeks. Following the diet, rats were implanted with telemetric ICP probes. Cutaneous allodynia was assessed via electric von frey and retinal anatomy was assessed by optical coherence tomography. Body composition was determined by dual x-ray absorptiometry.
Results
On the day of ICP surgery (baseline), DIO rats were 15% heavier than controls (365.9± 37.8 vs 316± 17.3 g, $P = 0.002$) with a greater abdominal fat percentage (43.2± 7.2 vs 28.9± 3.2 %, $P < 0.0001$). All rats had similar fasting glucose at baseline (6.3± 0.5 vs 5.8± 0.7 mmol/l, $P = 0.43$). DIO rats had raised ICP at baseline (2.77± 0.6 mmHg vs -0.17± 0.7, $P = 0.0052$) and the following 10 days ($P = 0.0075$) which correlates with abdominal adiposity ($r = 0.54$, $P = 0.016$). DIO rats demonstrate cephalic cutaneous allodynia (163.1± 8.0 vs 213.8± 5.1 g, $P < 0.0001$) at baseline, accordingly *Calca* and *Trpv1* expression was raised in the trigeminal ganglia. The cephalic threshold negatively correlates with abdominal fat percentage (r=-0.65, $P = 0.0005$). At baseline, DIO rats had swollen retinal nerve fibre layers (RNFL) (28.8± 0.6 vs 24.8± 1.1 μm, $P = 0.0026$), and RNFL thickness positively correlates with ICP ($r = 0.639$, $P = 0.0058$).
Discussion
Our data highlight that obesity increases ICP, accompanied by increased headache behavior and altered retinal anatomy, mimicking clinical findings. Our unique model will facilitate deeper understanding of the molecular underpinnings of raised ICP and the development of novel therapeutics to treat raised ICP.

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P49

Interplay of NUCB2/Nesfatin-1 and inflammation in white adipose tissue

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Background
Excess adipose tissue accumulation and obesity are characterised by a chronic, low-grade, systemic inflammation that contributes to obesity-related cardiometabolic disease. Nestfatin-1 is a neuropeptide derived from the precursor protein nucleobindin-2 (NUCB2), which was initially reported to exert anorexigenic effects. We have previously shown that NUCB2/Nesfatin-1 is highly expressed in human and mouse subcutaneous white adipose tissue (Sc-WAT) and that circulating nesfatin-1 levels significantly increase upon a high-fat diet (HFD) and in response to inflammation.
Objective
The present study aimed to investigate the effects of a HFD (12 weeks) in NUCB2 knockout (KO) mice and of nesfatin-1 treatment in LPS-stimulated 3T3-L1 cells.
Methods
Sc-WAT samples from wild type (WT) and NUCB2 KO mice that were fed a normal diet (ND) or HFD for 12 weeks were used for RNA and protein extraction, as well as immunohistochemistry. 3T3-L1 cells were also treated with 100nM nesfatin-1 during differentiation and stimulated with 10μg/mL LPS for measuring pro-inflammatory cytokines (mRNA and protein).
Results
Following the 12-week HFD, the mRNA expression of TNFα, IL6, IL1-beta, MCP1, adgre1 and HMGB1 significantly increased in the Sc-WAT of NUCB2 KO mice compared to ND (all p-values <0.05), whereas only IL1-beta, MCP1 and HMGB1 significantly increased in the Sc-WAT of WT mice (all p-values $<$ 0.05). Adiponectin and NRF2 expression significantly decreased in the Sc-WAT of HFD-fed NUCB2 KO (all p-values <0.05), without changes in HFD-fed WT mice. NF-kB activation was demonstrated by immunofluorescence and immunoblot in the Sc-WAT of HFD-fed NUCB2 KO mice. Furthermore, nesfatin-1 treatment in LPS-stimulated 3T3-L1 cells significantly reduced the expression of pro-inflammatory cytokines and HMGB1 (all p-values <0.05).
Conclusions
The present findings demonstrate that HFD induces significant inflammation in the Sc-WAT of NUCB2 KO mice, involving HMGB1 and the NRF2 and NF-kB pathways, whilst nesfatin-1 reduces the pro-inflammatory response in LPS-stimulated 3T3-L1 cells.

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P50

Lipocalin 2, a mediator or marker of adipocyte dysfunction?

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Background
Lipocalin 2 (NGAL) is considered a pro-inflammatory adipokine. Noting the conflicting reports as to the role of Lipocalin 2 in metabolic disease, it remains unclear whether an acute or chronic state affects its impact on adipocyte function. In an attempt to address this our current studies investigated for the first time in humans, whether Lipocalin 2 in abdominal subcutaneous adipose tissue (AT) may influence mitochondrial function and browning of adipocytes, as contributing mechanisms of obesity mediated type 2 diabetes mellitus (T2DM) disease.
Methods
Human abdominal subcutaneous (AbdSc) AT biopsies were collected (female; 31.6 $\pm$ 5.6 Yr, BMI: 27.8 $\pm$ 5.8 Kg/m^2, $n = 125$) in an ethically approved study. RNA was extracted from AbdScAT (lean: age: 32.3 $\pm$ 5.2Yr, BMI: 22.2 $\pm$ 1.9 Kg/m^2, $n = 43$; overweight: age: 31.06 $\pm$ 5.8Yr, BMI: 27.5 $\pm$ 1.3Kg/m^2, $n = 46$; Obese; age: 31.2 $\pm$ 5.8Yr, BMI: 35 $\pm$ 4.6Kg/m^2, $n = 36$) and gene expression quantified by qRT-PCR. Lipocalin 2, asprosin, mitochondrial, BRITE, and inflammatory genes were assessed.
Results
Lipocalin 2 mRNA expression in AbdScAT, increased mitochondrial biogenesis (PRC $P < 0.05$), but led to a reduction in mitochondrial function (COX4: $P < 0.0001\downarrow$) and mitochondrial fusion (MFN2: $P < 0.0001\downarrow$; OPA1: $P < 0.05\downarrow$). Rising Lipocalin 2 mRNA expression also led to reduced browning gene expression (CIDEA: $P < 0.05\downarrow$; ELOVL3: $P = 0.05\downarrow$; PLIN5: $P < 0.05\downarrow$) in AbdScAT. Lipocalin 2 did not appear influenced by adiposity, insulin or HOMA-IR. Lipocalin 2 was also positively correlated with the adipokine asprosin ($P <$ 0.0001).
Conclusions
In summary, Lipocalin 2 was associated with mitochondrial impairment, impacting mitochondrial dynamics, and a reduced browning phenotype in AbdScAT. These data therefore suggest that raised systemic lipocalin 2 levels in obese or T2DM subjects, may act as a secondary mediator or a biomarker of damage to critical adipocyte mitochondrial function, rather than the protagonist in inducing metabolic disease risk.

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P51

Can modulation of beta cell ER stress in the KINGS (*Ins2*$^{+/G32S}$) mouse abolish sex differences in diabetic phenotype?

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Background
The *Ins2*$^{+/G32S}$ mutation in the KINGS mouse drives beta-cell endoplasmic reticulum (ER) stress. The result of this is sexually dimorphic; males develop overt diabetes by 5-weeks (>16.7mM) whilst females remain normoglycemic. Previous studies have shown that high-fat feeding increases beta-cell ER stress, whilst GLP1-receptor agonists reduce this. We investigated whether altering ER stress could promote diabetes development in female KINGS mice or prevent it in males.
Methods
Female KINGS and WT mice were fed normal chow (NC) or a high-fat-high-sucrose (HFHS) diet from 3-weeks until 20-weeks. Blood glucose concentrations were monitored, and glucose tolerance tests performed. Western blotting was used to investigate ER stress in islets isolated from these mice. Male KINGS mice were injected daily with 200ug/kg liraglutide or PBS from 3-weeks until 6-weeks and daily blood glucose concentrations were measured and monitored for 2-weeks post-treatment.
Results
HFHS feeding increased several ER stress markers in the KINGS females compared to NC including BiP (expression fold WT-NC: HFHS-KINGS:3.236, NC-KINGS:1.769). Despite worsened glucose tolerance and a trend for increased non-fasted blood glucose concentrations (20-weeks: HFHS-KINGS:16.4mM $\pm$ 7.2, NC-KINGS: 9.1mM $\pm$ 1.6), HFHS-KINGS mice did not develop overt diabetes. Moreover, their fasted blood glucose concentrations were unchanged and non-fasted concentrations were substantially lower than those in age-matched NC-KINGS males (33.0mM $\pm$ 5.0). Liraglutide significantly lowered blood glucose concentrations and prevented diabetes development in KINGS males (6-weeks:KINGS-Liraglutide:12.33mM $\pm$ 1.7, KINGS-PBS:22.43mM $\pm$ 3.1). However, treatment cessation resulted in increased blood glucose concentrations comparable to the KINGS-PBS group by 49-days.
Conclusions
HFHS feeding increased islet ER stress in the KINGS females but did not induce overt diabetes. Liraglutide prevented the development of diabetes in KINGS males, however this effect was not sustained post-treatment. This indicates that female KINGS mice can adapt to beta-cell ER stress whereas males cannot. In conclusion, sex differences remain despite manipulation of beta-cell ER stress levels.

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P52

How would school children design a poster about diabetes, obesity, health technologies and emotional wellbeing awareness?

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Introduction
Knowledge about end-user perceptions is important to ensure educational resources have maximal impact.

Objective
To understand school children's perceptions and ideas about three endocrine topics.
Methods
This activity was done as part of Society for Endocrinology public engagement grant. Years 5 and 6 school children (aged 10-11 years) from Nonsuch Primary School in Birmingham were invited to create posters on three themes—diabetes and obesity, technology's use in health monitoring and supporting emotional wellbeing within the school environment. Following an 8-minute talk on each of the themes, students were given 20 minutes to create a poster. 56 students participated in groups of four. Six groups produced posters on emotional wellbeing, four on childhood obesity/diabetes and four on technology in healthcare. No additional preparation was involved, which meant the resulting work was a spontaneous assembly of thoughts. Posters were analysed using NVivo 12 software, utilising a thematic inductive qualitative method. The posters were initially coded by an independent study member and then reviewed by another study member to identify common themes.
Results
The most common themes in diabetes posters were exercise (approx. 2/3 of content) and diet (1/3rd). In emotional wellbeing posters, common themes were body changes associated with puberty and communicating feelings with a variety of different support networks such as friends, families and teachers. The common themes in technology posters were the use of heart rate and breathing rate monitoring using small personal portable devices such as watches and mobile phones, which allow for self-monitoring.
Conclusion
School children tended to focus on physical activity and open communication when they created obesity and wellbeing posters. Additionally, they focussed on familiar technologies and self-monitoring for technology posters. Further studies are needed to study the impact of resources based on children's interests or addressing gaps in knowledge.

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P53

DKA registry: Creating a single data collection system for DKA in the West Midlands has helped identify best practices across hospitals

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Background
There are several good practices to improve DKA management across hospitals. However, the lack of a unified system limits comparisons and learning from each other.
Objectives
To establish a DKA registry to identify best practices across centres in the West Midlands.
Methods
All people admitted with DKA at four hospitals in the West Midlands (named A, B, C, D for anonymity) from 1st January 2020 to 31st December 2020 were included in the study. Pseudonymised data was collected using a Google form. Comparison between hospitals was performed using the Independent-Samples Kruskal-Wallis Test.
Results
A total 341 DKA episodes were included (A-76, B-152, C-49 and D-64). Results are presented In comparison to recommendations by the Joint British Diabetes Societies Inpatient Care Group. There was no difference in administering fluids (A- median: 100.0%, B- 87.5%, C- 93.8%, D- 93.8%) and fixed-rate intravenous insulin infusion (A- 100.0%, B- 99.5, C- 100.0%, D- 96.0%) between the four hospitals. However, there were differences in glucose (A- 77.5%, B- 117.9%, C- 76.1%, D- 123.4%) and ketone monitoring (A- 10.0%, B- 56.2%, C- 10.5%, D- 14.0%). DKA duration was lower in Hospital B (A- 18.5h, B: 11.1h, C- 20.8h, D- 15.0h). However, there was no difference in the length of stay for people admitted with DKA (A- 2.9 days, B- 3.5 days, C- 3.9 days, D- 2.9 days).
Conclusion
Certain good practices such as better glucose and ketone monitoring and reduced DKA duration were identified. We recently met the stakeholders who shared their good practices and we are now working with the other hospitals to make improvements and provide the best possible and uniform care for people with DKA across centres.

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P54

Central adiposity and diabetes are causally associated with kidney stone disease

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Introduction
The pathogenesis of kidney stone disease (KSD) is poorly understood and has been linked to features of metabolic syndrome (MetS). Using conventional and genetic epidemiological analyses we studied associations of MetS phenotypes with risk of KSD.
Methods
Multivariate Cox-proportional hazard models were used to assess association of BMI and waist-hip ratio (WHR) with KSD in 492,380 UK Biobank participants. Causal relationships between WHR, BMI, hypertension, hyperlipidaemia, hypercholesterolaemia, fasting insulin, fasting glucose and type 2 diabetes (T2DM) and KSD were interrogated using Mendelian Randomisation (MR).
Results
Data from the UKBiobank demonstrated that high WHR (men ≥ 0.9, women ≥ 0.85) confers $>40\%$ increased risk of KSD in patients with BMI $\geq 25 < 30$ kg/m^2 compared to individuals of normal WHR in this BMI range. MR, using SNPs from published genome-wide association studies, demonstrated that one standard deviation (SD) increase in BMI conferred 28% increased risk of KSD and 1SD increase in WHR was associated with 43% increased risk of KSD. Multivariable MR incorporating WHR and BMI found that WHR retains 44% increased risk of KSD whereas the effect of BMI was attenuated. T2DM and high HDL conferred increased risk of KSD (8% and 18% increased risk per 1SD increase respectively). Multivariable MR incorporating T2DM and WHR showed that both parameters remained causal for KSD (OR 1.34 (95% CI 1.15-1.56) $P < 0.001$ and OR 1.08 (95% CI 1.03-1.15) $P = 0$ .004 respectively). Risk from high HDL showed horizontal pleiotropy. No other MetS phenotypes demonstrated causality with KSD.
Conclusion
Central adiposity and T2DM are causally associated with KSD; elevated HDL demonstrates a pleiotropic relationship with KSD suggesting that genetic variants associated with HDL increase risk of KSD by mechanisms other than a direct effect of altered HDL concentrations. These findings motivate weight management and glycaemic control in KSD prevention. Further studies are required to define mechanisms by which associations arise.

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P55

A novel approach to serum multi-steroid profiling using ultra high-performance liquid chromatography-tandem mass spectrometry with post column infusion ammonium fluoride

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Comprehensive multi-steroid profiling offers a powerful tool for the investigation, diagnosis and management of steroidogenic disorders by simultaneously quantifying multiple steroids from several pathways of steroid biosynthesis and

metabolism. Difficulties can arise when optimising chromatography and mass spectrometry conditions for many analytes in a single method. Low concentrations of ammonium fluoride have previously been shown to enhance the sensitivity of select analytes when used as an LC mobile phase additive; however, its impact on multi-steroid profiling has yet to be investigated. Here, we present the optimisation, validation and application of an ultra high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) assay for the profiling of 25 steroids in serum. Samples were mixed with isotopically labelled internal standards and extracted by liquid-liquid extraction. Steroids were chromatographically separated in 5.5 minutes using a Phenomenex Luna Omega C18 column (1.6 µm, 100 Å, 2.1 x 50 mm) and a water-methanol gradient. Quantification was performed on a Waters Xevo TQ-XS mass spectrometer using electrospray ionisation in positive ion mode. Ammonium fluoride (6 mmol/l, post-column infusion (PCI)) and formic acid (0.1 % (v/v), mobile phase additive) were compared as ionisation additives. PCI of ammonium fluoride significantly enhanced ionisation in a structure-dependent fashion compared to the use of formic acid as mobile phase additive, with the exception of androstanediol that showed reduced ionisation efficiency with NH_4F. Using PCI NH_4F, accuracy was acceptable for 23/25 analytes (bias range 14.0% to 11.9%). Imprecision for serum and spiked surrogate matrix samples ranged from 2.3% to 23.9% and was $<15\%$ for 18/25 analytes. PCI of the mobile phase additive increased both ionisation of the steroids and column lifetime. PCI enabled the simultaneous, sensitive profiling of 25 steroids from glucocorticoid, mineralocorticoid and androgen biosynthesis pathways allowing for a comprehensive assessment of the steroid metabolome in serum.

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P56

Novel regulation of GR mediated gene expression by PARP-1 in mouse skeletal muscle cells

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The glucocorticoid receptor is constitutively expressed and fundamental to life. Activity of GR is partially governed by interacting partners whose actions skew the frequency with which GR produces meaningful transcriptional outcomes. Moreover, the tissue-specific actions of GR are themselves defined, with binding patterns being distinct in various tissue types. These features mean full molecular understanding of this steroid hormone receptor remains incomplete. As glucocorticoid activation of GR and the enzyme poly(ADP-ribosyl) polymerase1 (PARP1) have prominent roles in the regulation of inflammation we sought to establish if PARP1 influences the genome binding and transcriptional productivity of GR. Murine muscle C2C12 cells were transfected with silencing RNA targeting PARP1 then treated $\pm$ dexamethasone (1uM) for 2 and 24 hours ($n = 5$). RNAseq was conducted on lysates to understand short and longer-term influence PARP1 holds over GR behaviour. Knockdown of PARP1 had no influence over the ability of dexamethasone to activate archetype target genes including *DUSP1, MURF1, ATROGIN1* and *GILZ.* Silencing PARP1 significantly impacted the expression of 434 genes with Dexamethasone treatment (2hours) (164 up regulated and 270 genes down regulated). Pathway analysis of these genes show that cell-cycle regulation was significantly overrepresented (adj$P = 0$ .0002). Significant changes were measured in cytoskeletal tubulin genes (*TUBA1A* adj$P = 0$ .008, *TUBA4A* adj$P = 0$ .003, *TUBB2A* adj$P = 0$ .01, *TUBB5* adj$P = 0$ .04 and *TUBB4B* adj$P = 0$ .02). ChIPseq of Dexamethasone treated C2C12s revealed shifts in GR and PARP1 binding enrichment, indicating PARP1 moderates its activity in response to glucocorticoids. Analysis of siPARP1 RNA treated for 24 hours Dexamethasone resulted in modest changes in change expression. (23 significant changes 20 upregulated and 3 downregulated). These data suggest PARP1 influences short-term transcriptional behaviours of the glucocorticoid receptor and glucocorticoids themselves impact PARP1-genome interaction events. These findings not only have importance in the understanding of general GR mechanisms but also to the wdespread functional decline observed during chronic glucocorticoid excess.

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P57

Transcriptomic profiling of human enteroendocrine cells in primary ileal and duodenal organoid culture

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Introduction
Enteroendocrine cells (EECs) are hormone-secreting cells within the intestinal epithelium that play an important role in regulating food absorption, insulin secretion and appetite. To understand the molecular mechanism governing the function of EECs, it is important to investigate cell-type-specific gene expression. The aim of this study was to identify the transcriptome of human EEC populations from organoid culture.
Methods
To label the full spectrum of human EECs in organoids from adult human proximal small intestine (duodenum) and distal small intestine (ileum), CRISPR-Cas9 followed by homology-directed repair was used to insert a P2A ribosomal stutter sequence, followed by the fluorescent protein Venus sequence at the 3' end of the chromogranin-A (CHGA) coding sequence, a general marker of EECs, in chromosome 14. Venus-positive EECs were collected by flow cytometry. Single-cell RNA-seq was performed using the 10x Genomics 3, GEX V3.1 platform.
Results
The transcriptional profiles of 10,016 cells and 5,911 cells from the duodenal and ileal organoids respectively were analysed. Cluster analysis identified six major EECs populations in ileal organoids and ten in duodenal organoids. Gut hormones were amongst the top differentially expressed genes for each of the labelled clusters, including SST-expressing D cells, MLN/GHRL expressing M/X cells, and TPH1-expressing enterochromaffin cells in both regions, while GAST/-GIP/CCK expressing G/K/l cells were detected in the duodenum, and GCG-expressing L cells in the ileum. Interestingly, clusters of mature EECs were detected in both duodenum and ileum that do not express known hormonal markers. The expression of G-protein coupled receptors differed between clusters, suggesting that EECs are regulated differentially.
Conclusion
In this study, we have generated high-resolution transcriptomic profiles of human EECs from proximal small intestine (duodenum) and distal small intestine (ileum) which provide an important foundation to guide future genomics-based interrogation of EECs functions and their sensory apparatus.

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P58

Outcomes of postmenopausal women with non-alcoholic fatty liver disease (NAFLD)

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Background
Non-alcoholic fatty liver disease (NAFLD), encompasses hepatic steatosis alone (NAFL), steatohepatitis (NASH), NAFL/NASH with fibrosis and cirrhosis. Severe fibrosis and cirrhosis are associated with increased risk of morbidity and mortality (due to cardiovascular events, end-stage liver failure and cancer). Postmenopausal women are a high-risk group of patients that have worse outcomes, but the specific factors that place them at higher risk are incompletely understood.
Methods
We performed a retrospective analysis of patients with clinically or histologically diagnosed NAFLD, followed-up in the multi-disciplinary Metabolic Hepatology Clinic at Imperial College Healthcare NHS Trust, with an initial clinic visit between 2010 and 2017.
Results
Within this cohort of 220 patients, 34% were women $\geq$55 years (presumed to be postmenopausal), 31% were men $\geq$55 years, 45% were White. In terms of outcomes, 22% had cirrhosis and 8% died during the follow-up period (up to 11 years). 11 (65%) of the patients who died and 11 (23%) of the patients with cirrhosis were postmenopausal women. There was a significantly higher proportion of women $\geq$55 years who had a baseline FibroScan liver stiffness measurement (LSM) $\geq$8kPa (increased risk of advanced fibrosis) compared to

men ≥55 years, (59% vs 41%, $P = 0.032$, using chi-squared tests). Multivariate logistic regression demonstrated that women ≥55 years were more likely to have follow-up LSM ≥8Pa (OR 2.5 [1.1-5.8], $P = 0.019$) and type 2 diabetes (OR2.4 [1.0-5.5], $P = 0.026$), whilst men ≥55 years were more likely to have ischaemic heart disease/stroke ($P = 0.032$).

Conclusions

Postmenopausal women represent a significant proportion of NAFLD patients referred to specialist care, and they may be more likely to have advanced fibrosis when they are initially reviewed. Some co-morbidities may be more prevalent in postmenopausal women compared to other groups. Further work is required to fully phenotype these patients, so that modifiable factors can be targeted to improve outcomes.

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P59

Acidosis reduces 11β-HSD1 activity in human primary muscle cell cultures

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Background

Acidosis activates the hypothalamic-pituitary-adrenal (HPA) axis and induces glucocorticoid-mediated atrophy of skeletal muscle. The enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts inactive cortisone to active cortisol and modulates glucocorticoid signalling locally within skeletal muscle. Here, we address a gap in knowledge how acidosis affects 11β-HSD1 activity in human skeletal muscle cells.

Methods

Quadriceps muscle tissues were acquired from consented adult patients undergoing elective joint replacement for osteoarthritis. Myoblasts were isolated, cultured *in vitro* and differentiatedto form multinuclear myotubes. Myotubes were incubated in media with added HCl or NaOH for pH adjustment (pH range 6.8 - 7.6) for 48 hours. 11β-HSD1 enzymatic activity was measured directly using radiolabelled cortisone and thin-layer chromatography, and normalised to total protein. Furthermore, effects of acidosis on cortisone-induced gene expression were assessed by rtPCR. All experiments were repeated in cells from 3-4 different muscle tissue donors.

Results

Muscle tissue donors were 57 – 84 years old and 2/6 were female. There was a significant trend for decreasing 11β-HSD1 activity with decreasing pH over a range from 6.8 to 7.6 ($P < 0.01$). Acidosis at pH 7.1 caused no significant change in gene expression of 11β-HSD1 or the co-factor enzyme H6PD compared to the control condition at pH 7.4. Interestingly, cortisone-induced mRNA expression of the catabolic genes FOXO1 and TRIM63 was diminished in the presence of acidosis compared to the control condition (FOXO1: $P < 0.05$; TRIM63: $P < 0.01$).

Conclusion

Acidosis reduced glucocorticoid activation by 11β-HSD1 in human skeletal muscle cells. Furthermore, acidosis diminished cortisone-induced activation of catabolic genes, a downstream effect of glucocorticoid activation by 11β-HSD1 function. These results suggest that reduced 11β-HSD1 activity locally in skeletal muscle may counteract effects of systemic HPA axis activation in acidotic conditions. The mechanism how acidosis changes 11β-HSD1 activity requires further investigation.

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P60

Mimicking chronic hyperglycaemic conditions in primary human endothelial cell cultures using pathophysiological concentrations of glucose in prediabetes and type 2 diabetes

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Introduction

In the UK alone, diabetes affects nearly 4 million people and an additional 13.6 million people are estimated to be at high risk of developing type 2 diabetes (T2DM). Diabetes is associated with vascular complications which path the development of cardiovascular diseases such as strokes and heart attacks. Previous studies have shown various pathways in which hyperglycaemia leads to endothelial dysfunction and insulin resistance. However, current reports of *in vitro* studies employed supraphysiological concentration of glucose which induces apoptosis in cell cultures, limiting the translational value of the research and failing to provide insights into the effect of pathophysiological hyperglycaemia in prediabetes and T2DM on endothelial function.

Hypothesis

Pathophysiological hyperglycaemia in prediabetes and T2DM impairs vascular endothelial insulin sensitivity.

Methods

To mimic the effect of chronic hyperglycaemia on the endothelium in patients with prediabetes or T2DM, primary human umbilical vein endothelial cells (HUVECs) were incubated in growth media supplemented with glucose at pathophysiological concentrations (control: 5.55mM; prediabetes: 6.9mM; T2DM: 7.8mM) for 72 hours. HUVECs were then lysed (unstimulated) or stimulated with 100nM insulin for 15 min. Protein expression was determined using Western blot.

Results

Hyperglycaemia (7.8mM)-treated HUVECs expressed a higher unstimulated level of Akt (S473) and RAPTOR (S792) phosphorylation compared to the control, despite Akt (T308) phosphorylation level was unchanged. Upon insulin stimulation, hyperglycaemia (6.8mM and 7.8mM)-treated HUVECs possessed a higher expression of insulin receptor β, but a smaller extent of insulin-stimulated Akt (S473) phosphorylation. No changes in phosphorylation of endothelial nitric oxide synthase (eNOS) or extracellular signal regulated protein kinase (ERK)1/2 were detected across all treatment groups.

Conclusion

Prolonged hyperglycaemia in prediabetes and T2DM conditions increased basal Akt phosphorylation and impaired insulin-induced Akt phosphorylation in endothelial cells *in vitro*. Future work shall focus on examining the functional readout and determining the changes in downstream Akt signalling of hyperglycaemia-treated cells.

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P61

The Effect of Bariatric Surgery on the proteome of people achieving remission of Type 2 Diabetes

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Background

Bariatric surgery (BS) results in metabolic pathway recalibration. When major metabolic change occurs, blood protein components have a key role and can be altered significantly. We set out to identify potential biomarkers of change in plasma following BS in people achieving remission of type 2 diabetes mellitus (T2DM).

Methods

Longitudinal analysis was performed on serum samples from 10 individuals who all achieved remission of T2DM following Roux-en-Y gastric bypass ($n = 7$) or Sleeve gastrectomy ($n = 3$). Sequential window acquisition of all theoretical fragment ion spectra Mass Spectrometry (SWATH-MS) was on serum samples taking at 4 months before and 6 and 12 months after BS.

Results

467 proteins were quantified by SWATH-MS. Principal component analysis resolved samples from distinct time points after selection of key discriminatory proteins: Twenty-five proteins were differentially expressed between pre-surgery and 6 months post-surgery; thirty-nine proteins between baseline and 12 months. Eight proteins were significantly different to pre-surgery samples at both 6- and 12-months post-surgery. These were: sex hormone binding globulin(SHBG), Serotransferrin(TF), Proteoglycan 4, Apolipoprotein A4(APOA4), Leucine-rich alpha-2-glycoprotein, Heat shock 70 kDa protein 4(HSPA4), Bifunctional epoxide hydrolase 2 and N-acetylmuramoyl-L-alanine amidase. The panel of proteins identified as consistently different, included peptides related to insulin sensitivity (SHBG increase)(FC: Fold change 12 months vs baseline), p value)(1.95, $P < 0.01$), systemic inflammation (TF and HSPA4 – both decreased) (TF Fold change 12 months vs baseline -0.78, $P < 0.01$; HSPA4 Fold Change 12 months vs baseline -0.38, $P < 0.05$), and lipid metabolism (APOA4 decreased) (APOA4 Fold Change 12 months vs baseline -1.38, $P < 0.05$).

Conclusion

Using the technique of SWATH-MS to generate proteomic maps, we have shown significant change in serum protein levels for a number of metabolically relevant proteins from pre-BS to 6- and 12-months post-surgery. Several of these proteins are key components in critical metabolic and inflammatory pathways.

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P62

Hypoglycaemia in non-diabetics. An Endocrinologist's perspective

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Hypoglycaemia, a life threatening complication, occurs as part of a wide variety of disease processes. Though a common side effect of diabetes medications, it can be secondary to other factors including, endocrine and, metabolic disorders, severe sepsis, rare malignancies and non-diabetic medications. We present a case series of 3 non-diabetic patients who presented to Princess of Wales, Bridgend with Hypoglycaemic Episodes (HE):

1. 23 year old student nurse with episodes of sweating and tremors coinciding with HE (2.2 to 3.5 mmol/l) throughout the day and history of gaining 15Kg weight. Her sister had Type 1 diabetes. Thyroid function test, Short Synacthen test and anti-GAD antibody were normal. We conducted a 72 hour fast during which blood glucose did not drop $<$3.1mmol/l, along with appropriate suppression of Insulin ($<$3.0pmol/l) and C-peptide (299pmol/l). Sulphonylurea screen was negative. Dietary modifications resolved fasting HE but postprandial HE persisted. With a clinical diagnosis of postprandial reactive hypoglycaemia, trial of Acarbose along with dietician input was recommended. Due to patient's reluctance, symptoms persist. She is now seeking a 4th opinion!
2. 85 year old woman with heart failure presented with severe sepsis and HE of 1.4mmol/l which persisted even after successful treatment of sepsis. Medication review led to Sacubitril as rare cause for HE, proven on resolution of HE after withdrawing Sacubitril.
3. 27 year old man without co-morbidities presenting with neuroglycopaenic symptoms and HE, with family history of maternal neuroendocrine tumour. A positive 72 hour fast demonstrated hypoglycemia of 1.8mmol/l, and inappropriately raised C-peptides (718 pmol/l) and Insulin (25.7pmol/l) levels. MRI pancreas demonstrated 1cm lesion in tail. MRI pituitary was normal in spite of elevated prolactin of 687mIU/l. Patient started on Diazoxide while awaiting pancreatic surgery. Genetic testing is negative for MEN 1.

Hypoglycaemia can affect people without diabetes and this beehoves us to extract history carefully, examine and review the medications keeping rare causes in mind as well.

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P63

Polygenic lipid risk as a precipitant in Type III hyperlipidaemia

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Background
Type III hyperlipidaemia (T3HL) is characterised by equimolar increases in plasma triglyceride and cholesterol on an *APOE2/2* genotype background and conveys a high risk of early-onset cardiovascular disease (CVD). Phenotypic penetrance of T3HL is $<$10% and precipitated by several endocrine/metabolic disorders such as obesity, diabetes and hypothyroidism. We explored the effect of triglyceride-raising polygenic score precipitating T3HL, in the context of known precipitants and CVD.
Methods
A weighted polygenic score (TG.PS) was developed using 107 independent triglyceride-raising genetic variants identified from GLGC-GWAS. The TG.PS was applied to the Oxford Biobank (OBB, n = 6,952) and the UK Biobank (UKB, n = 460,037) to analyse effects on plasma lipid phenotypes. The relationship between *APOE2/2* status and prevalent or incident CVD was examined in UKB.
Results
TG.PS was strongly associated with an increase in triglyceride concentration in OBB and UKB (1 TG.PS SD equalled to +13-15%, $P = 5.52\times10^{-128}$ (OBB), $P < 10^{-300}$ (UKB)). Similarly, *APOE2/2* carrier status increased triglycerides by 19% (P = 0.039, UKB). Males were more susceptible to TG.PS effects (interaction-$P = 1.44\times10^{-05}$ (OBB), interaction-$P = 6.40\times10^{-25}$ (UKB)). There was no interaction between the *APOE2/2* genotype and TG.PS, BMI, sex or age in raising triglycerides. *APOE2/2* carriers had lower apoB ($P = 5.97\times10^{-34}$ (OBB), $P < 10^{-300}$(UKB)). In cross-sectional CVD analysis, restricted to males with *APOE2/2* and *APOE3/3* genotypes, T3HL exhibited no more risk of CVD compared with similarly hypertriglyceridaemic participants (OR 1.08, 95%CI 0.81-1.44, P = 0 .61). However, in normolipidaemia (triglycerides $\leq$ 3mmol/l), *APOE2/2* carriers had less prevalent CVD (OR 0.77, 95%CI 0.62-0.94, P = 0 .01), but no difference in incident CVD (OR 0.91, 95%CI 0.71-1.15, P = 0 .42).
Conclusion
TG.PS confers an additive risk for developing T3HL, of comparable effect size to the other known hyperlipidaemia precipitants, and has a greater effect in males. The protective effect of *APOE2/2* genotype for prevalent CVD is consistent with the intrinsically lower apoB concentration.

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P64

The Variability In Glycosylated Haemoglobin (HbA1c) Testing Interval In People With Diabetes Is Linked To Long-Term Diabetes Control, Independent of HbA1c Test Interval

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Introduction
Worldwide guidance advocates regular HbA1c testing for people with diabetes mellitus, usually 2-4/yr. We previously showed that HbA1c testing frequency is linked to outcome in terms of HbA1c control. Here we examine the effect of variability (standard deviation = SD) in test interval on change in HbA1c over 7 yrs (Jun 2012-Jul 2019) using laboratory data.
Methods
We focused on people with HbA1c within the first 2 years who also had a HbA1c 5 years$\pm$ 3 months later and $\geq$6 tests (total 23582 people). We grouped cases based on the number of tests between $t_0$and $t_{0+5yrs}$and calculated the SD decile for each group. We examined the link between SD deciles and DHbA1c level,stratifying by starting HbA1c.
Results
We showed that higher variability in testing frequency was linked to worsening HbA1c control. This effect was most evident in those with lower starting HbA1c levels. In those with a starting HbA1c of $<$59mmol/mol, the lowest SD decile was associated with an increase in mean HbA1c of 3.9mmol/mol while for those with the highest decile, it was more than double this (7.9mmol/mol). In those with an initial HbA1c of 59-75mmol/mol, the lowest SD decile had a mean reduction of 3mmol/mol, while those in the highest decile showed a 4mmol/mol rise. In those with starting values of $>$75mmol/mol, the same trends were seen, but were less marked. These effects were independent of testing interval. Mean HbA1c level increased with increasing SD decile, irrespective of starting HbA1c (P = 0.009).
Conclusion
These findings indicated that HbA1c testing consistency/regularity, not just numbers of tests/yr, is important in maintaining diabetes control, especially in those with on-target HbA1c levels. This has implications for the management of people who attend sporadically for testing and suggests the need for developing systems to improve regularity of testing.

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P65

Meeting the Challenge of Bariatric Surgery during the first wave of Covid -19 in a patient with a BMI $>$100kg/m^2

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Introduction
The super-super-obese category of patient (BMI $>$60) tend to respond poorly to conservative weight interventions. Bariatric surgery is therefore considered the best form of intervention. Only a few UK centres have expertise to manage

patients with a BMI $>100kg/m^2$ and careful counselling is essential as those standing to benefit the most from these procedures (through reduced risk of cardiovascular disease, diabetes and malignancy) also face the highest risk of morbidity and mortality. The first wave of Covid-19 presented the East Midlands Bariatric and Metabolic Institutes multidisciplinary team with multiple challenges to ensure that our very high risk patients could continue to safely access bariatric surgery. The combined Covid-19 and surgical risk were successfully minimised through careful planning of the management of patient, staff and the environment.
Case Summary
A 24 year old female with Class IV super super obesity (baseline BMI 109, 287kg) attended for consideration of surgical management. Her co-morbidities were lymphoedema, recurrent leg cellulitis and reduced mobility (wheelchair dependent). In preparation for surgery she undertook a tier 3 program followed by a pre-op very low calorie diet for 4 weeks liraglutide injections for 6 weeks. With this regime she attained a pre-op weight of 264kg (BMI 100). She underwent an uncomplicated laparascopic sleeve gastrectomy lasting 85 minutes with an uneventful post-operative recovery. At follow up 5 months after her operation she reports a total weight loss of 75.7kg with an excess weight loss of 34.1% (BMI of $80.5kg/m^2$, 211.3kg). She is managing her early satiety well with small, frequent meals and has noted an improvement in her mood, better mobility and is keen to continue to increase her physical activity as lockdown restrictions ease.

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P66

Challenges in the management of severe hypertriglycridaemia causing acute pancreatitis

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Pancreatitis has multiple aetiologies of which commonest are gall stones and alcohol. Hypertriglyceridaemia is a less common (1-14 %) cause of pancreatitis. We present three case histories of acute pancreatitis due to severe triglyceridaemia and its management challenge in people with diabetes.
Case history
1. A 33-year-old man with BMI of 41 kg/m^2 with Hodgkin lymphoma, thyrotoxicosis and diabetes, but no history of alcohol use was diagnosed to have pancreatitis. Biochemical profile revealed total cholesterol (TC) 26.8 mmol/l (nr 0-5), triglyceride 90.5 mmol/l (0.8-1.8), HDL-cholesterol (HDL-C) <0.08 mmol/l. No gall stones were detected. He was treated with intravenous insulin and plasma exchange which lowered triglyceride levels to 6.8 mmol/l. He was later initiated on atorvastatin, fibrate and biphasic insulin.
Case history
2. A 23-year-old man with type 2 diabetes and no history of alcohol use or gall stones was diagnosed with pancreatitis. Biochemical profile revealed TC 11.5 mmol/l, triglycerides 44.9 mmol/l and HDL-C 0.31 mmol/l. He was treated with intravenous insulin infusion initially and later with atorvastatin, fibrate and biphasic insulin. Triglyceride levels were lowered to 3.5 mmol/l.
Case history
3. A 53-year-old man with pancreatitis thought to be due to non-obstructive gall stones 6 months previously, was awaiting elective laparascopic cholecystectomy. Pre-operative bloods tests revealed TC 20.7 mmol/l, triglyceride 59.4 mmol/l and HDL-C 0.22 mmol/l. He was initiated on metformin, biphasic insulin, atorvastatin, fibrate and ezetimibe. TC went down to 3.9 mmol/l, triglyceride to 4.39 mmol/l and HDL-C to 0.66 mmol/l.
Conclusion
Our case histories highlight the importance of checking lipid profile in every patient with diabetes presenting with acute pancreatitis. Insulin therapy, either intravenously or sub-cutaneously seems to rapidly reduce triglyceride levels in such patients.

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P67

Association of Vitamin D and Adiposity in Children and Adolescents with type 1 diabetes: a case-control study

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Background
Vitamin D (25(OH)D) deficiency is a global public health issue. An association with obesity and diabetes has been described in adult and paediatric populations. This study investigates the prevalence of 25(OH)D deficiency and its correlates in population of Emirati children and adolescents attending a large diabetes centre in the United Arab Emirates.
Methods
Participants aged 4-19 years were selected based on diabetes status [type 1 diabetes (T1D), normoglycaemic non-diabetic (NG)] from Abu Dhabi Diabetes and Obesity Study. Body composition was assessed using bioelectrical impedance analysis (Tanita®). BMI percentile was categorized based on CDC recommendation. 25(OH)D cut-offs were defined as deficient (<30nmol/l), insufficient (30-50nmol/l) and sufficient (>50nmol/l) using WHO Criteria.
Results
In total, 148 participants with T1D and 296 age and sex-matched normoglycaemic controls were included. The prevalence of 25(OH)D (<30nmol/l) deficiency was 22.3% ($n = 33$) in T1D and 40.5% ($n = 120$) in control group. A decline in 25(OH)D levels was observed with increasing age in both groups, from 4-7 years to 15-19 years [T1D, $P = 0.018$), NG, $P = 0.0001$]. A larger proportion of females were 25(OH)D deficient in both groups (NG: 52.6% vs 23.6%, $P < 0.0001$; T1D: 31.7% vs 10.6%, $P = 0.0020$). After adjusting for age and sex, children and adolescents with BMI $\geq 95^{th}$ percentile were 2.5 times more likely to have 25(OH)D deficiency (OR: 2.69; 95% CI: 1.56, 4.64) than those with BMI 5^{th}-$<85^{th}$ percentile. A negative correlation was observed between adiposity measures and 25(OH)D levels in both groups (T1D $P < 0.01$, NG, $P < 0.001$).
Conclusion
Vitamin D deficiency is common among Emirati children and adolescents. The lower prevalence among T1D population described here may represent better treatment compliance. Our study also confirms an association between vitamin D deficiency with obesity in general and with body fat mass in particular.

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P68

Rhino-orbital-cerebral mucormycosis in diabetes patients with COVID-19

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During the second wave of COVID-19 pandemic in some parts of the world especially in India there were significant numbers of rhino-orbital mucormycosis cases were reported. These cases were remarkably found in COVID-19 patients with diabetes, new-onset diabetes, DKA, stress hyperglycaemia, high ferritin levels, concomitant corticosteroid therapy defective phagocytic activity due to diabetes itself or immunosuppressive agents. COVID-19 is witnessed with widespread manifestations of opportunistic bacterial, fungal and parasitic infections. The mucorales spores germinate in hyperglycaemic, hypoxic and acidic environment that usually found in prolonged hospitalised patients with or without mechanical ventilation. Rhino-orbital mucormycosis is an angioinvasive disease caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia of Order Mucorales being in class of Zygomycetes. The Rhizopus Oryzae is most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral mucormycosis, and especially during this COVID-19 pandemic with an overall 46% mortality. In a large meta-analysis of 851 cases done in 2018, found diabetes remains the leading risk factor of mucormycosis (Odds ratio [OR] 2.69; 95% Confidence Interval [CI] 1.77–3.54; $P < 0.001$). After the landmark RECOVERY trial of UK, there are a trend of wide-spread use of steroid in more or less every cases of COVID-19 but surprisingly the emergence of mucormycosis was unheard in UK and elsewhere but in India. Even before the pandemic the sporadic incidences of mucormycosis were reported in India. In a recent case series of 101 mucormycosis cases in Covid-19, where 80% cases had diabetes, and more than two-third (76.3%) received a course of corticosteroids. These findings suggest a trinity of mucormycosis, diabetes and injudicious use of steroid, in people with COVID-19. Correction of risk factors, surgical debridement and a course of Amphotericin B are the main line of treatment.

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P69

Persistent Lactic Acidosis after resolution of DKA in Young Patients with Poorly Controlled Diabetes Mellitus

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Background
Lactic acidosis is a common finding in critically ill patients. In patients with poorly controlled diabetes for a prolonged period of time, Glycogenic hepatopathy (GH), can cause lactic acidosis which is a rare condition that develops due to excessive accumulation of glycogen in the hepatocytes.
Cases
Two cases with poorly controlled diabetes and glycogenic hepatopathy are presented. First patient was a 28 year old female with 20 year history of diabetes, HbA1c of 77 mmol/mol, BMI 24.1 kg/m^2, 4 admissions with DKA in last 12 months; was admitted with lactic acid of 3.0 mmol/l. On presentation, labs showed Glucose 37.1 mmol/l, H+ 114 nmol/l, HCO3 3 mmol/l. She was treated for DKA which resolved in 34 hours. Lactate peaked at 7.4 mmol/l. Ultrasound showed hepatomegaly with normal LFTs apart from ALP of 163 U/l. Second case was another 28 year old with a 17 year history of diabetes, HbA1c of 118 mmol/mol, BMI 23.6 kg/m^2, 3 admissions with DKA in last 12 months; was admitted with lactic acid of 2.7 mmol/l. On presentation, labs showed H+ 88 nmol/l, HCO3 6 mmol/l, Glucose 41.6 mmol/l. She was treated for DKA which resolved in 29 hours. Lactate peaked at 5.5 mmol/l. Ultrasound showed hepatomegaly (19.5cm) with normal LFTs apart from ALP of 153 U/l. Basal bolus insulin regimen was continued and biopsy was not permed in either of the cases.
Discussion
In these 2 patients with history of poorly controlled diabetes and hepatomegaly on ultrasound, lactate levels continued to rise during and after resolution of the DKA, with GH likely cause of the hepatomegaly. It is important to differentiate it from NAFLD as it does not progress to cirrhosis and can improve with better glycemic control.

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P70

Real-world metabolic outcomes of semaglutide use in patients with type 2 diabetes: a retrospective study from a single centre in the United Arab Emirates

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Background
The Glucagon-like peptide-1 receptor agonist (GLP1RA) semaglutide has shown improvements in glycaemia and other metabolic parameters for patients with type 2 diabetes (T2D) in clinical trials. Published real-world data are sparse and there are none from the Middle East where semaglutide became available in 2020.
Method and Results
We retrospectively gathered data for 289 patients (median age 50 years (IQR 42-57), 36% female, 87% Emirati and 8% other Arab ethnicity) who took continuous once weekly semaglutide injection for 6 months. At initiation median HbA1c was 7.4% (6.6-8.6) and median BMI was 35.3kg/m^2 (31.6-39.3). Median fall in HbA1c at 6 months was 0.7% (0.1-1.3, $P < 0.001$). Median BMI fell 3.0% (0.9-6.3, $P < 0.001$), significantly more in female patients [3.8% (1.1-6.7) vs 2.6% (0.02-4.9) ($P = 0.01$)] than in men. LDL cholesterol reduced significantly by median 0.24mmol/l (0.05-0.64, $P < 0.001$), as did triglycerides which fell by 0.28mmol/l (-0.04-0.68, $P < 0.001$). There was no significant change in blood-pressure, nor was there a reduction in number of medications to treat T2D, dyslipidaemia or hypertension. Comparing those switching from alternative GLP1RA ($n = 106$) to the GLP1 naïve group ($n = 183$), the difference in performance was small and not significant (HbA1c -0.5% vs -0.7%, and BMI -2.9% vs -3.0% respectively). Bariatric surgery did not significantly affect outcomes ($n = 24$). Mean semaglutide dose over the period was 0.77 mg/week (median 1 mg/week). Documented adverse effects led to discontinuation in 8% of patients.
Conclusion
We observed real-world weight loss consistent with existing clinical trial data. This bodes well for patients with obesity who may benefit further from longer treatment and higher doses of semaglutide. However, improvement in glycaemia was modest, which may partially be explained by the relatively low starting HbA1c. Patients previously taking alternative GLP1RAs improved comparably. It is unclear why women in our population lost more weight as baseline BMI was not different to men.

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P71

Lipopolysaccharide signalling modulates brown fat transcriptome and cytokine secretion

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Background
Brown adipose tissue (BAT) thermogenesis offers an appealing prospect to combat obesity. Obesity is characterised by a state of chronic inflammation in adipose tissue mediated by the secretion of a range of inflammatory-cytokines. Our previous work has highlighted that a gut-derived inflammatory agent, lipopolysaccharide (LPS), reduces brown adipocyte activity, insulin sensitivity and mitochondrial-function and is increased with obesity and type 2 diabetes mellitus (T2DM). However, the wide range effects of LPS on brown adipocyte function are unclear. Therefore, the aims of this study were to investigate the spectrum of LPS actions in brown adipocyte and their secretory function, as well as to identify novel factors to explore their therapeutic potential against obesity.
Methods
Murine immortalized brown adipocytes were differentiated with or without LPS (100ng/ml). mRNA and secreted-protein were collected for RNA-sequencing and Proteome Profiler Array analysis.
Results
RNA-Seq analysis revealed that thermogenesis and extracellular matrix (ECM)-receptor interaction were among the top KEGG-pathways significantly (negatively/positively, respectively) enriched in LPS-treated brown adipocytes ($P < 0.0001$), which also included negatively-enriched mitochondrial respiration and oxidation pathways ($P < 0.0001$). In accord with RNA-Seq data, LPS-treated brown adipocytes showed not only increased secretion of classical inflammatory factors but also increased levels of novel cytokines, compared to control. Nineteen cytokines were identified as being induced by LPS. Within this group were novel brown adipocyte-secreted cytokines: VCAM-1 (5.5 fold increase, $P<0.01$), Endostatin (4.5 fold increase, $P < 0.05$), Angiopoietin-1 (4.5 fold increase, $P < 0.0001$).
Conclusions
This study provides evidence that LPS alters the thermogenic components of brown adipocytes at transcriptional and secretion levels. The inflammatory microenvironment results from secretion of cytokines from brown adipocytes themselves upon LPS-treatment, representing an important target to prevent reduced thermogenic potential in brown adipocytes during obesity. Therefore, combatting the effects of inflammation in BAT may help to reduce the impact of obesity and its subsequent consequences.

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P72

Impact of PCSK9 Inhibitors on hypercholesterolaemic patients at a tertiary centre lipid clinic

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Background
Elevated low-density lipoprotein cholesterol (LDL-C), which arises due to genetic and environmental factors, has a causal role in the pathogenesis of cardiovascular disease (CVD). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are approved for patients with familial hypercholesterolaemia (FH) and patients at high risk of CVD due to non-familial hypercholesterolaemia (non-FH). In clinical trials, PCSK9 inhibitors are well-tolerated and lead to reductions in LDL-C of up to 67%. However, evidence regarding the efficacy and tolerability of the drug in real-world clinical practice remains scarce.
Aims
This study aimed to evaluate the tolerability and efficacy of PCSK9 inhibitor therapy at a tertiary centre lipid clinic. Subanalyses were performed to determine whether outcomes differ between patient subpopulations.
Methods
This was a retrospective study involving patients who commenced PCSK9 inhibitor therapy at Imperial College Healthcare Trust lipid clinic, between 1st January 2017 and 31st December 2019. Demographics, clinical characteristics and laboratory results were collected at the time of PCSK9 initiation, and after 3, 6, 12 and 24 months, where applicable. Outcome measures included mean and percentage change in LDL-C over time.

Results
37 patients were analysed after exclusions, of which 30 patients had FH, and 7 patients had non-FH. Within the whole cohort, there was a significant reduction in mean LDL-C of 34% within 3 months ($P < 0.001$), which was sustained for at least 2 years. There was a non-significant difference in responsiveness to therapy between FH and non-FH groups, and at 12 months, there was regression of LDL-C to above baseline in the non-FH group.
Conclusion
PCSK9 inhibitor therapy was well-tolerated and produced significant reductions in LDL-C within 3 months in this patient cohort. Reasons for divergent responses between FH and non-FH groups require further exploration.

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P73

Beer Potomania Hyponatraemia: a discordant medley of symptoms of osmotic demyelination syndrome with ataxia and dysarthria

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A 41 year old gentleman presented with collapse and vomiting for one week was found to be hyponatraemic with sodium of 103. He was treated with a sodium chloride 0.9% over 100 ml/hour and once sodium was increased to 118 in less than 24 hours. He was deescalated from intensive care on day3. He had developed severe ataxia, slow speech and was highly emotional. He was previously high functioning, maintaining a job and independent. It had transpired that he had been drinking 18 cans of larger a day for the past 3 years with no contact with a physician, meaning the chronicity of hyponatraemia was unknown. The Differential for his ataxia and dysarthria was either cerebellar vermis atrophy secondary to chronic alcohol intake or central pontine myelinosis because of rapid correction of sodium. To investigate this, a brain magnetic resonance was done which revealed features of osmotic demyelination syndrome (ODS)- a life threatening demyelinating condition. ODS is classically in males between 30-50 years old predisposed by chronic alcohol use and the underlying cause of ODS is frequently rapid correction of severe hyponatraemia causing rise in tonicity. Although the symptomatology of weakness in ODS is either symmetrical limb weakness or extra pyramidal features like ataxia or dysarthria. Retrospectively, he developed permanent clinical symptoms manifesting from central pontine (dysarthria) as well as extra-pontine (ataxia, neurobehavioural symptoms-depression, emotional instability) demyelinosis. Despite careful correction of hyponatraemia, extra awareness in a patient with high risk factors of ODS (alcoholism) is needed, especially vigilance in the discordant presentations of symptoms manifesting from ODS.

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P74

Long-term follow-up of hemichorea-ballism syndrome associated with acute hyperglycemic crisis

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Background
Diabetic striatopathy (DS) is a rare dyskinetic syndrome associated with acute decompensated hyperglycemia that commonly presents as hemichorea-ballism. Its natural history following resolution of the hyperglycemic crisis is not well delineated.
Methods
The study was a prospective evaluation of the long-term clinico-radiological outcomes of patients presenting with DS. Neuroimaging (CT/MRI) was performed at baseline and follow-up (>3 months). Ancillary work-up included calcium profile, slit-lamp examination, and FDG-PET selectively.
Results
There were 7 patients; 2 young males with T1DM presenting with diabetic ketoacidosis (DKA) and 5 post-menopausal females with T2DM presenting with hyperosmolar hyperglycemic syndrome (HHS). All had acute-onset left-sided hemichorea-ballism. DS was the presenting manifestation of DM in 2 patients. Mean HbA1c at admission was 14.2 $\pm$ 3.1 %. The most common pattern on CT was bilateral striatal hyperdensities (67%) and on MRI was bilateral T1, T2 hyperintensities (67%). Discrepancy between CT and MRI was seen in 16.7% of patients. Clinico-radiological discordance was noted in 28.5% of patients, in terms of either laterality of lesions or persistent dyskinesia with normal MRI. Resolution of dyskinesia was seen with glycemic optimization alone in 33% and additional therapy in the rest (tetrabenazine (50%), clonazepam (17%)). One patient, who did not receive any specific therapy, had persistent symptoms. The duration of resolution of dyskinesia was earlier in patients who presented with DKA (<1week) than with HHS (median 5 (2-15) months). Follow-up imaging (>3 months) revealed loss of striatal volume and dilation of the frontal horn of the lateral ventricles in 50% of patients, mixed intensity lesion (residual hyperintensity and new-onset hemosiderin-related hypointensity) in 16%, and new-onset hemosiderin hypointensity alone in 34%.
Conclusion
Clinical resolution of DS is common with the restoration of euglycemia but may require additional medical therapy. Prospective imaging reveals unilateral ventricular dilation, focal gliosis, or hypointensity suggestive of hemosiderin deposition.

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P75

"The eyes have it": a case of treatment-induced neuropathy of diabetes

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A male in his 40's diagnosed with type 2 diabetes in 2011 (BMI:20.7kg/m^2) was admitted with DKA (Dec 2018) after a period of poor glycaemic control on oral hypoglycaemic agents (Feb 2017: HbA1c-105mmol/mol, Nov 2018: HbA1c-115mmol/mol). There was dramatic improvement in glycaemic control after commencing him on subcutaneous insulin (April 2019: HbA1c-56mmol/mol). GAD65 antibodies were positive (24u/mL; normal<5u/mL) and a diagnosis of latent autoimmune diabetes (LADA) was made. After the initiation of insulin and rapid improvement in glycaemic control, the patient began to experience severe debilitating "burning" and "shooting" pain (10/10) across his abdomen, back, thighs and shins with hyperalgesia and allodynia. On examination the patient had normal strength in all limbs (MRC power grading 5/5), no muscle wasting, and no clinical large fibre deficits. He had an irritable nociceptor phenotype with mechanical brush stroke allodynia. Nerve conduction studies were at the lower end of the normal range (sural/peroneal nerve conduction velocity/amplitude: 42.9m/s; 7.5μV and 42.9m/s; 3.9m/s, respectively). MR brain imaging to rule out a central pain aetiology e.g. thalamic infarct was normal. However, corneal confocal microscopy (CCM), a measure of small sensory nerve fibre pathology was abnormal. Corneal nerve fibre length (CNFL) (6.0mm/mm^2), fibre density (CNFD) (12.9/mm^2) and branch density (CNBD) (6.7/mm^2) were all markedly reduced indicative of small fibre degeneration (normative values CNFL:> 12.5mm/mm^2, CNFD:>20.6 no/mm^2, CNBD:>22.7no/mm^2). A diagnosis of treatment-induced neuropathy of diabetes (insulin neuritis) due to rapid improvement in glycaemic control was made based on sudden onset of neuropathic pain and objective evidence of small fibre degeneration. He received multidisciplinary support in the form of maximal dose anti-neuropathic drug therapy, psychological therapy and physiotherapy. After nine months, there was a significant improvement in pain (3-4/10), CCM measures of small nerve fibres showed regeneration (CNFL: 13.1mm/mm^2; CNFD: 24.8/mm^2; CNBD: 18.7/mm^2) and he returned to work.

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P76

Anaemia among patients with type 2 diabetes mellitus in Kano, Northwestern Nigeria

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Introduction
Anaemia is the most prevalent haematological complication among patients with type 2 diabetes mellitus. It has an adverse effect on the development and progression of microvascular and macrovascular complications among these patients. Despite this problem, there is paucity of data on the condition in Kano, Northwestern Nigeria. Hence the need for the baseline research.
Methodology
The study was a cross-sectional hospital-based study which recruited 200 type diabetes mellitus patients as participants. After obtaining ethical approval and consent, data were collected using a structured questionnaire. Anthropometric measurements and blood pressure were done. Laboratory tests such as haemoglobin levels, red cells indices and glycated haemoglobin were done. The data were analysed using SPSS version 22.
Results
The mean age of the participants was 51.4 ± 14.2 years and 68% of them were females. Most of the participants are overweight or obese with a mean body mass index of $26.4 \pm 5.8 kg/m^2$. Glycemic control was poor with an average glycated haemoglobin level of $8.3 \pm 5.8\%$. The prevalence of anaemia among the participants was 36%. Using red cell indices, microcytic anaemia was found among 14% of the anaemic patients, macrocytic anaemia among 37% and normocytic anaemia was found among 21% of the anaemic participants. Adavance age was the single determinant for the development of anaemia among these participants ($P = 0.028$).
Conclusion
Anaemia is very common among patients with type 2 diabetes mellitus in Kano, Northwestern Nigeria and hence there is need for further evaluation of the condition in order to curtail its deleterious effect on the management of these group of patients.
Keywords: Anaemia, Type 2 diabetes mellitus, Kano
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P77

Relationship Between β-cell Function and Proteinuria in a Cohort of Type 2 DM Patients at OAUTHC Ile-Ife, Nigeria

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Background
T2DM has been described as a complex mix bag of insulin resistance and β-cell defects in varying proportions. Several works have described in quantitative terms insulin resistance among diabetics and its relationship with proteinuria, the relative contribution of β- cell dysfunction have largely been extrapolated. This work is an attempt to provide the missing link in our clime.
Objectives
The study aims to describe, in quantitative terms, β-cell (dys)function and explore its relationship with proteinuria in diabetics.
Methodology
A cross-sectional study of selected T2DM patients. Relevant data were obtained on demographics and anthropometry. Samples were drawn for FPG, Insulin, Creatinine and Albumin. eGFR was calculated with CKD-EPI. β-cell function was derived from computation of insulin and FPG from a calculator HOMA2 v2.2.3. Data was analysed with SPSS V22
Results
There were 83 subjects made up of 30 (36.1%) male and 53(63.9%) female. The mean age was 56.1yrs, while the average duration of DM was 1.4yr. About 2/3rd reported had hypertension but mean SBP/DBP was 131.4/77.3mmHg. Nearly half complained of frothy urine, but none reported oedema. The mean values of FPG, HBA1C, HOMA%β, and eGFR were 6.5mmol/l; 7%, 58.9%, and 78 ml/min/1.73m^2. About 50% had proteinuria of which $> 75\%$ was micro-albuminuria. Subjects with poor control had significantly lower mean values of β-cell function (HOMA%β: 29.5% Vs 78.8%). There was no correlation between β-cell function and ACR. There was a significant positive correlation between β-cell function and measures of glycaemic control.
Conclusions
β-cell dysfunction remains a major feature in of our diabetics and even when not related to proteinuria may indeed connote poor metabolic control and adverse CVS outcome. Routine assessment of β-cell function in the management of T2DM may not be substantiated, nonetheless, physicians should be aware of the significant burden of β-cell dysfunction as this may influence the choice of therapy.
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P171

The effects of caloric restriction on adipose tissue and metabolic health are sex- and age-dependent

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Caloric restriction (CR) is a nutritional intervention that reduces the risk of age-related diseases in numerous species, including humans. CR's metabolic effects, including decreased fat mass and improved insulin sensitivity, play an important role in its broader health benefits, yet many aspects of the CR response remain poorly understood. In particular, sex differences in metabolic function are increasingly well recognised, but the extent and basis of sex differences in CR's health benefits have been largely ignored. Herein, we addressed this gap in knowledge. In young (3-month-old) male mice, CR decreased fat mass and fasting blood glucose and improved both glucose tolerance and insulin sensitivity; however, in young female mice these effects were blunted or absent. Indirect calorimetry revealed that females' resistance to fat and weight loss is not explained by decreased energy expenditure, positron emission tomography-computed tomography with ^{18}F-fluorodeoxyglucose showed that altered peripheral glucose uptake does not account for the sex differences in glucose tolerance. Instead, the latter is associated with altered hepatic function, with CR decreasing gluconeogenesis and altering liver ceramide content in males but not females. To determine if oestrogen contributes to these sex differences, we next investigated the metabolic effects of CR initiated in aged mice (18-months old), when females are anoestrus. Strikingly, in these aged mice CR decreased fat mass and improved glucose homeostasis to a similar extent in both sexes. Finally, we found that CR-induced fat loss in humans is also sex- and age-dependent, with younger females resisting fat loss compared to younger males. Collectively, we identify age-dependent sex differences in the metabolic effects of CR and highlight adipose tissue, the liver and oestrogen as key determinants of CR's metabolic benefits. This has important implications for understanding the interplay between diet and health, and for maximising the benefits of CR in humans.
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P172

ATP-Binding Cassette Subfamily C Member 1 (ABCC1) influences adiposity, glucose homeostasis and insulin sensitivity

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Background
Glucocorticoids (GCs) modulate glucose homeostasis by acting on metabolic tissues including liver, adipose, and skeletal muscle. ABCC1 is a transmembrane

'drug-resistance' transporter expressed in adipose tissue and skeletal muscle with previously unknown physiological function. We recently showed that ABCC1 modulates intracellular GC concentrations and action in adipose. Here, we tested the hypothesis that Abcc1 regulates GC concentrations in skeletal muscle as well as adipose, and influences glucose metabolism and insulin sensitivity.
Methods
Global Abcc1 knockout (Abcc1$^{-/-}$)and wild-type mice were fed with chow diet or high-fat diet (HFD; 58% fat and sucrose) for 9 weeks before glucose and insulin tolerance tests and sampling for plasma and tissue GC concentrations measured by Liquid Chromatography Tandem Mass Spectrometry, and tissue GC-responsive markers (mRNA and protein) by RT-qPCR and Western blot.
Results
On chow diet, deletion of *Abcc1* increased levels of corticosterone in plasma, subcutaneous adipose tissue (sWAT), and gastrocnemius muscle. This was accompanied by reduced total body fat mass (sWAT, gWAT and BAT) and lower fasting plasma insulin, with normal glucose tolerance. Reduced *Lpl*mRNA in sWAT, but not muscle, suggests Abcc1$^{-/-}$mice have lower lipid uptake in adipose. On HFD fat mass gain was comparable between genotypes, but Abcc1$^{-/-}$mice developed impaired glucose and insulin tolerance, and hyperinsulinemia. Strikingly, this worsened metabolic phenotype presents without measurable alterations in plasma or tissue GC levels.
Conclusions
These results suggest that ABCC1 influences adiposity, glucose metabolism, and insulin sensitivity by mechanisms which are likely to be GC-dependent only in part. These results introduce ABC transmembrane transporters as novel regulators of metabolic function.

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P173

Associations between reduction in body mass index (BMI) and proteins linked to neural function after 12 months of bariatric surgery

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Background
Bariatric surgery (BS) can have significant effects on multiple body systems and has been an effective intervention for morbid obesity, improving many comorbid medical conditions that are associated with mental health and cognitive dysfunction. It was previously shown that cognitive impairment was partly reversible in obese patients after BS [1], however, the effects of BS on proteins associated to central nervous system (CNS) still unknown. We evaluated if there are associations between changes in body mass index (BMI) after BS and circulating proteins.
Methods
SWATH MS proteomics was performed on serum samples taken at baseline (pre-surgery), 6 and 12 months after BS and concurrent analyses of inflammatory/metabolic parameters carried out. Change in absolute abundances of those proteins showing significant change at both 6 and 12 months was tested for correlation with absolute and percentage change in BMI.
Results
BMI declined significantly at 6 (t=9.29, $P < 0.0001$) and 12 (t=7.82, $P < 0.0001$) months. Significant correlations between % change in BMI (6 months X baseline) and fold change in the following proteins: APOM ($r = 0.639$, $P = 0.047$), APOA4 ($r = 0.649$, $P = 0.042$), PGLYRP ($r = 0.650$, $P = 0.042$), HSPG2 ($r = 0.760$, $P = 0.048$), SERPIND1 ($r = 0.788$, $P = 0.007$). At 12 months post-BS, we found correlations between TF ($r = 0.682$, $P = 0.043$), ITIH3 ($r = 0.695$, $P = 0.038$), L1CAM ($r = 0.788$, $P = 0.02$) and AMBP ($r = 0.697$, $P = 0.037$).
Conclusions
Specific group of proteins were associated with percentage change in BMI in two different time points. At 6 months post-surgery evidencing proteins related to lipid transport, circulatory system and immunity, while at 12 months, proteins related to important brain functions, such as synaptic plasticity and neuronal function. These results suggest that changes in circulatory proteins related to brain functions may reveal an important BS outcome after 12 months associated with weight loss. Future studies are needed to clarify underlying mechanisms in how BS may influence neural functions, such as cognition and memory.

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P174

Vitamin D status in horses and its association with adiposity

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Obesity and metabolic syndrome are highly prevalent in horses and ponies worldwide. Equine Metabolic Syndrome (EMS) shares much of the same pathophysiology with its human counterpart including adipose tissue dysfunction and insulin dysregulation. Vitamin D deficiency is strongly associated with obesity and insulin resistance in humans and supplementation is often recommended. In horses our understanding of vitamin D biology is limited and its association with EMS unknown. The limited data available suggest that horses have comparatively low circulating total 25OHD, and it is almost entirely $25OHD_2$ obtained through their diet. To further investigate vitamin D status in horses plasma concentrations of $25OHD_2$ and $25OHD_3$ were measured by UHPLC-MS in 22 racehorses receiving 6600-8800IU/day of D_3 supplementation and 34 ponies kept at pasture and not supplemented. Grazing ponies ($n = 18$) were sampled in summer and winter to determine the effect of sunlight exposure. Regression analysis was used to determine the effect of age, breed, sex, morphometric scores, serum insulin on vitamin D status in horses/ponies with ($n = 33$) and without EMS ($n = 74$). Total plasma D concentrations were much lower in horses than in humans (< 25nM). $25OHD_3$ was detected only in supplemented horses (8.6 ± 3.2nM) and was undetectable all year-round in non-supplemented horses ($P < 0.01$) indicating, horses do not synthesise D3 in the skin. $25OHD_2$ was detected in all horses (11.3 ± 4.0nM) and at significantly higher levels in the grazing herd ($P < 0.01$) suggesting grass is the primary source of D_2. In contrast to humans, increased adiposity was associated with higher $25OHD_2$($\beta = 0.17$, $P < 0.01$) and there was no association with serum insulin. These comparative data raise important questions on our understanding of vitamin D biology suggesting that unlike humans, horses do not synthesise $25OHD_3$ and vitamin D status is positively influenced by adiposity. Further investigation is warranted to understand this unusual observation.

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P175

Pressure from pericytes: angiotensin II induced neuropathic pain development as a complication of hypertension

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The renin angiotensin system (RAS) is targeted as means of medical intervention for hypertensive associated complications of stroke, heart failure and obesity. Ultimately, the inhibition of Angiotensin II(ANGII)/Angiotensin II type 1 (AT1) receptor complex has been key in reducing raised blood pressure. Diabetic neuropathic pain (NP) is highly prevalent in the United Kingdom, associated with an increasingly aged population. There is growing acknowledgment that the vascular component with the central nervous system is attributable to NP development through diminished blood flow in the somatosensory system. Alterations in vascular tone in neuropathology are in part modulated by pericyte regulation of capillary dynamics. Our preliminary work has identified AT1-positive pericytes, a population of contractile cells abluminally positioned on small capillaries, within spinal cord (SC) nervous tissue. Here it is hypothesised that ANGII signalling in pericytes impedes capillary function and consequent blood flow to drive NP phenotypes. Our initial studies *in vitro* demonstrate that in mouse SC NG2-positive pericytes ANGII (100nM) induces increased intracellular calcium response ($*P < 0.016$, $n = 6$, post-natal day7). *In vivo* studies demonstrate that an hour post intrathecal (i.t.) ANGII (100nM, $n = 15$) administration, mice develop hypersensitivity to mechanical ($****P < 0.0001$) and thermal ($**P < 0.004$) sensory stimuli tests compared to vehicle treated group (PBS, $n = 9$). To support pericyte activation within the dorsal horn, fluorescently stained paraformaldehyde-fixed SC indicated an increased proportion of constricted CD31-vessels associated with NG2-pericytes 30-minute post i.t. ANGII injection vs vehicle ($*P < 0.039$). Co-administration of i.t. Losartan with ANGII reduced hypersensitivity to pain compared to ANGII alone ($*P < 0.01$) 1-hour post-dose, while returning to basal level after 24 hours. These studies highlight an ANGII dependent modulation of pericyte vasocontractility

via AT1 signalling in the SC that is a contributing factor in NP development. This work highlights that the modulation of AT1 in the SC maybe a putative candidate to treat diabetic NP.

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P176

Asprosin impact on mitochondrial metabolism in obese adipose tissue, a tale of two depots?

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Background
In an obese state, pro-inflammatory adipokines can lead to mitochondrial dysfunction and reduced brown adipocytes properties in white adipocytes (BRITE adipocytes), all of which contribute to the pathogenesis of obesity and type 2 diabetes mellitus (T2DM). A recent novel adipokine, asprosin, that influences appetite and glucose homeostasis, appears to drive inflammation in obesity. However, asprosin expression in human adipose tissue (AT) depots, its impact on mitochondria, and the browning process is unknown, which this study sought to investigate.
Methods
Human abdominal (Abd) subcutaneous (Sc) and Abd omental (Om) AT paired biopsies were collected (female; age: 31.6±6.1Yr; BMI: 27.9±5.9Kg/m^2; n = 126) in an ethically approved study. RNA was extracted from AbdAT (lean: n = 43 lean, overweight: n = 47, obese: n = 36, subjects) and asprosin, mitochondrial, BRITE and inflammatory gene expression was quantified by qRT-PCR. Mitochondrial function analysis was undertaken using Seahorse Analyzer to measure oxygen consumption rate (OCR).
Results
Asprosin was readily expressed in both abdominal depots. Obesity reduced asprosin mRNA expression in AbdScAT (obese: 11.4%↓$P < 0.01$) but not in AbdOmAT (obese; P = N.S). In AbdScAT, increased asprosin expression positively correlated with mitochondrial biogenesis (PRC: $P < 0.001$; NRF1: $P < 0.05$), but led to a reduction in mitochondria function (COX4: $P < 0.0001$↓), mitochondrial fusion (MFN2: $P < 0.0001$↓), and a rise in oxidative damage (SOD2: $P = 0.0287$↑) and inflammation (MCP1: $P < 0.05$↑). Rising asprosin mRNA expression also led to BRITE gene reduction (CIDEA: $P < 0.01$↓; ELOVL3: $P = 0.0144$↓; PLIN5: $P < 0.01$↓). In AbdOmAT, asprosin had less impact on mitochondrial and browning genes. Asprosin treatment also influenced AbdSc adipocyte OCR.
Conclusions
In summary, asprosin was predominately associated with mitochondrial dysfunction and reduced BRITE phenotype in AbdScAT, whilst the influence on AbdOmAT was minimal. Taken together, these data suggest that raised systemic asprosin levels in obese subjects would further damage critical AbdSc (rather than AbdOm) adipocyte function, to increase their metabolic disease risk.

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P177

Obesity-induced upregulation of chemokine Ccl4 in mouse visceral adipose tissue: effects on β-cell function

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Introduction
Adipose tissue-derived peptides, known as adipokines, act as key regulators of metabolic homeostasis, but little information is available on adipokine-mediated cross-talk with β-cells via islet GPCR interactions, nor whether this is altered in obesity. The expression profile of islet GPCR peptide ligand mRNAs in visceral adipose tissue from lean and diet-induced obese mice was therefore defined and the functional effects of Ccl4 on β-cells were characterised.
Methods
155 islet GPCR ligand mRNAs were quantified by RT-qPCR in epididymal adipose tissue retrieved from 24-week-old C57BL/6 male mice fed either control (CD:10% fat) or high-fat diet (HFD:60% fat) for 16 weeks. The effects of Ccl4 on cell viability, proliferation and apoptosis in MIN6 β-cells were investigated using standard assays.
Results
45 and 40 islet GPCR peptide ligand mRNAs were detectable in CD and HFD adipose tissue, respectively, and Ccl4 mRNA expression was significantly upregulated by HFD (11.13-fold increase vs control, $P < 0.001$, n = 5). Ccl4 (10-100ng/mL) did not significantly affect β-cell viability (% viable: control: 97.2±1.2; +10ng/mL Ccl4: 90.6±3.7; +50ng/mL Ccl4: 88.9±6.1; +*100 ng/mL Ccl4: 85.2±6.0; ns, n = 4). Ccl4 stimulated concentration-dependent protective effects against palmitate-induced β-cell apoptosis (caspase-3/7 activities, % control: –palmitate: 100±6.2; +palmitate: 291.5±14.3; +10 ng/mL Ccl4: 222.7±13.6; +50ng/mL Ccl4: 197.5±12.7; +100ng/mL Ccl4: 195.1±9.7; $P < 0.0001$, n = 3) and protective effects were also observed in the presence of cytokines (caspase-3/7 activities, % control: –cytokines: 100±7.9; + cytokines: 595.2±37.0; +10ng/mL Ccl4: 502.8±18.0; +50ng/mL Ccl4: 497.8±19.5; +100ng/mL Ccl4: 469.1±24.5; $P < 0.01$, n = 3). Ccl4 significantly reduced serum-stimulated β-cell proliferation (BrdU incorporation, % control: 0% FBS: 100.0±4.9; 10% FBS: 176.1±6.5; +10ng/mL Ccl4: 162.0±7.9; +50ng/mL Ccl4: 156.7±9.5; +100ng/mL Ccl4: 129.8±5.3; $P<0.0001$, n = 3).
Discussion
Visceral fat Ccl4 mRNA expression is significantly increased in obesity. Ccl4 exerts concentration-dependent anti-apoptotic and anti-proliferative actions at β-cells, providing evidence of adipokine-mediated regulation of β-cell function in obesity.

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P178

Abstract withdrawn

P179

Impact of α-MSH on glucose tolerance in healthy participants: The first in human randomized, double-blind, placebo-controlled, physiological study

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This abstract has been withdrawn at the request of the first author and Imperial College London.
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P180

Neurotensin improves glucose tolerance via activation of peripheral NTSR1-expressing neurons

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Neurotensin is a 13-amino acid peptide expressed in both the brain and the gastrointestinal tract where it acts as a neuropeptide and gut hormone, respectively. Centrally, neurotensin plays a role in appetite, analgesia and thermoregulation, whereas peripheral neurotensin regulates lipid absorption, gastric emptying and exocrine pancreatic secretion. The role of neurotensin in the control of glucose homeostasis currently remains unclear. We found peripheral administration of neurotensin dose-dependently improved acute glucose tolerance in lean and obese mice. This effect was lost in the presence of a NTSR1-specific antagonist. Interestingly, oral administration of olive oil similarly improved glucose control, and this effect was also lost in the presence of a NTSR1-specific antagonist. Neurotensin administration increased circulating insulin levels. Together these data suggest a crucial role for peripheral neurotensin in mediating the glucoregulatory response to lipid. There are three main neurotensin receptors of which the NTSR1 has the highest-affinity for neurotensin. We found the NTSR1 to be highly expressed in the vagal nodose ganglia, hypothalamic arcuate nucleus and enteric nervous system, with negligible expression in pancreatic islets. Using a range of models, we identified that neurotensin did not improve glucose tolerance via activation of pancreatic-, vagal- or brain-NTSR1. Blockade of the muscarinic-3 receptor, a receptor expressed on pancreatic β cells that drives cholinergic-mediated insulin secretion, blunted neurotensin-mediated insulin secretion, suggesting a role for neurotensin in the enteropancreatic axis. Using NTSR1-Cre:tdTomato mice, NTSR1 expression was identified in the myenteric plexus of the murine enteric nervous system and in vitro calcium imaging using cultured myenteric neurons confirmed NTSR1-mediated neurotensin activation. Our data suggest that gut to pancreas neuronal signalling mediates the effects of neurotensin on glucose control, and we are currently testing this hypothesis using cre-dependent retrograde adeno-associated viruses expressing chemogenetic excitatory and inhibitory DREADD receptors in the pancreas of NTSR1-Cre mice.

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P181

Bio informatic Analysis Reveals Hundreds of Differentially-Expressed lncRNAs with Potential Roles in β-Cell Proliferation

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Background and Aims
As a loss of functional β-cell mass contributes to type 2 diabetes (T2D), increasing β-cell proliferation is a potential therapy to compensate for impaired insulin output. Long non-coding RNAs (lncRNAs) regulate several key β-cell genes and the presence of more than 1100 human β-cell enriched lncRNAs raises the potential for wider roles. Here we have identified 5 independent studies that capture the β-cell transcriptome during adaptive and maladaptive changes to proliferation in human and mouse and bioinformatically investigate lncRNAs with potential roles in β-cell expansion.
Methods
Islet and β-cell RNA-Seq datasets were selected from Gene Expression Omnibus to cover a range of conditions that affect β-cell proliferation. These included pregnancy, dietary or monogenic models of obesity, glucose tolerance (GT) and development. Reads were mapped using Hisat2 and quantified with FeatureCounts. Differential expression analysis was performed using DESeq2 and gene lists were filtered using Ensembl biotypes to identify lncRNAs.
Results
Differentially-expressed (DE) lncRNAs were identified in each study with padj <0.1 as shown below.

Study Summary	Authors/Date	Organism: tissue	DE lncRNAs
Day 14.5 pregnancy vs. non-pregnant mice	Horn et al., 2016	Mouse: islets	**426**
High-fat vs. normal chow diet	Zhang et al., 2020	Mouse: islets	**1057**
Db/db mice vs. control	John et al.,2018	Mouse: islets	**378**
Islets from T2D/ impaired GT/normal GT donors	Fadista et al., 2014	Human: islets	**156**
Adult vs. fetal β-cells	Blodgett et al., 2015	Human: β-cells	**457**

Conclusions
Hundreds of lncRNAs were identified across a range of conditions influencing proliferation in β-cell studies in human and mouse. Patterns observed between these lists could provide insight into undiscovered players involved in core β-cell proliferation pathways.

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P182

Rat primary hypothalamic, but not cortical, astrocytes increase use of glutamate to fuel metabolism after recurrent low glucose

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Aims
A critical function of astrocytes is to recycle glutamate to neurons as glutamine to sustain glutamatergic neurotransmission. In the hypothalamus, this is required for effective counterregulatory hormone release in response to hypoglycaemia. However, after recurrent hypoglycaemia *in vivo*, this is attenuated. The aim of this study was to characterise how rat primary hypothalamic and cortical astrocytes adapt to recurrent low glucose (RLG) with repeated exposure to glutamate. We hypothesised that the additional metabolic challenge of glutamate recycling would alter cellular metabolism and the astrocytes would metabolise it as an alternative fuel source.
Methods
Rat primary cortical (CRTAS) and hypothalamic (HTAS) astrocytes were exposed to 0, 1, or 4 bouts of low (0.1 mM) glucose for three hours over four days with and without glutamate (100 μM). Mitochondrial and glycolytic flux were measured using the Seahorse Bioanalyser platform as well as extracellular and intracellular glutamate and glutamine levels.
Results
Like human primary astrocytes, RLG increased basal mitochondrial oxygen consumption rate (OCR) in HTAS and CRTAS. However, concurrent glutamate treatment attenuated the adaptation in HTAS but exacerbated it in CRTAS. This coincided with an increased dependency for glutamine metabolism in HTAS, and enhanced depletion of glutamate in the extracellular medium. Intracellular glutamate concentrations were unchanged.
Conclusions
Together these data show that HTAS increase their dependency for and use of glutamate as a fuel source after RLG with concurrent glutamate treatment. This adaptation we believe helps maintain intracellular energy supply during decreased glucose availability. If this is the case *in vivo,* then glutamate, which should be recycled to neurons, is metabolised by the 'selfish' astrocyte and may impair hypoglycaemia-induced glutamatergic signalling in the hypothalamus and attenuate counterregulatory hormone release.

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P183

The influence of metabolic states and a high fat meal on circulating chemerin

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Background
Chemerin is a multifunctional adipokine involved in pathogenesis of metabolic disease by regulating inflammation, adipocyte plasticity and glucose metabolism. It is known to be influenced by age, adiposity and triglycerides, and supports

important roles in systemic lipid and glucose metabolism.However, the direct acute effects of circulating chemerin on varying metabolic disease states given a high–saturated fat meal has not been addressed.
Methods
Subjects ($n = 54$) were given a high-fat meal (75g fat, 5g carbohydrate, 6g protein) after an overnight fast (non-obese control (NOC): age 39.0±4.04, BMI 25.7±1.31, $n = 7$; impaired glucose tolerance (IGT): age 39.4±4.43, BMI 32.4±1.73, $n = 8$; obese: age 40.0±4.87, BMI 33.7±0.73, $n = 5$; type 2 diabetes mellitus (T2DM): age 45.4±2.34, BMI 29.0±1.07, $n = 18$). Serum was collected before and 4hr post meal for biochemical analysis.
Results
Circulating chemerin was significantly increased across the metabolic states from baseline assessment (NOC: (107.3±8.17ng/mL) Vs IGT: (132.1±4.43ng/mL) 1.2-fold↑, $P < 0.05$; NOC Vs Obese (179.4±4.87ng/mL) 1.7-fold↑, $P < 0.0001$). Obese participants had significantly raised chemerin levels compared with IGT (1.36-fold↑, $P < 0.05$) and T2DM participants (1.48-fold↑, $P < 0.001$). Across the entire cohort there was association between chemerin and increased body fat percentage pre- ($R^2 = 0.37$↑, $P < 0.01$) and post-high-fat meal ($R^2 = 0.46$↑, $P < 0.001$). These findings also showed that, 4hr after a meal, obese subjects had higher circulating chemerin levels (91%↑) than NOC subjects ($P < 0.001$).
Conclusions
This study highlights that irrespective of a single high-fat meal, circulating chemerin in an IGT and obese metabolic state remain elevated. Noting this elevation was substantial in obese subjects prior to an IGT or T2DM metabolic state. In Conclusions, these data suggest that prior to a compromised metabolic state such as T2DM, in obesity, chemerin levels remain high irrespective of fasting or high-fat meal, and may promote glucose dysfunction more rapidly due to the greater exposure to chemerin.

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P184

Does human serum impact differentiation and mitochondrial function of human LHCN-M2 skeletal muscle cells?

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Introduction
Skeletal muscle cells enable investigation of myogenesis and metabolic function *in vitro*. Exposure to human serum can provide insight into the impact of endocrine factors upon differentiation and mitochondrial function of skeletal muscle. The aim of these experiments was to optimise the culture conditions using human serum, which it was hypothesised would enhance myogenesis and mitochondrial function of LHCN-M2 human skeletal muscle cells.
Methods
LHCN-M2 skeletal muscle myoblasts were differentiated in serum-free media, 0.5% or 2% healthy human serum, for 0, 5 and 10 days. Skeletal muscle myotube formation was assessed morphologically by immunofluorescence (Myosin Heavy Chain (MHC)) and differentiation transcriptionally by mRNA expression (Myogenic differentation1 (MyoD1)) and (Myogenic regulatory factor 5 (Myf5)). At day 10, extracellular flux analysis was used to determine mitochondrial function following differentiation in different concentrations of serum.
Results
Differentiation with human serum increased the mRNA expression of MyoD1 (6.58 ± 1.33 fold at day 5 and 4.60 ± 1.43 fold at day 10 vs day 0) and reduced Myf5 (0.21 ± 0.11 fold at day 5 and 0.07 ± 0.03 fold at day 10 vs day 0) with time ($P < 0.05$). However, there was no difference in mRNA expression between conditions (P = NS). Extracellular flux analysis showed no differences in basal, maximal, ATP or spare capacity between conditions (P = NS). However, coupling efficiency was significantly lower following differentiation in 2% human serum compared to serum-free media (79.68 ± 3.62% vs. 92.08 ± 7.19%; $P < 0.05$).
Conclusions
These preliminary findings contradict the hypothesis and reveal that the concentration of human serum does not affect the mRNA expression of myogenic transcription factors during LHCN-M2 differentiation or mitochondrial respiratory capacity, with the exception of coupling efficiency, which is attenuated in 2% serum. These experiments have wider implications for investigating how human serum is used in skeletal muscle metabolism research.

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P185

Measurements of skin temperature in lean and obese humans at thermoneutrality and following cold exposure

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Background
Infrared thermography (IRT) can assess human brown adipose tissue (BAT) activity non-invasively. However, it remains unclear if skin temperature is altered in obesity. We compared skin temperatures of lean and obese individuals following cold exposure and studied its relationship with energy expenditure (EE).
Methods
10 lean (age 28.3±2.1y, BMI 21.5±0.4kg/m^2) and 10 obese (age 28.2±2.1y, BMI 36.2±1.3kg/m^2) gender-matched subjects were placed in a warm (thermoneutral, 23-24°C) followed by cold room (16-17°C) for 2 hours each. Skin temperature was obtained through IRT every 15-30 minutes at 2 locations; supraclavicular fossae (T_{SCV}), where human BAT is located and mediastinum (T_{med}), which served as a reference for comparison. EE was measured by indirect calorimetry hourly. Data are expressed as mean±SEM.
Results
EE was higher in obese subjects but increased following cold exposure only in lean group (by 158±47 vs 86±52kcal/24h). Core (tympanic) temperatures in warm and cold were similar between groups. T_{SCV} and T_{med} were higher at both temperatures in lean subjects. Cold exposure induced a greater decrease in T_{med} (2.7±0.2°C vs 1.7±0.2°C) and T_{SCV} (1.4±0.2°C vs 1.0±0.1°C) in obese than lean subjects, increasing the cold-induced temperature differential between supraclavicular and mediastinal regions in obese subjects. T_{med} and T_{SCV} during both temperature conditions negatively correlated with BMI, body weight and fat mass. Cold-induced thermogenesis (CIT) negatively correlated with EE at thermoneutrality ($P < 0.05$) and, in lean subjects, tended to correlate with the change in T_{scv} during cold exposure ($P = 0.1$).
Conclusions
Obese subjects have lower skin temperatures even at thermoneutrality, potentially due to adipose tissue insulation. This may confound measurements of BAT activity if not taken into account. Reduced CIT in obesity during cold exposure may be due to reduced requirement for thermogenesis from increased basal EE.

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P186

Predictors of adverse outcomes in COVID-19: A retrospective cohort study comparing the first two waves of COVID-19 hospital admissions in London, with a focus on diabetes

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Introduction
Diabetes has been associated with poorer outcomes with COVID-19 infection, but precise predictors of mortality in patients with diabetes remain unclear. We assessed predictors of adverse outcomes in patients hospitalised with COVID-19 in Imperial College Healthcare NHS Trust (ICHNT) hospitals during the first and second waves of COVID-19 to determine if outcomes for patients with diabetes have evolved with new variants and treatments.
Methods
Data were collected from all 1372 patients hospitalised with COVID-19 between 01/11/2020 and 31/01/2021 (Wave 2) and from all 889 patients admitted between 09/03/2020 to 22/04/2020 (Wave 1). The composite primary outcome was death or ICU admission within 30 days of COVID-19 diagnosis. Multivariate proportional odds analyses were performed to determine the independent predictors for the primary outcome in all patients and patients with diabetes.
Findings
Demographic/clinical characteristics were similar in both waves, with 61% of patients from non-White ethnic backgrounds as is representative of the community served in London. 37% (331/889 in wave 1) and 33% (456/1372 in wave 2) of patients admitted with COVID-19 had diabetes (97% Type 2 over both waves). In wave 2, patients with diabetes had reduced odds of the primary outcome (OR 0.75, 95% CI 0.56-1.00, $P = 0$ .04). The OR for primary outcome in patients without diabetes in wave 2 vs wave 1 was 0.14 (95%CI 0.09-0.19), $P < 0.01$). Renal impairment was the strongest independent predictor (out of 19 clinical variables) of poor outcome in all patients ($n = 2265$) and in patients with diabetes ($n = 787$). Dexamethasone (OR 0.42 (95%CI 0.31-0.56, $P < 0.01$)) and

tocilizumab (OR 0.44 (95%CI 0.24-0.77), $P < 0.01$) use, independently reduced risk of death in all patients.
Conclusions
Patients with diabetes and associated complications remained at risk of poorer outcomes throughout the COVID pandemic. However patients with diabetes significantly benefitted from the advances in treatment options available during wave 2.

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P187

Asprosin induces acute pro-inflammatory effects on THP-1 macrophages

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Introduction
Asprosin is a novel adipokine that is released in response to fasting and can elicit orexigenic and glucogenic effects. Circulating asprosin levels are elevated in a number of cardio-metabolic diseases, including obesity and type 2 diabetes mellitus. *In vitro* studies have reported pro-inflammatory effects of asprosin in pancreatic β-cells and skeletal muscle cells, which appear to be mediated via a toll-like receptor 4 (TLR4) mediated pathway, and may contribute to the metabolic dysregulation observed in such diseases. The aim of the present study was to further elucidate the role of asprosin in inflammation by exploring its potential effect(s) in THP-1 macrophages.
Methods
Differentiated THP-1 macrophages were treated with either 1, 10, 100 nM asprosin, 100 ng/mL LPS or both 100 nM asprosin and 100 ng/mL LPS for 4 and 24 hours. Caffeic acid phenethyl ester (CAPE; 10 μM) was used as an inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). Cell and supernatant samples were collected and analysed by luminometry, flow cytometry, RT-qPCR and ELISA.
Results
Asprosin promoted gene expression and release of key pro-inflammatory cytokines, including TNFα ($P = 0.044$ and $P = 0.0006$, respectively), IL-1β ($P < 0.0001$ and $P = 0.0084$, respectively) and IL-8 ($P = 0.021$ and $P < 0.0001$, respectively), after 4 hours of treatment, which subsided by 24 hours. Asprosin-stimulated secretion of TNFα from THP-1 macrophages was significantly decreased with the addition of CAPE after 4 hours of treatment ($P = 0.033$). Although asprosin did not induce superoxide release, it significantly attenuated LPS-induced superoxide release from THP-1 macrophages ($P = 0.0071$). Asprosin did not significantly affect the cell surface expression of TLR4 in THP-1 macrophages.
Conclusions
The present study demonstrates that asprosin acts partly via the NFkB pathway to induce an acute pro-inflammatory response in THP-1 macrophages. Further studies are required to elucidate the involvement of additional signalling pathways in these pro-inflammatory effects.

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P188

Exploring the translational potential of the NPY Y4 receptor for treating Type 1 Diabetes

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Type 1 diabetes (T1D) is an autoimmune, heterogenous disease caused by immune-mediated destruction of insulin-producing β-cells in the pancreas. The only approved treatment strategies are exogenous insulin replacement therapy and islet transplantation. Leading experimental approaches have focussed on suppression and/or modulation of the immune system. However, efforts to increase β-cell survival are also of great interest. Recent studies in our lab have identified neuropeptide Y (NPY) receptors as novel targets for promoting human β-cell survival. Amongst them, the NP Y4 receptor, has features which make it the most promising NPY receptors candidate for treating T1D. Our Collaborator Prof. Beck-Sickinger, has developed a long-acting synthetic NPY4 receptor agonist K22. This compound has an EC50 of 5.1nM with no or minor potencies for the other NPY receptors. The compound shows excellent *in vivo* stability in terms of function, bioavailability and is bioactive for 40 hours. We have shown that K22 protects mouse and human islets from multiple toxic insults including cytokines and ER stress and maintains β-cell functionality. Cxcl10 has been identified as a key chemokine driving immune recruitment to islets of T1D patients. We found addition of K22 abolished cytokine induction of Cxcl10 expression and secretion from islets. Using a chemokine profiling assay enabled us to identify a set of immune related genes that are associated with cytotoxic damage of islets, and which are attenuated by K22. Previous studies have shown activation of M1 macrophages is an important initiating step in the pathogenesis of T1D. We modelled this using a pseudo-islet platform generated from murine and human islets. This permitted us to study macrophage infiltration of islets *in vitro* using an invasion assay and we found K22 completely prevented islet macrophage invasion. Together our data suggests that K22 has important therapeutic potential for delaying T1D disease onset or halting the disease progression.

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P189

BMI category-specific waist circumference thresholds for predicting the risk of cardiometabolic diseases: A nationwide population-based study

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Background
There is no existing longitudinal study to support ethnicity-specific and body mass index (BMI) category-specific waist circumference (WC) thresholds and their potential clinical utility to assess the risk of obesity-related diseases.
Methods
We performed a prospective assessment of 5,852,702 subjects in large-scale population-based cohort dataset obtained from the Korea National Health Insurance System. BMI was categorized into 6 subgroups (< 18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, and ≥ 35.0 kg/m^2). Time-dependent receiver operating characteristic curve analysis was used to determine BMI category-specific WC thresholds for predicting the development of type 2 diabetes and at least 1 other cardiometabolic risk factor (hypertension and/or dyslipidemia).
Results
During a mean follow-up of 8.2 years, 130,106 subjects were diagnosed with the main outcomes. The optimal BMI category-specific WC thresholds for men were determined to be 73, 79, 84, 89, 98 and 104 cm from the lowest to highest BMI categories. The corresponding values for women were 66, 72, 78, 83, 90 and 100 cm, respectively. Compared with the recommended single WC thresholds (men, 90 cm; women, 85 cm), the BMI category-specific WC thresholds showed an improved balance between sensitivity and specificity for all BMI categories, particularly for normal-weight and overweight individuals. In all BMI and WC categories, there was a significant increase in the hazard ratios for incident type 2 diabetes and comorbidities in proportion to the increases in WC thresholds for the given BMI categories ($P < .001$, respectively).
Conclusions
We determined optimal BMI category-specific WC thresholds, which provide additional information with which to identify individuals at a high risk of developing type 2 diabetes and comorbidities.

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P190

Outcomes of Bariatric surgery in adolescents and youth in an Arab population: a single centre experience

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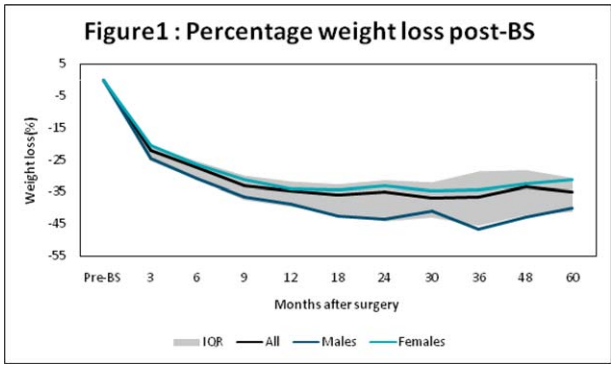
Background
Obesity is increasing in prevalence in younger people, including children and adolescents. Bariatric surgery (BS) is well-established and efficacious treatment for morbid obesity in adults. BS is being performed in younger age groups more frequently.

Objective
To describe outcomes of BS under the age of 25 in Emirati individuals having follow-up at Imperial College London Diabetes Centre (ICLDC).
Methods
Patients recruited for the Abu Dhabi Diabetes and Obesity Study - 2B (ADOS2B) who had BS below age 25 were included in this study. Relevant data were collected at the time of recruitment or extracted from ICLDC patient database. Follow-up period was up to 5 years. Results are presented as median (IQR).
Results
107 (56.3% female) patients included in the study ($n = 866$) underwent BS under age 25yrs [21.8 (20.0-22.8)]; 98 had sleeve gastrectomy (LSG) and 9 Roux en-Y Gastric Bypass (RYGB). Maximum weight loss was achieved between 18-24 months (Figure 1). Weight loss (%) post-BS between the LSG and RYGB patients were comparable [36.4 (30.7 - 42.6) V 36.7 (32.5 - 37.5), $P = 0.884$]. Men lost more weight compared to women [40.1 (33.6 - 46.7) V 34.9 (29.1 - 38.3), P<-001]. Similar weight loss (%) observed between under 19 and 19-25 yrs [37.5 (33.2 - 40.8) V 36.4 (30.7 - 46.4), $P = 0.997$]. Diabetes remission at 2 years post-BS was observed in 10/12 patients with type 2 diabetes. Pregnancy post-BS in 3 patients was uneventful except for the need for iron infusion to tackle anaemia.
Conclusions
A significant group of individuals with morbid obesity are opting for BS which is effective for weight loss, weight loss maintenance, and diabetes resolution. Lifestyle measures need to target paediatric population to prevent need for BS at an early age.



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P191

How does FreeStyle Libre Glucose management indicator (GMI) compare with HbA1c and fructosamine in patients with type 1 diabetes and what are the determinants of the difference?

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Objective
To compare FreeStyle Libre Glucose management indicator (GMI) with HbA1c and fructosamine and assess factors related to the difference.
Methods
Persons with type 1 diabetes on FreeStyle Libre from a single diabetes centre whose sensor was active >70% of the time were included. Baseline characteristics, latest HbA1c, fructosamine, full blood count, total protein and albumin were collected from medical records. Ambulatory glucose profile data for 28-, 60- and 90-days period ending at the date of last available HbA1c and 14- and 21-days period ending at the date of last available fructosamine were collected from LibreView.
Results
A total 412 (54.1% females, age 43±15 years) type 1 diabetics were included. Median (IQR) HbA1c, GMI and fructosamine were 63 (54-73) mmol/mol, 58 (52-65) mmol/mol and 376 (338-419) mmol/l respectively. HbA1c correlated ($P < 0.001$) with 28-day ($\rho = 0.827$), 60-day ($\rho = 0.838$) and 90-day ($\rho = 0.828$) GMI. HbA1c correlated with 60-day GMI ($P < 0.001$) in Caucasian ($\rho = 0.825$, $n = 248$), Asian ($\rho = 0.924$, $n = 25$) and Black ($\rho = 0.846$, $n = 13$) ethnic groups. HbA1c was 3 (IQR -1 to 7) mmol/mol higher than 60-day GMI ($P < 0.001$, $n = 304$). The difference between GMI and HbA1c was ≤10% in 66% and ≤20% in 94% of patients. The difference did not differ across ethnicities ($P = 0.379$) but correlated ($P < 0.01$) positively with HbA1c and age, and negatively with time in target. Fructosamine ($n = 103$) correlated ($P < 0.001$) with 14-day ($\rho = 0.449$) and 21-day ($\rho = 0.500$) GMI and the correlation did not differ when fructosamine was corrected for albumin ($\rho = 0.431$ and $\rho = 0.462$ respectively; $P < 0.001$) or total protein ($\rho = 0.469$ and $\rho = 0.500$ respectively; $P < 0.001$).
Conclusions
Despite being lower than HbA1c, the 60-day GMI was within ±10% of HbA1c in 66% of patients. The correlation of HbA1c with corresponding GMI was stronger compared to that of fructosamine. GMI may be a good tool to identify patients with a glycation gap.

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P192

N-acetylmuramoyl-L-alanine amidase is a biomarker for remission of type 2 diabetes after bariatric surgery

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Aims
We used sequential window acquisition of all theoretical fragment ion spectra Mass Spectrometry (SWATH-MS) to identify proteins acting as markers of remission of type 2 diabetes (T2DM) in patients who lost weight after bariatric surgery.
Background
Bariatric surgery results in remission of T2DM in up to 80% of patients. The mechanisms underpinning are largely unknown. N-acetylmuramoyl-L-alanine amidase (PGLRYP2) is an immune response enzyme that breaks down glycopeptides, with a principal role in fighting bacterial infection. It is expressed constitutively from hepatocytes and previous proteomic studies have suggested utility in diagnosing sepsis. No studies have examined the role this enzyme plays in T2DM.
Methods
Longitudinal analysis was performed on plasma samples from ten individuals who achieved remission of T2DM post Roux-en-Y gastric bypass ($n = 7$) or Sleeve gastrectomy ($n = 3$). SWATH MS was performed on baseline/6 month/12 month

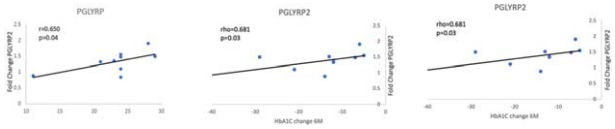

Table 1	Log FC 6-Months Vs Baseline	Log FC 12 Months Vs Baseline	P Value
Serotransferrin	-1.0677252	-0.7764836	$P < 0.001$
Proteoglycan 4	-0.8979797	-0.77934	$P < 0.05$
Sex hormone-binding globulin	1.48545057	1.95102943	$P < 0.05$
Bifunctional epoxide hydrolase 2	-0.4118723	-0.4725174	$P < 0.05$
Apolipoprotein A-IV	-0.7125427	-1.3811785	$P < 0.05$
PGLYRP2	0.39129906	0.43772459	$P < 0.05$
Heat shock 70 kDa protein 4	-0.4967544	-0.3887322	$P < 0.05$
Leucine-rich alpha-2-glycoprotein	0.5324538	0.5912797	$P < 0.05$

samples.
Results
SWATH-MS identified and quantified 467 proteins post-surgery. Twenty-five proteins were differentially expressed between pre-surgery and 6 months post-surgery; 39 proteins between baseline and 12-months. Eight proteins were significantly different at both 6-and 12-month time points. These are listed in Table 1. The fold change of PGLYRP2 showed a significant negative correlation with change in HbA1c at 6-months and at 12-months and change in BMI at 12-months.
Conclusions
Using SWATH-MS we identified significant changes in PGLYRP2 which correlated with both BMI and HbA1c consistently, suggesting a role for this protein in the remission of T2DM post BS which warrants further investigation.

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Magnesium: The forgotten sibling of electrolytes. A study of two audits conducted over 4 years

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The role of magnesium in electrolyte homeostasis is well established. ATP/ADP structure, refractory hypokalemia and calcium homeostasis are some of the established roles in literature, well known to Endocrine. However, currently no NICE guidelines exist for low magnesium. Our first audit in 2018 focused on patient admissions during January 2018. We found 49 patients with Mg $<$ 0.5. Majority were care of the Geriatrics, 8 under Gastroenterology, 4 under Endocrinology. 31 patients were found to be on proton pump inhibitors (PPI's). However we found that only 8 patients had their PPI's discontinued on discharge and only 8 patients had hypomagnesemia on noted on their discharge letter. Most common causes listed on requests by acute/general medical wards included diabetics, on drugs (PPI), alcohol excess, diarrhoea. Second audit in 2021 was spread over a collection period of 01/11/20 - 01/02/21. A total of 5424 patients were analyzed. We found Mg $<$ 0.4 in 37 patients, Mg 0.4-0.5 in 95 patients, Mg 0.5- 0.7 in 1469 patients and Mg $<$ 0.7 in 1601 patients. A majority of investigations were from endocrine/gastro/hematology wards ($>$70%) with acute medicine having only 12% of these requests despite maximum admissions. Incidence of Mg requested for concurrent potassium level less than 3.0 was 67%. 41/132 of patients with potassium less than 3.5 were found to have a magnesium less than 0.5. PPI's were discontinued in patients with Mg less than 0.5 in only 20 out of 87 patients. Hypomagnesemia was mentioned on discharge summary (when Mg less than 0.5) for only 65 out of 120 patients. Both studies done over a gap of 4 years revealed significant gaps in knowledge of hypomagnesemia. We agree that we need to establish strong local, regional and national guidelines for hypomagnesemia.
*All units in mmols/l.

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Abstract withdrawn

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Diabetes and Young COVID: A two country and two wave study of associations

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Authors agree that although mortality for COVID 19 is low, comorbidities may contribute to severe disease and mortality. Chinese center for disease control and prevention reported three times higher mortality in patients with diabetes. However, most studies do not take into account age of patients. Our study aimed to evaluate association of COVID in patients lesser than 65 years of age in two countries, India and United Kingdom with diabetes. We excluded patients with co-morbidities including advanced liver disease, cancer, patients with reduced ceilings of care and social needs prolonging hospital admission. Our UK arm evaluated a total of 657 patients. We found pre-diabetes in 9.6%, new diagnosis of diabetes in 11.4% and known diabetes in 17.9%. 23% of total patients did not have an HbA1c. Mortality was higher at 11.9% in diabetics compared to 5.4% in non diabetics ($P < 0.05$). Length of stay of diabetics was significantly longer with an average stay of 12 days compared to 4 days in non diabetics ($P < 0.05$). No significant increase in mortality was seen when comparing HbA1c levels. Our Indian arm evaluated a total of 904 patients. We found pre-diabetes in 16.6%, new diagnosis of diabetes in 22.1% and known diabetes in 33.8%. 87% of total patients had an HbA1c. Mortality rate was 33.1% in pre-diabetes/diabetics compared to 7.7% in non diabetics ($P < 0.05$). Length of stay of diabetics was significantly longer with an average stay of 17 days compared to 10 days in non diabetics ($P < 0.05$). Increased HbA1c revealed a close relationship with poorer outcomes. This is the only study to date evaluating diabetes in a younger age group and spread across two countries. We have proven significant relationship of COVID with diabetes irrespective of age. Gap in screening was found in UK implying need for education of diabetes and COVID.

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P196

Studies of the novel essential invadolysin metalloprotease in human blood

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The classic *Drosophila* model system has been utilized by the Heck laboratory for the characterization of novel and conserved genes essential for cell cycle and cellular physiology. The *invadolysin* mutation was first identified in *D. melanogaster*, which gave rise to abnormally-condensed chromosomes and had a lethal effect on the late larval stages. Invadolysin is a novel zinc-metalloprotease that we have shown to link cell division and cell migration in *D. melanogaster*. Invadolysin localizes to lipid droplets in mammalian cell lines, and *Drosophila* invadolysin mutants have a decreased triglyceride:protein ratio. Invadolysin also plays a role in insulin signalling and adipogenesis - in the fly and in vertebrate *in vitro* models. Recently, we discovered an extracellular form of invadolysin in *Drosophila* hemolymph and human plasma, and invadolysin is present in the extracellular vesicle-enriched fraction of human plasma. As invadolysin is essential for life, we are suggesting that the secreted form of invadolysin may play an important role in maintaining normal physiology. In this research, we are developing biochemical strategies to enrich invadolysin from human plasma, which improves the detection and analysis of the extracellular form of invadolysin. Preliminary results reveal that the extracellular form(s) of invadolysin differ between the enriched fractions of human serum and plasma. We are looking to understand these differences, and detect associated enzymatic activity of the secreted form(s) of invadolysin. Importantly, our long-term aim is to address whether the secreted form(s) of invadolysin play a role in normal physiology or serve as a potential biomarker for any human disease states.

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P197

Case report of a Patient With Maturity Onset Diabetes of the Young 6: a novel NEUROD1 mutation

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Introduction
Maturity onset diabetes of the young (MODY) is a group of monogenic, autosomal, dominant diseases characterized by a single genetic mutation that

results in beta-cells disfunction with consequent hyperglycemia. It Accounts for 1-5% of all cases of diabetes. At the moment, optimal treatment has not been established and it relies on the individual response. A mutation of NEUROD1 gene, a transcription factor expressed by pancreatic and nervous tissues, has been found to cause beta-cells dysfunction, inadequate insulin secretion, and hyperglycemia (MODY 6). A recent case report has documented for the first time a new missense mutation (p.Met114Leu c.340A> C) of the NEUROD1 gene that is pathogenetic for diabetes mellitus.
Case
We report the case of a 50 years-old man in treatment with basal-bolus insulin regimen and initial poor glycemic control. After thorough genetic testing, NEUROD1 mutation was found. Treatment adjustment aimed at optimal glycemic control allowed rapid analog withdrawn and initiation of gliclazide. Interestingly, our patient had an early onset dilated cardiomyopathy. No other data about cardiac diseases in patients with MODY 6 is available.
Discussion
Patients with family history of diabetes, normal BMI, early onset and no autoimmunity should be screened for known MODY mutation. Diagnostic criteria for MODY can overlap with other types of diabetes and most cases are still misdiagnosed as diabetes type 1 or 2.
Conclusions
Once MODY is diagnosed, treatment optimization should consider sulphonylureas and incretin based-antidiabetic drugs before insulin basal-bolus regimen is instituted.

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P198

Corticosterone excess alters metabolic rate in male and female C57BL/6J mice

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Introduction
Glucocorticoids are vital for regulating metabolic processes, as well as use in medical treatments. However chronic glucocorticoid excess is known to cause negative metabolic effects including hyperglycaemia, muscle atrophy and fat accumulation. The effect on energy metabolism and metabolic rate remains undefined and merits investigation in both male and female mice.
Methods
20 male and 20 female C57BL/6J mice were randomly assigned to a corticosterone (100 mg/l, approximately 300μg/day) or a vehicle control group. Mice were treated ad libitum via drinking water for 3 weeks, whilst being fed a standard chow diet. Mice were placed into a TSE Phenomaster system for the final week of treatment for indirect calorimetry assessment.
Results
Corticosterone treatment resulted in a typical phenotype of glucocorticoid excess with female mice experiencing significantly greater fat accumulation and bodyweight gain. Females treated with corticosterone exhibited increased energy expenditure (EE, 25±5.9%), oxygen consumption (21.7±10.0%) and carbon dioxide production (36.4±14.3%) during the day compared to controls, but males did not. However, corticosterone did significantly elevate the respiratory exchange ratio (RER) towards 1 in both males (10.7±5.7%) and females (11.8±7.0%) during the day. At night, when mice are naturally more active, female corticosterone mice no longer had elevated EE, oxygen consumption and carbon dioxide production compared to controls. However, RER remained elevated in females (7.6%±4.8%) and moderately so in males (3.2±2.6%), staying close to or exceeding 1 in both. Corticosterone treated mice were hyperphagic throughout with food and water intake peaking at night.
Conclusions
These findings provide further insights into the metabolic consequences of glucocorticoid excess in male and female mice. Whilst energy metabolism and metabolic rate are altered in both, the metabolic effects of glucocorticoid excess might be more pronounced in females.

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P199

Paraneoplastic Insulin Resistance Syndrome: a case of Fibromatosis (Desmoid Tumour)

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Introduction
Paraneoplastic endocrine syndrome such as hypercalcemia in malignancy is well-known. However, paraneoplastic insulin resistance is rarely described and its management is challenging.
Case history
A 33 years old teetotal gentleman with BMI of 37.5 kg/m^2 and histological diagnosis of desmoid tumour presented with osmotic symptoms, weight loss, hyperglycemia and normal ketones. He was hemodynamically stable with no clinical or biochemical evidence of diabetic ketoacidosis. He had acanthosis nigricans. There was no previous history of diabetes or genetic disease. He had extensive excisional surgery to remove the intra-abdominal desmoid tumour followed by chemotherapy. His father had type 2 diabetes controlled with metformin.
Investigations
HbA1c = 142 mmol/mol, c-peptide = 2.91nmol/l[0.34 –1.8], insulin = 55.3 miu/l [2.0-25.0] and random glucose = 26.8 mmol; interleukin 6 = 8.8 pg/ml (0.0-7.0). Diabetes autoantibodies and coeliac screen were negative. Cholesterol = 4.7 mmol/l, triglycerides = 2.9 mmol/l and HDL = 0.9 mmol/l. Full blood count, renal function and thyroid profile were normal. ALT = 151u/l; ultrasound scan showed fatty liver and liver biopsy confirmed severe steatosis with mild steatohepatitis.
Results and treatment
Weight loss and osmotic symptoms warranted the initiation of insulin therapy in addition to metformin. Total daily insulin dose was 130 units daily. Semaglutide was added considering its effect on liver fat. Fasting blood glucose fell from 20 mmol/l to 6 mmol/l; ALT fell from 151u/l to 33 u/l; HbA1c fell from 140 mmol/mol to 40 mmol/mol within 7 months. The future plan is to wean off all medications and commence strict caloric management in a multidisciplinary setting.
Conclusions and points for discussion
Paraneoplastic insulin resistance syndrome associated with desmoid tumour (fibromatosis) is very rare. Desmoid tumour produces pro-inflammatory cytokines such as Interleukin 6 which are implicated in the pathophysiology of insulin resistance. Treatment should be focused on interventions to reduce insulin resistance by reducing visceral (liver) fat content.

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P200

Management of the common within the uncommon: Euglycemic ketoacidosis in Bloom's syndrome

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Background
Bloom's syndrome is a rare autosomal recessive disorder due to chromosomal instability. It is associated with endocrinopathies such as growth deficiency, insulin resistance, type 2 diabetes, dyslipidemia and hypothyroidism. We present a case to highlight the challenges in management of diabetic emergencies in patients with complex syndromes.
Case report
A 38-year-old male of Asian descent known to have Bloom's syndrome presented to A&E with severe diarrhoea and poor oral intake. He had ongoing chemotherapy for mixed phenotype acute leukaemia and Type 2 diabetes of nine years duration treated with oral hypoglycemic agents. During his previous hospital admission, he was discharged on Metformin, Alogliptin and Dapagliflozin. On examination he was short statured, emaciated with BMI 13.4kg/m^2

and signs of severe dehydration. At presentation, Glucose 13 mmol/l, Ketones 6 mmol/l, pH 7.32 and HCO3 14.7 mmol/l, indicative of diabetic ketoacidosis (DKA) likely precipitated by neutropenic sepsis, SGLT-2 use and preceding starvation. A paediatric scale was initially contemplated but was then commenced on the adult fixed rate insulin infusion (FRII), intravenous antibiotics and product transfusion. After 24 hours he had persistent hyperglycaemia with no ketoacidosis. FRII was changed to variable rate insulin infusion (VRII) and he was commenced on Lantus. Blood cultures revealed multiple bacteremias and echocardiography, Chest Xray and Urine microscopy revealed no abnormality. He was on empirical treatment for sepsis. Over the next 24hours glycaemia improved, VRII was stopped, and Lantus continued in glycemic control.
Conclusions
Fluid resuscitation in DKA is guided by severity of dehydration and body weight in pediatric patients; however, in adults it is standardized. We highlight the lack of evidence-based recommendations we for DKA management in adults with requirements that differ from the normal population.

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P201

Phospho-regulation of Acetyl-CoA-Carboxylase (ACC1) in Pancreatic Beta Cells

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Background
Acetyl-CoA-Carboxylase (ACC1), the rate-limiting enzyme of de novo lipogenesis, plays a critical role in beta cell growth and insulin secretion. In spite of plethora evidence for the role of ACC1 in insulin secretion and beta cells function both *in vivo* and *in vitro*, very little is known about how ACC1 activity is regulated in pancreatic beta cells. The aim of the current study was to screen for novel phospho-sites that may regulate ACC1 activity in beta cell.
Methods
ACC1 protein was purified from INS1 beta cells cultured with different glucose concentrations. Unbiased quantitative phosphoproteomics was performed to characterise ACC1 phospho-sites: LC-MS/MS was undertaken using a Q-Executive mass spectrometer and data analysed using MaxQuant and Perseus. We generated phospho-specific antibodies against key phospho-sites identified by our screen that exhibited a dynamic response to glucose stimulation, which were validated by western blotting.
Results
Using quantitative phosphoproteomics, we identified twenty phospho-sites on the ACC1 protein in beta cells. ACC1S1215 was highly phosphorylated at 2 mmol/l glucose and showed a marked and significant reduction in phosphorylation in response to 15 mmol/l glucose, in contrast to the more modest changes in phosphorylation of ACC1S79. Phosphorylation of ACC1S25 was lower at basal glucose and increased upon glucose stimulation. Validation by western blotting confirmed that ACC1S1215 phosphorylation was highly regulated by glucose.
Conclusions
This study was undertaken to expand our understanding of ACC1 regulation in beta cells. To this aim, we have generated a high-resolution phosphoproteomics profile for ACC1 protein in beta cells. We identified novel phospho-sites that show significant and dynamic regulation by glucose and may play a role in regulating beta cell ACC1 activity and insulin secretion.

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P202

Estimation of body fatness in obesity and partial lipodystrophy in relation to eligibility for bariatric surgery: What should be measured?

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Introduction
Eligibility for bariatric surgery in the Unighted Kingdom is based on specific body mass index (BMI) thresholds and the presence of obesity-associated complications. Patients with partial lipodystrophy (LD) often have an abundance of metabolic and cardiovascular complications, but their abdominal adiposity does not always substantially increase BMI. The consequence is that patients with LD may be inappropriately excluded from obesity treatments when judged by BMI alone. We have therefore performed a detailed analysis of body composition in a large cohort of obese individuals and patients with LD to develop an algorithm to reflect the relative adiposity of the two groups.
Methods
A cohort of women with a BMI >40 kg/m^2 from the Oxford Biobank who had undergone dual X-ray absorptiometry ($n = 55$) to obtain absolute measurements of regional fat masses were analysed, along with 7 female patients with Familial Partial Lipodystrophy (types 2 and 3) and patients with partial lipodystrophy without an identified genetic mutation.
Results
For a given degree of android fat mass, all LD patients had a corresponding BMI that was below the 5th percentile of regularly obese patients. Two LD patients underwent bariatric surgery and, during the weight loss phase, their repeated dual X-ray absorptiometry measurements continued to track below the 5th percentile.
Conclusion
The use of BMI cut offs for prioritisation for bariatric surgery (or other weight loss treatments) in LD patients vastly underestimates the degree of android adiposity. The data we provide enables the estimation of the "true" BMI of LD patients if their adipose tissue fat mass were to be evenly distributed. The data also argue against using strict BMI cut offs for prioritization for weight loss interventions such as bariatric surgery.

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P203

An Audit assessing Management of COVID patients on Dexamethasone with High Capillary Blood Glucose (CBGs) from 01/01/21 to 19/3/21

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Dexamethasone reduces mortality in COVID patients who require oxygen therapy. Dexamethasone-related hyperglycaemia however is a known complication. Capillary blood glucose (CBGs) above 10.0 mmol/l have been linked to increased mortality in COVID patients. Approximately a third of COVID patients with dexamethasone-related hyperglycaemia may develop diabetes later. It is therefore important to manage acute episodes of hyperglycaemia effectively and identify these patients for follow-up in the community. Diabetes UK COVID-19 guidelines recommend at least once daily CBG monitoring for non-diabetics and at least 4 times daily monitoring for diabetics. When managing acute dexamethasone-related hyperglycaemia, diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) should be excluded before commencing subcutaneous rapid-acting insulin therapy. The audit analysed management

of acute hyperglycaemia in COVID patients on dexamethasone therapy in a central London hospital during the COVID pandemic from 1/1/2021 to 19/3/2021. The main analyses included (1) appropriate intervals of CBG monitoring, (2) ruling out of DKA/HHS, and (3) if the correct dose of rapid-acting insulin was given in accordance to Diabetes UK COVID-19 guidelines. A total of 65 encounters of hyperglycaemia were identified, with the highest CBG during admission analysed. Our results showed that 9.2% did not have their CBGs monitored at appropriate intervals (at least OD for non-diabetics, QDS for diabetics). Moreover, 67.7% did not rule out DKA/HHS when their CBGs were >12 mmol/l , one of which had CBG >30 mmol/l (no documentations or tests to rule out HHS/DKA). Only one encounter had the correct dose of insulin administered in accordance with Diabetes UK guidance; 57% had no insulin given. A teaching presentation was done with the foundation doctors to highlight the results and the importance of identifying and managing COVID patients with hyperglycaemia. In addition, we are currently in the process of developing a trust-standardised EPIC smart-phrase for foundation doctors, especially for out-of-hours.

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P204

Early detection of Peripheral Diabetic Neuropathy – A correlative study of symptoms with Digital Biothesiometry

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Aim
To assess the utility of early detection of diabetic peripheral neuropathy using Vibration perception threshold (VPT) via digital Biothesiometer and correlation with patient reported symptoms. Type of study: Audit of peripheral neuropathy assessment in all diabetes patients Standard: NICE guideline on Diabetic foot problems (NG 19- Updated October 2019)
Methods
The NICE guidelines recommend neuropathy assessment on all patients with Type 2 Diabetes. 100 consecutive Type 2 diabetes patients attending the OPD of Jeevans Diabetes and Endocrine Centre, Kerala, India were assessed for symptoms of diabetic peripheral neuropathy and subsequently underwent digital Biothesiometry using the Digital Biothesiometer (BIOTHEZI-VPT) to detect any signs of diabetic neuropathy. Biothesiometer is a device which can pick up early cases of neuropathy and works on the principle of an electrical tuning fork. A response to a stimulus value $< /=$ to 15 volts was considered normal; a value of 16-25 volts to appreciate the stimulus was classified as Grade 1 neuropathy and a value of >25 volts was considered as Grade 2 Neuropathy.
Results
100 patients with Type 2 diabetes were included in the study. 70 patients were female and 30 patients were male. The age range was from 27 – 76 yrs. Only 10 patients reported any symptoms suggestive of peripheral neuropathy. When examined with Biothesiometer, 26 patients had normal (<15 volts) value, 50 patients had grade 1 neuropathy (16-25 volts) and 24 had grade 2 neuropathy ($>$ 25 volts) on the Biothesiometer.
Conclusion
Reliance on patient reported symptoms can lead to many patients of diabetic neuropathy going undetected. VPT is considered as a gold standard test for detection of diabetic peripheral neuropathy. Other tests though simple may be biased by subjective observer variation. Use of VPT using Biothesiometer is a simple and sensitive assessment for early detection of significant diabetic peripheral neuropathy in OPD setting.

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P205

Assessing and Improving junior doctors' knowledge and confidence in managing Diabetes Mellitus in the end-of-life setting

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An anonymised online survey was created to evaluate junior doctor's competency and confidence with decision-making scenarios in managing patients with diabetes at the end-of-life. 26 doctors working at the Beacon Hospital completed the online survey. A structured education programme was then delivered to the junior doctors where the critical information pertaining to the management of diabetes at the end-of-life was discussed, based on the ABCD 2011 and Diabetes UK 2013 and 2018. Our sample consisted of 38.46% Interns, 38.46% Senior House Officers (SHOs) and 23.08% Registrars. The doctors worked across a number of different specialities with 11.54% were working in cardiology and oncology respectively, 15.38% working in general medicine, 26.92% working in general surgery and finally 34.62% working in other specialities. 52% of respondents stated that they were now "comfortable" in dealing with diabetes in the palliative care setting, compared to 20% before the educational intervention. Furthermore, the number of junior doctors who stated that they felt "very uncomfortable or completely out of their depth" decreased from 36% to 16%, following the educational intervention. In terms of assessing the knowledge and competence among junior doctors in managing these patients, the understanding that there is generally no set "acceptable" blood sugar reading in a patient with diabetes in their final days of life but rather the focus should be on "keeping the patient comfortable and asymptomatic" increased from 42.31% to 91.67% among junior doctors, following the educational intervention. Our study showed that there is a lack of confidence among junior doctors in managing diabetes care in patients at the end of life. Our study also showed that short, structured education programmes on the management of diabetes at the end of life can help improve junior doctor's knowledge and competency in the area, as well as giving them more confidence.

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P206

A quality improvement project to assess the management of diabetes in out-patient clinic as per the NICE guidelines

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Purpose
The aim of diabetes management is to prevent the micro/macrovascular complications. We have designed a quality improvement project to monitor how we are doing in term of glycaemic control and overall management of diabetes in our out-patient facility and how can we improve the outcome further.
Methods
Parameters checked (HbA1C, blood pressure, lipid profile, annual fundus examination, podiatry, urine for ACR). Retrospective study of 112 patients who attended the OPD in 2020 and then re-audited for the same number one year later.
Findings
The first cycle showed that our sampled patients' HbA1c and blood pressure was not controlled, but these has improved further after implication of suggested changes, HbA1C control has improved by 25% in T1DM, 12% in T2DM, and the blood pressure control improved by 19%. Likely because of Covid-19 and cancellation of clinics, some of the parameters could not be improved and need further action plans.

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P207

Omeprazole induced hypomagnesemia leading to hypocalcemia

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Case History
A 58 year old female was referred by the GP to hospital for symptoms of tingling and numbness in fingers and toes, muscle cramps in arms and legs and swollen legs. The patient had a history of gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), hypertension, fibromyalgia, iron deficiency anaemia, knee osteoarthritis, and heart failure.
Investigations
On admission, a corrected calcium level was 1.9 mmol/l and serum magnesium 0.37 mmol/l . Her Parathyroid hormone (PTH) was 7.6 pmol/l and Vitamin D-level was 48 nmol/l.
Results and Treatments
She was treated with intravenous calcium and magnesium. However, the calcium levels still didn't normalise till she had magnesium infusion. It was identified that she was taking omeprazole for a long time and the dose was recently doubled as she had worsening of reflux symptoms two months ago. Therefore, omeprazole was immediately stopped and replaced with famotidine (H2 blocker), and then serial calcium and magnesium levels became stable. She was discharged on Vitamin D and calcium supplement. A repeat set of bloods was done one month later, and all electrolytes levels were normal without omeprazole.

	Prior to admission	On admission	Omeprazole stopped (Day 1)	Day 2	Day 3	Follow up bloods
Calcium (2.10-2.55 mmol/l)	1.85	1.90	1.94	2.01	2.35	2.54
Adjusted calcium (2.2-2.6 mmol/l)	1.95	1.99	2.04	2.17	2.32	2.5
Magnesium (0.7-1 mmol/l)	-	0.37	1.07	0.83	0.74	0.87
Vitamin D (75-200 nmol/l)	46	48	-	-	-	
PTH (2-8.5 pmol/l)	-	7.6	-	-	-	

Conclusion
Chronic use of omeprazole can lead to hypocalcaemia and hypomagnesemia. It has been proposed that increased luminal pH in the intestine caused by proton pump inhibitors may alter the affinity of the TRPM6/7 channel responsible for absorption of magnesium, resulting in reduced active transport of magnesium.

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P208

The unmasking of chronic diabetes mellitus, presenting as severe diabetic ketoacidosis following traumatic pancreatic injury, without pancreatitis

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A 43-year-old gentleman with no known medical illnesses presented with progressive abdominal distension and pain. This happened following a fall from 2-metre height with direct impact on his abdomen. On examination he had signs of abdominal peritonism and was managed as a trauma case. He was haemodynamically stable. CT of his abdomen showed suspected large pancreatic haematoma, consistent with significant pancreatic injury with no evidence of active haemorrhage or pancreatitis. However, he had left the hospital before further evaluation and was brought to the hospital 48 hours later with confusion and tachypnoea. Repeat CT scan showed similar appearances of the suspected pancreatic injuries. However, he was found to be in severe diabetic ketoacidosis with glucose 34.4 mmol/l , pH 6.94 and ketones 6 mmol/l . Lactate was 1.5 mmol/l . Serial amylase was within the normal range. Following aggressive medical therapy, his ketoacidosis had resolved and glucose improved significantly within 12 hours. The pancreatic injury was managed conservatively. Further correlation with MRCP was inconclusive but it was suggested that the pancreatic duct had been transected in the neck of the gland. HbA1c during admission was 86 mmol/mol indicating background of undiagnosed diabetes mellitus. He was discharged with Metformin, Gliclazide and Dapagliflozin and repeated HbA1c 6 weeks later showed significant improvement to 64 mmol/mol.
Discussion
This case illustrates the unmasking of diabetes mellitus presenting as severe DKA secondary to severe pancreatic injury with no evidence of pancreatitis. This could have happened due to the transient loss of endocrine pancreatic function resulting in absolute insulin deficiency. This gentleman has type 2 diabetes with good initial response to oral anti-hypoglycaemics.
Conclusion
Thorough medical evaluation for possible hyperglycaemic emergencies should be performed in patients with significant intra-abdominal injury, as this could be missed due to priority given to the trauma itself.

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P209

Gender-specific prevalence of hyperuricemia and association with metabolic disorders in China: a hospital population based retrospective real-world study

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Objective
To investigate the prevalence of hyperuricemia in Chinese population, and the association between serum concentrations of uric acid and related metabolic disorders.
Methods
This study was based on de-identified hospital information system (HIS) data collected from four tertiary hospitals in three provinces of China. A total of 432,002 patients with at least one medical visit recorded SUA measurement were screened and 374,506 were enrolled. Hyperuricemia was defined as SUA $\geq$7.0 mg/dl in male or $\geq$6.0 mg/dl in female.
Results
Among enrolled subjects, 49.7% was male while 50.3% was female. The total prevalence of hyperuricemia and gout were 14.8% and 0.5%. Significant differences were observed between genders where prevalence in male was higher than in female (17.6% vs 12.0%, 0.8% vs 0.1%, both $P < 0.001$). Higher SUA level groups had significantly increased adjusted OR of dyslipidemia and chronic kidney disease in both genders, while difference was observed with type 2 diabetes mellitus. In the cohort study, the change of SUA from baseline was negatively correlated with the change of eGFR and HbA1c (r = -0.319 and -0.074, both $P < 0.001$) and positively correlated with the change of TC, TG, LDL-C, HDL-C (r = 0.110, 0.144, 0.082, and 0.012 respectively, all $P < 0.05$) among males. After adjustment of covariates, SUA change was still significantly negatively associated with eGFR and HbA1c, while with TC, TG, LDL-C and glucose positively (all $P < 0.001$). Similar outcomes were observed in female objects.
Conclusion
Gender-specific prevalence of hyperuricemia was observed in Chinese population. Hyperuricemia was associated with dyslipidemia, CKD in both genders, cross-sectionally and longitudinally.

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Neuroendocrinology and Pituitary

P78

The role of FGF signaling pathway in the pituitary stem cell compartment

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The FGF signalling pathway regulates cell proliferation, differentiation, migration and cell specification in mutliple developing and adult tissues. It has also been implicated in tumor development and progression with a significant role in the cancer pathobiology of several malignant tumors including melanoma, breast, pancreas, head and neck and non-small lung cell cancer. FGF signalling plays a major role in the postnatal hypothalamic-pituitary (HP) axis, with dysregulation of FGF pathway components, including FGF1, FGF8 and FGFR1, linked to disorders including Kallmann syndrome, septo-optic dysplasia and congenital hypopituitarism. FGF8 and FGF10 expressed by the ventral diencephalon are required for proper development and expansion of Rathke's pouch, with early loss of Rathke's pouch in FGF10 null mutant mice. In the hypothalamus, FGF10 promotes the maintenance of tanycytes in an uncommitted state, suppressing neurogenic differentiation. To conduct an in-depth analysis of the expression of *Fgf* genes and their receptors across the different cell types of the anterior pituitary gland, we have computationally mined published single cell sequencing data of the murine postnatal gland. We present the heterogenous expression of FGF pathway components including ligands, receptors and targets. Notably, *Fgf10* is expressed by multiple Rathke's pouch derivatives in the postnatal pituitary, including subsets of stem cells, lineage-committed progenitors and hormone producing cells. We have validated these findings in mice expressing beta-galactosidase under the control of the *Fgf10* promoter (*Fgf10-LacZ*), through immunofluorescence analyses at different postnatal stages. Additionally, using CellChat DB computational analysis, we have identified that anterior pituitary stem cells signal to other committed populations in the gland through FGF1-FGFR1 ligand-receptor interactions. The complete validation of our computational data will provide new insights about the specific roles of FGF signalling members in the maintenance and regulation of the anterior pituitary cell compartments.

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P79

MRI bone shape in patients with acromegaly: a novel technique for the characterisation of the acromegalic arthropathy

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Objective
Arthropathy is the commonest morbidity in acromegaly and the main determinant of quality of life in these patients. Most of current knowledge is derived from studies using conventional x-rays. This study aims to characterise acromegalic arthropathy using modern imaging techniques.
Methods
Case control study comprising of 60 acromegaly patients (29 males, mean age 54.8 ± 12.9yrs) and 300 age/gender-matched controls from the publicly available Osteoarthritis Initiative (OAI) database. Bilateral knee MRI scans were obtained. Knee bone shape, joint space width (JSW) and cartilage thickness were measured based on automated segmentation of MR images of knee bones and calculation of bone area using active appearance models.
Results
Acromegaly patients had increased medial JSW compared with controls [6.21mm (95% CI 6.03-6.40) vs. 5.78mm (95% CI 5.70-5.87), $P < 0.001$] and increased lateral and medial femorotibial cartilage thickness. Patella and medial tibia bone areas were also increased in acromegaly patients. B-score (a biomarker associated with severity and risk of progression of osteoarthritis) was significantly higher in patients than controls [1.7 (95% CI 1.32-2.08) vs. 1.01 (0.84-1.18), $P = 0.001$]. Twenty-one acromegaly patients (35%) had B-score ≥ 2, which is indicative of osteoarthritis. These patients had higher GH levels at diagnosis of acromegaly and required higher number of therapeutic interventions compared with patients with B-score < 2 ($n = 39$). Additionally, patients with B-score ≥ 2 had significantly larger femoral, tibial and patella bone areas, increased medial JSW and lateral and medial femorotibial cartilage thickness compared with the remaining patients.
Conclusions
Acromegaly patients despite higher B-score and larger bone area have preserved and/or increased JSW due to increased cartilage thickness. The higher pre-treatment GH values and higher number of therapeutic interventions seen in patients with B-score ≥ 2, indicate that exposure to excessive GH is a risk factor for more pronounced changes to knee bone shape and potentially more severe arthropathy.

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P80

ACROBAT Advance: progress report on a study of long-term safety and efficacy of paltusotine for the treatment of acromegaly

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Paltusotine is a once-daily, oral selective nonpeptide somatostatin receptor type 2 (SST2) agonist, which is in clinical development for the treatment of acromegaly. Maintenance of insulin-like growth factor 1 (IGF-1) control and toleration was demonstrated in phase 2 studies evaluating paltusotine in biochemically controlled (IGF-1 $\leq$1xULN) [ACROBAT Evolve (NCT03792555)] and uncontrolled (1> IGF-1 $\leq$2.5xULN) [ACROBAT Edge (NCT03789656)] patients with acromegaly treated with stable long-acting octreotide or lanreotide. Patients in both parent studies were switched to oral paltusotine for up to 13 weeks. We hypothesized that continued paltusotine therapy would result in the long-term maintenance of IGF-1 control with acceptable toleration and safety. Subjects who completed ACROBAT Evolve or Edge were eligible to participate in ACROBAT Advance (NCT04261712), an ongoing single-arm, open-label 208-week extension study. Patients were eligible to enroll into Advance directly upon completion of the parent trial or after a gap period on standard of care treatment. In Advance, all subjects initiate 10 mg/day of paltusotine, the dose is then titrated to a maximum of 40 mg/day based on IGF-1 control and toleration. Despite delayed activation of many study sites due to the COVID-19 pandemic, Advance is expected to complete enrollment soon with an anticipated total of 41-43 of 49 eligible patients (84-88%). Open-label titration of paltusotine dose over the first 3-6 months of Advance study participation is complete for many subjects. As of June 1, 2021, 14 subjects have reached the Week 48 visit. An interim data cut is planned in August 2021, and a summary of key endpoints will be reported including summary statistics of IGF-1 and growth hormone (GH) compared to baseline. In addition, the incidence of treatment-emergent adverse events will be summarized. Analyses from this interim data snapshot will provide initial insights into the long-term safety and efficacy of paltusotine treatment for acromegaly.

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P81

Is gigantism different from acromegaly in terms of causes of death, comorbidities and treatment? A preliminary retrospective study of 156 UK giants

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Introduction
Although acromegaly and pituitary gigantism have the same pathological cause, they have different disease characteristics.
Aim
To study tumour size, treatment course and the most common comorbidities in a population with young-onset acromegaly.
Materials and Methods
UK Acromegaly Register (UKAR, 22 centres, 1997-2017) retrospective analysis, enriched with patients from the FIPA-consortium. We defined gigantism as diagnosis of GH excess at $<$20yrs, or $+$3SD height for UK population. We recruited 156 giants: 111 from 3309 UKAR patients, and 90 from FIPA-consortium (45 overlapping). The remaining cohort from UKAR formed acromegaly control group (AG).
Results
Giants had pituitary macroadenoma and extrasellar extension more often than AG (84.9% vs 68.8%, $P = 0.001$ and 53.2% vs 33.9%, $P < 0.001$). Most patients underwent surgery (giants:87.4%, AG:83.9%%). Giants had repeated surgery and transcranial surgery more often than AG (27.8% vs 9.0%, $P < 0.001$ and 11.9% vs 4.2%, $P < 0.001$). There was no difference in radiotherapy (59.1% vs 58.8%). Medical treatment was comparable for dopamine agonist (34.8% vs 37.8%, $P = 0.456$), and pegvisomant (10.3% vs 7.2%, $P = 0.148$), but higher for somatostatin analogues in giants (53.5% vs 44.6%, $P = 0.028$). The total number of treatment modalities was higher for giants (2.88 ± 1.52 vs 2.49 ± 1.38, $P = 0.003$). Polyps/cancers in colonoscopy and hypertension were more frequent in acromegalics in age adjusted analysis (25.4% vs 42.1% $P = 0.008$ and 24.5% vs 52.3%, $P < 0.001$). Diabetes does not have higher frequency in acromegaly (32.7% vs 28.3%, $P = 0.280$). Death rate in giants was lower than acromegalics (12.8% vs 19.5%, $P = 0.038$), but with lower age of death in giants (64.9 vs 73.48yrs, $P = 0.006$). From the genetically screened giants (59.6% of cases), 41.9% harboured an *AIP* mutation.
Conclusions
Pituitary gigantism patients more frequently have extrasellar macroadenoma, and require more invasive treatment (re-surgery, transcranial approach, more medical treatment, more overall treatment modalities). Comparison of morbidity, mortality and GH/IGF-1 control adjusted for decades are further needed in these patients. *On behalf of the UK Acromegaly Register Study Group 2019 and the FIPA-consortium UK members*

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P82

Pituitary and gonadal axes in patients with 'Long COVID': post hoc analysis

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Background
It is apparent that COVID-19 may cause persistent symptoms beyond 12 weeks ('long COVID'). However its underlying pathophysiology is unclear. Several symptoms of long COVID draw similarities to that of endocrine diagnoses. We recently observed that adrenal and thyroid function were normal in survivors of COVID-19 at follow-up. Here we assess additional endocrine axes that could plausibly have a role in long COVID to determine their relationship to ongoing symptoms.
Methods
Prospective observational study of 70 survivors of COVID-19 who attended for a research visit $\geq$3 months post-presentation. During this visit (08:00-09:30), a medical history including regarding persistent symptoms, and blood tests for pituitary and gonadal axis assessment, were taken.
Results
In our cohort, 59 (84.3%) patients had $\geq$1 persistent symptoms of COVID-19 at follow up, consistent with long COVID. Those with $\geq$7 symptoms were younger than those with none (mean age 40.1yrs vs 60.6yrs, $P = 0.002$), and a greater proportion were female ($P = 0.002$). Growth hormone and IGF-1 were similar in those with fatigue, compared to those without, and did not alter with number of persistent symptoms. Similarly, prolactin did not differ by number of symptoms ($P = 0.72$). Out of 47 males, 9 had total testosterone $<$9.2nmol/l, and 20% had calculated free testosterone $<$0.225nmol/l. However neither total nor calculated free testosterone altered with number of ongoing symptoms ($P = 0.34$ and $P = 0.94$ respectively). Pre-menopausal women had more symptoms than post-menopausal women ($P = 0.03$) although serum AMH did not alter by number of symptoms.
Conclusion
A large proportion of survivors of COVID-19 had ongoing symptoms $\geq$3 months post-presentation. However, there was no apparent correlation between the hormonal parameters assessed and number of symptoms experienced. Whilst this cohort is small, it suggests that extra-endocrine factors may contribute to 'long COVID', although further research is required to determine persistent effects of COVID-19 on endocrine function.

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P83

Screening for diabetes insipidus with copeptin after overnight water deprivation

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Introduction
Water deprivation testing (WDT) is considered the gold standard test in differentiating between craniogenic diabetes insipidus (DI), nephrogenic DI and primary polydipsia. However, it requires day case admission for monitoring of sodium and osmolality. Copeptin, derived from pre-provasopressin, is secreted in an equimolar amount with arginine vasopressin and has a potential role in facilitating the diagnosis of DI and reducing the need for WDT. Copeptin was gradually introduced at Royal Derby Hospital in 2019 as a screening test for DI. Here we discuss our experience and the impact it has had on our protocol for the investigation of DI.
Methods
All patients (13) who had received a copepetin test as part of their work up for DI were selected. The results of serum/urinary osmolality tests and any WDT were also analysed. The impact of copeptin on the final diagnosis of DI were reviewed and discussed at the local joint Endocrinology & Biochemistry meeting.
Results
Of the 13 patients analysed, only two copeptin results proved difficult to interpret as there was no associated urine osmolality. Of the 11 which could be interpreted, WDT was avoided in 3 patients with only 2 progressing to testing following the screening test. A further 6 WDT tests could potentially have been avoided if the copeptin level had been taken following an overnight fast.
Discussion
WDT is a time consuming, logistically challenging and unpleasant test for any patient with DI to undergo. Furthermore, the Covid-19 pandemic has made day case admissions challenging. By introducing an overnight fasting copeptin test (or $>$4hrs in very symptomatic cases) into our local protocol we were able to continue to investigate patients for DI during the Covid-19 pandemic whilst reducing the need for water deprivation testing.

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P84

Cinnamomum zeylanicum bark extract showed ameliorative properties against streptozotocin-induced insulin resistance in the hippocampus of experimental wistar rat

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Insulin resistance is one of the metabolic pathogenesis of Type 2 diabetes mellitus which cause neurodegeneration, due to its effects on insulin signaling pathway. The present study focused on the intracerebroventricular administration of streptozotocin (STZ) to induce insulin resistance directly in brain, accounting for alteration in insulin signaling pathway and thus the possible therapeutic effect of *Cinnamomum Zeylanicum* on the impairment hippocampus of diabetic rats. A total of 32 adult male Wistar rats were divided thus: Groups were labelled A, B, C and D. Group A served as the control and animals were fed *ad libitum,*receiving a single icv injection of normal saline, Group B animals were administered a daily dose of 200 mg/kg of C. *Zeylanicum,* In the Group C each animal each animal received 3 mg/kg body weight of STZ intracranially at the beginning using a mechanical stereotaxic apparatus while in the Group D which animal was administered STZ intracranially followed with daily oral dose of *Cinnamomum Zeylanicumm*. The experiment and animals treatment lasted 28 days. 29 and 30, all neurobehavioural tests were done. Memory patterns were generally altered in the experimental group relative to the control. A significant depletion were observed in open arm entry/duration, close arm duration significantly increased with a reduction in close arm entry, total entry, number of trial and % of alternation in behavioural performance. RNA analysis showed memory deficits in insulin resistance rats as there was a significant increase in BACE-1 and GSK-3β gene with noticeable increases in Insulin and Insulin receptor (IRS) gene when compared to control. Histological demonstration of the hippocampus and immunostaining revealed depolarization of the dendritic with milder neurodegeneration field and Amyloid beta plague generation respectively. *Cinnamomum Zeylanicum* due to its antioxidant and anti-inflammatory content was seen to have positive effects on STZ-induced insulin resistance on the hippocampus.

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P85

Clinical presentation of 209 surgically operated non-functioning pituitary macroadenomas

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Background
The clinical presentation of non-functioning pituitary adenomas (NFAs) can range from an incidental finding on imaging to pituitary hormone deficiencies and visual compromise.
Objective
To assess the clinical presentation of patients who had undergone surgical resection of histologically proven NFAs.
Methods
Patients presenting to the University Hospital of Wales, Cardiff, with non-functioning pituitary adenomas (histologically proven) between 2011-2019 were studied by examining biochemical, histological and radiological data.
Results
A total number of 209 patients with histologically-proven non-functioning pituitary macroadenomas were identified (130 male, 79 female). The mean age at surgery was 57yrs (range 24-86yrs). 81.9% patients presented symptomatically and 18.1% asymptomatically. *In the total group:*21.1% NFAs were found incidentally on brain imaging performed for another reason. 44/209 (21.1%) patients had their NFA diagnosed by an incidental field defect routinely at the optician ($n = 21$) or ophthalmology which they were attending for another reason ($n = 23$). *In the symptomatic group:* presenting complaints were reduced visual acuity (55.7%), headaches (38.3%), lethargy/tiredness (24.5%), reduced libido /erectile dysfunction (15.6%), visual field loss (10.8%) and galactorrhoea /menstrual disturbance (9%). 12 patients (7.2%) presented with pituitary apoplexy. The mean duration of symptoms before diagnosis was 16.9 months. 86.4% patients had chiasmal compression on imaging and 75.9% had visual field defects. 94 patients had pituitary hormone deficiencies. *In the asymptomatic group:* 75% had chiasmal compression and 52.8% had visual field defects. 21 asymptomatic patients had pituitary hormone deficiencies.
Conclusions
In our cohort of operated NFAs, 21.1% were found incidentally on brain imaging and routine visual field testing. Most patients presented symptomatically, commonly with visual symptoms or headaches, over a mean duration of 16.9 months. Given the cohort were operated NFAs, a large proportion had chiasmal compression and field defects. Of the asymptomatic patients, around half were found to have a visual field defect relating to chiasmal compression.

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P86

A rare case of sellar pathology: Coinciding IgG4-related hypophysitis and pituitary adenoma

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A 69-year-old man was referred to our Pituitary Service for a 3-month history of progressive right visual loss and a finding of "pituitary enlargement" on brain MRI. He reported erectile dysfunction and his medical history included asthma, DM2 and meningitis (8 years ago). Neuro-ophthalmology review showed visual acuity 6/60, optic neuropathy, marked visual field loss with residual superonasal island in right eye, mild 6th nerve palsy. Pituitary MRI: infiltrative lesion within the fossa extending to the right over the anterior clinoid process affecting the dura related to the dorsum sellae and the optic canal and overlying the planum sphenoidale, pituitary stalk thickening and a separate well-defined 8 mm mass in the left side of the fossa (presumed microadenoma). He had mild hyperprolactinaemia and hypogonadotropic hypogonadism; IGF-I, TSH and ACTH reserve were normal. There was no evidence of diabetes insipidus. CSF cytology suggested inflammatory process involving B- and plasma cells. PET-CT revealed intense uptake activity in two pancreatic masses and in para-aortic, aortocaval and retroperitoneal lymph nodes. EUS-biopsy of one pancreatic lesion showed evidence of fibrosis, significant excess of plasma cells and IgG and IgG4 expression. Serum IgG4 levels were also increased [9.20 g/l (0-1.3)]. IgG4-related disease was diagnosed. Prednisolone was initiated (four-week course; 30 mg with gradual tapering to 5 mg daily) leading to full recovery of his right visual field and acuity, shrinkage of the sellar and pancreatic lesions and lymph nodes, and decrease in serum IgG and IgG4 levels. The presumed microadenoma had remained unchanged. This is an unusual case of rare sellar pathology coinciding with a pituitary adenoma. Although hypophysitis is the most common manifestation of IgG4-related disease in the sellar region, in our patient, dural involvement was also present. This case also highlights the importance of broad differential diagnosis when approaching pituitary abnormalities on imaging.

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P87

Persistent gestational diabetes insipidus

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We report a 33 year old female who presented at 23 weeks gestation with rapid onset polyuria and polydipsia. Fluid input and output was approximately 12 litres per day. She denied any other symptoms. She did not have signs of hypopituitarism, Acromegaly or Cushing's syndrome. Visual fields were normal to confrontation. Her standard glucose tolerance test, Hba1c, creatinine and calcium were normal. Gestational Diabetes Insipidus was (GDI) suspected. Given her pregnancy, a water deprivation test was not performed. She was able to carry out a short overnight fast from midnight to 6am. Urine output during this period was nearly 2500mls. Fasting urine and serum osmolality were 152mosm/kg (100-900mosm/kg) and 297mosm/kg (285-295mosm/kg) respectively, with a serum sodium of 144mmol/l (133-145 mmol/l). Cortisol measured 1198nmol/l (> 400nmol/l), Free T4 13.3pmol/l (12-22pmol/l), TSH 2.0mU/l (0.2-4.0mU/l) and IGF1 17.0nmol/l (14.6-39.9nmol/l). A non-contrast MRI pituitary scan suggested the presence of a 6-8mm microadenoma, which was thought to be insignificant. She was commenced on desmopressin. Symptoms responded well and the rest of her pregnancy was uneventful. She delivered a healthy baby at 39 weeks gestation. Early follow up was arranged with a view to gradually wean off desmopressin. However, we were unable to reduce the dose on several attempts as she reported recurrence of symptoms within hours of missing a dose. She continues to be dependent on desmopressin five years after pregnancy. A repeat MRI pituitary scan with contrast demonstrated a normal pituitary gland. The pituitary bright spot was retained. GDI is normally transient and resolves post

partum. A normal MRI pituitary scan here excluded acquired cause of central diabetes insipidus in pregnancy. This suggests that some cases of GDI may persist long term after pregnancy, and it is important to evaluate the situation carefully to avoid abrupt withdrawal of treatment and relapse of symptoms.

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P88

Effects of ethanol extract of allium sativum L. On the hippocampus of male wistar rats with streptozotocin-induced brain insulin resistance

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The hippocampus is majorly involved in memory formation. The insulin pathway regulates the level of GSK-3β, which is involved in the formation of amyloid beta and Tau. *Allium sativum*has been shown to reduce amyloidogenesis and increase brain insulin sensitivity. 32 male Wistar rats were used in this experiment. They were grouped into 4, each with 8 rats. Group A (Sham), B (3 mg/kg of streptozotocin), group C (3 mg/kg of streptozotocin +300 mg/kg of *Allium sativim L.*), group D (300 mg/kg of *Allium sativum L.*). Treatment lasted 2 days. Neurobehavioral tests carried out were elevated plus maze and Y maze. The animals were sacrificed by cervical dislocation. Basic demonstration of the hippocampus was done using H&E stain and Cresyl Fast Violet special stains. RNA gene expression of insulin, insulin receptor substrate, BACE-1 and GSK-3B was checked. Groups A and B showed more exploratory activity when compared to the other groups. The photomicrographs analysed showed evidence of pyknosis and vacuolation in groups B and C, with group C usually showing less evidence of these attributes. A reduced expression of Nissl bodies was seen in groups B and C, with group C having a higher expression than group B. More amyloid beta proteins were seen in groups B and C, with group B having a higher number of this specific protein. The study concludes that *Allium sativum L.*was able to reduce the effects of Streptozotocin on the hippocampus, and also reduce amyloidogenesis. This research recommends that more research work should be carried out to check for the effect of graded doses of *Allium sativum L.* on the hippocampus after an intracerebroventricuar administration of streptozotocin.

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New presentation of asymptomatic acromegaly in patients with macroprolactinomas

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Background
Current guidance for the management of macroprolactinomas recommends full pituitary profile at baseline and subsequently only if symptomatic. Pituitary adenomas that co-secrete growth hormone and prolactin at presentation are well-recognised. Case reports of acromegaly after prolactinoma treatment are associated with symptomatic acromegaly. We present two patients with asymptomatic acromegaly years after diagnosis of macroprolactinoma.
Patient 1
A 47-year old gentleman presented with erectile dysfunction and investigations confirmed hypogonadatrophic hypogonadism due to hyperprolactinaemia (prolactin 29,599mIU/l, testosterone 3nmol/l, LH 0.7IU/l). Remaining pituitary profile was normal, IGF-1 26.1nmol/l. MRI showed 28mm x 40mm macroprolactinoma, without optic nerve compression. He commenced cabergoline and subsequent MRI demonstrated significant reduction of the tumour. Pituitary profile 3.5 years later identified a raised IGF-1 (47.1nmol/l), failure to suppress GH during OGTT (nadir 1.5 mg/l) but no clinical features of acromegaly. He underwent pituitary adenomectomy. Histology confirmed a mixed somatotroph-lactotroph adenoma. Two months post-operatively, small residual adenoma remained with corresponding raised IGF-1 (34.5nmol/l) and prolactin (4403mIU/l).
Patient 2
A 39-year old woman investigated for subfertility, secondary amenorrhoea and galactorrhoea was found to have an elevated prolactin (2968mIU/l) and normal other pituitary hormones (IGF-1 20.2nmol/l). MRI demonstrated a microadenoma, cabergoline was commenced and prolactin normalised. Four years later, MRI showed a macroadenoma (16 x 10 x 10mm) stretching the optic chiasm with normal visual fields. The following year, she developed a severe headache due to pituitary apoplexy. Biochemistry found raised IGF (35nmol/l), prolactin (3009mIU/l), low TSH (0.38mU/l; T4 10.7pmol/l), cortisol (67nmol/l) and gonadotrophins. GH failed to suppress on OGTT (nadir 0.59 mg/l) and repeat MRI demonstrated reduction in tumour volume. She did not have clinical features of acromegaly.
Discussion
These cases demonstrate new-onset, asymptomatic GH co-secretion from macroprolactinomas. If there is interval growth or failure of tumour shrinkage with cabergoline, we suggest annual IGF-1 testing.

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P90

Hypo and hypernatraemia on admission are associated with increased length of stay in unselected acute hospital admissions

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Introduction
Hyponatraemia is a common biochemical abnormality, complicating up to 15% of all hospital admissions and associated with increased mortality. Hypernatraemia, occuring less frequently, is strongly associated with mortality and is almost always due to a free water deficit. There is limited data about hospital healthcare burden of these two relatively common electrolyte imbalances. We analysed the length of stay, for acute admissions, with reference to the admission sodium value.
Methods
Clinical data for all unscheduled admissions were retrieved from the electronic health record (EHR). We used the CogStack ecosystem to access structured fields in the EHR. We analysed a 12-month cohort of all patients who had an A&E discharge summary created between 1st Jan 2017 and 1st Jan 2018. For each admission, the laboratory U&Es were obtained. Cox proportional hazard model evaluated the independent effect of the first sodium on likelihood of discharge, with first eGFR, age and sex as covariates, both treating sodium as categorical data (hyponatraemia <135 mmol/l and 'hypernatraemia' ≥ 145mmol/l) and continuously using linear spline terms (boundary knots at 135 and 145 mmol/l).
Results
In 12-months, there were 138,307 visits by 98,357 unique patients in the Emergency Department. Laboratory sodium was measured in 36,630 attendances. Hyponatraemia was found on the initial sample in $n = 5338$ (14.6%), hypernatraemia in $n = 360$(1%) and eunatraemia in $n = 30932$ (84.4%). In the multivariable model, hypo- (HR: 0.700, 95% CI 0.678 - 0.722 $P = <0.0001$) and hypernatraemia (HR 0.572, 95% CI: 0.507 - 0.646 p $<$ 0.0001) were independent predictors of remaining in hospital, after adjusting for eGFR (HR 1.009 (95% CI 1.008 - 1.009; P <0.0001) and age (HR 0.990, 95% CI 0.989-0.990; $P = <0.0001$). The spline model demonstrated an inverted V shaped relationship between admission Sodium and hazard of discharge against time.
Conclusion
Both low and high sodium are independently associated with prolonged length of stay for acutely hospitalised patients. Further work needs to address if active management of sodium imbalance or salt and water imbalance would achieve earlier discharge.

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P91

Rathke's cleft cyst with a very unusual course

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A 31-year-old man without previous medical history presented to his local hospital with one week history of generalised severe headache. Brain CT was reported as negative for acute intracranial pathology. Five weeks later, he re-

presented with worsening headache and blurring of vision. Brain CT revealed a large area of hypodensity centred on the left thalamus/basal ganglia and subsequent MRI with contrast showed a medium size pituitary cyst with suprasellar extension and two contiguous tandem cysts with thick enhancing walls along the left optic tract. The sellar cyst was compressing the optic chiasma and the lateral cysts were causing perilesional oedema of the left basal ganglia. He had bitemporal field defects. Pituitary function tests showed hypogonadotropic hypogonadism and mild hyperprolactinaemia (538mU/l, 73-407). There was no polyuria/polydipsia. CRP was 31 mmol/l and ESR 29 mm/hr. At that stage, he was referred to neurosurgery and discussion in the pituitary and brain MDTs suggested a high grade optic glioma, as the main differential. Endoscopic transsphenoidal biopsy was performed and frank pus in the pituitary fossa was found intraoperatively. The pus was evacuated and the cyst wall was sampled for biopsy. Initial culture grew a staphylococcus aureus. Pathology showed a benign cyst with acute on chronic inflammation consistent with inflammed Rathke's cleft cyst. Septic screen revealed no source of infection. A prolonged course of IV antibiotics were given with good radiological and visual improvement. The sellar cyst has not recurred and the two presumed abscesses along the left optic tract have significantly reduced in size. Abscess in a Rathke's cleft cyst with extension along the optic pathways has been very rarely reported. The course of the development of the abscess and the atypical findings on imaging make our case unique and highlight the value of intraoperative findings and careful pathological review.

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P92

Age- gender- and tanner stage-specific reference intervals for serum insulin-like growth factor binding protein 3 (IGFBP-3) and the insulin-like growth factor I (IGF-I) to IGFBP-3 molar ratios in healthy school children of a north indian city

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Context
Serum IGF-binding protein-3 (IGFBP-3) and molar IGF-I to IGFBP-3 ratio can aid the diagnosis of GH-related diseases. However, their clinical utility is limited by lack of validated reference intervals.
Objectives
To establish age-, gender- and Tanner stage-specific reference intervals for IGFBP-3 and IGF-I to IGFBP-3 ratio for Indian ethnicity.
Setting and Participants
We conducted a cross-sectional epidemiological study (age 5-18 years) from the north Indian city of Chandigarh including 2191 apparently normal subjects (1141 males; 1050 females). With robust exclusion criteria, 1746 subjects (males = 889; females = 857) were available.
Main Outcome Measures
Serum IGFBP-3 (ng/mL) and IGF-I (nmol/l) to IGFBP-3 (nmol/l) ratio by the Immunodiagnostic Systems (IDS) iSYS assays were measured and reference intervals (2.5th to 97.5th centiles) were generated.
Results
Both IGFBP-3 and the IGF-I to IGFBP-3 ratio are mainly determined by age and gender. In females, median IGFBP-3 peak was at 13 years (4095.9), and in males it was at 16 years (4225.3). Determined by the high pubertal peak in IGF-I, the peak in the IGF-I to IGFBP-3 ratio, occurred with an earlier and higher peak in females [36.8 (14 years)] compared with males [32.7 (16 years)]. IGFBP-3 concentrations were higher in females until age 13, with males developing a higher peak and having higher values after 13 years. In Tanner-specific data (n = 1735), females (n = 855) had IGF-I to IGFBP-3 ratio median peak in Tanner stage IV (39.5), while for males (n = 880) it was in stage III (32.3). IGFBP-3 had median peak in stage V (4049.1) for females and stage IV (4203.3) for males.
Conclusions
We presented the largest cohort with Indian ethnicity data on age-, gender- and Tanner stage-specific reference intervals for IGFBP-3 and molar IGF-I to IGFBP-3 ratio and demonstrated distinct gender and Tanner stage-specific differences. These data will support the diagnostics of growth disorders.

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Healthcare professionals' survey on the inpatient safety of Diabetes Insipidus

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Background
Knowledge of glucocorticoid use during acute illness is widely known, however, knowledge of Diabetes Insipidus (DI) is suboptimal amongst healthcare professionals. In 2009, a series of medical and management failures led to the death of 22 year old from DI in a London hospital. Since then increased efforts have been made to raise awareness about the inpatient management of DI and dangers associated with delay and/or omission of desmopressin. An NHS England patient safety alert was also issued in 2016 highlighting this risk.
Aim
To assess knowledge, awareness and concerns regarding DI among medical personnel in an inpatient setting.
Method
A survey with 10 questions was sent to 150 healthcare professionals.
Results
107 responded: (3 Consultants; 6 Registrars; 18 SHO; 5 FY2; 13 FY1; 13 Medical students; 33 Nurses; 1ACP; 8 Pharmacists; 5 HCA). Of these, less than 50% of responders knew the consequences in delay of treatment. Only about 25% of nurses had an idea on how to treat DI. None of the junior doctors know how to access desmopressin, compared to 15% of medical students.
Discussion
Inpatients with DI require heightened medical attention and care due to the risk and fatal consequences arising from lack of knowledge of healthcare professionals. Improved education, easier access to desmopressin, earlier Endocrinology consult, trust-wide safety initiatives and guidelines, electronic pharmacy alerts may all be useful interventions in improving the safety of patients with DI.

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P94

A case of pituitary abscess – a rare clinical entity

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Background
Pituitary abscess is a rare entity which is often not suspected in pituitary lesions differential diagnoses; arising de novo or as a consequence of sinus infection, meningitis, or haematogenous spread. The diagnosis is challenging and mostly made during surgery.
Case Report
A 54-year-old male patient presented with 3 days of severe headaches, vomiting, and left eyelid drooping. He was afebrile, BP 90/61mmHg, and had a left third nerve palsy with a superior visual field defect. Investigations showed hyponatremia 126mmol/l, cortisol 33nmol/l, prolactin 29mU/l, LH 0.6 iU/l, FSH 4 iU/l, Testosterone $<$ 0.4 nmol/l, TSH 0.57 mU/l, FT4: 13.4pmol/lm CRP 167 mg/l. He was resuscitated with intravenous fluids and hydrocortisone. OCT showed normal optic nerve. A pituitary MRI scan showed a 14 x 23 x 16 mm heterogeneous mass displacing the optic chiasm in contact with the left ICA. A diagnosis of pituitary macroadenoma with apoplexy was made. After initial conservative management, his visual dysfunction was thought to be worse than the volume of the adenoma leading to a suspicion that there may have been an additional process causing nerve irritation from a combination of direct pressure and inflammation. Hence early surgical decompression was reconsidered to facilitate resolution of third nerve palsy. During endoscopic decompression, pus was drained. Microbiology revealed Staphylococcus Lugdunensis sensitive to cotrimoxazole and flucloxacillin and histology showed an infarcted FSH-secreting adenoma. He was commenced on antibiotics for 6 weeks duration.
Conclusions
Pituitary abscess is a rare potentially life-threatening condition with few distinct features to that of pituitary lesions presenting acutely. Presurgical diagnosis is uncommon and thus pituitary abscess should be considered in this clinical scenario.

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P95

Coronary artery bypass grafting (CABG)-related pituitary apoplexy

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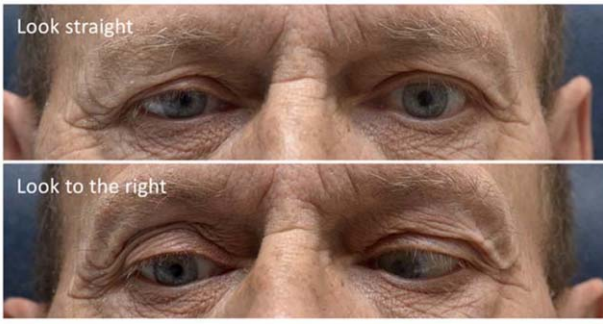
Background
Pituitary apoplexy is a relatively rare but important clinical syndrome which may be associated with acute headache, visual compromise and hypopituitarism. It can be the initial presentation of a previously unsuspected pituitary macroadenoma. Recognised risk factors include hypertension and the use of antiplatelet agents and/or anticoagulant therapy. It may be life-threatening, requiring emergency endocrine (e.g hydrocortisone) replacement therapy[1] and surgical decompression for associated visual loss.
Case
We report a 63-year-old man who underwent elective coronary artery bypass grafting (CABG) for ischaemic heart disease. In the early post-operative period he developed acute severe headache with double vision and altered consciousness. On clinical examination he had hypotension (102/70mmHg), altered mental state (GCS 14/15), signs of meningism, reduced visual acuity bilaterally, bitemporal hemianopia and right 3rd, 4th and 6th cranial nerves palsies (Fig-1). Investigations revealed acute hyponatraemia [Na= 122 (133 – 145 mmol/l)] and a low random serum cortisol (128 nmol/l). Pituitary MRI revealed a large sellar mass with suprasellar and right parasellar extension, and radiological evidence of apoplexy (Fig-1). Following stabilisation and initiation of hydrocortisone, he underwent urgent transsphenoidal decompression. Intraoperative findings were consistent with pituitary apoplexy. Post-operatively his vision improved significantly (normal visual fields) with complete recovery of his 3rd and partial recovery of his 4th and 6th nerve palsies.
Conclusion
The diagnosis of pituitary apoplexy should be considered in all cases of acute headache and ophthalmoplegia in the early postoperative period following major surgery, especially in the context of a prior history of macroadenoma. Cardiac bypass surgery presents a particular risk. Early involvement of the multidisciplinary team (endocrinology, ophthalmology, neurosurgery, neuroradiology and cardiology) is essential in formulating a patient-tailored management plan.



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P96

Primary empty sella syndrome (PESS) audit in a southwest tertiary hospital

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Empty sella is an incidental finding characterised by the herniation of subarachnoid space into the sella turcica with resultant flattening of pituitary gland to varying extent. It was considered benign. But recent reviews have shown its association with some neuroendocrinopathies.
Aims and Objectives
To determine if patients with radiological diagnosis of PESS were;
1. Referred to Endocrinology team?
2. What percentage of them had pituitary hormonal assessment?
3. Association with pituitary hormonal abnormalities and which axes were involved?
4. Whether patients require clinic follow up for serial pituitary hormonal monitoring?

Materials and Methods
Patients that had a CT/MRI at our center in the last 25 years, for various reasons but with the finding of primary empty sella were included. Those with diagnosis of secondary ESS were excluded. Review of the clinical notes and search of the Endocrine unit database to determine those that had contact with the Endocrinology team, had pituitary hormonal profile, and whether these results changed overtime.
Results
A total of 62 patients were found to have radiological diagnosis of ESS. However, only 33(53%) with primary ESS were Audited. Of these, 16(48.5%) had assessment by the Endocrinology team, though 87.7% had some pituitary hormonal assessment done. 11 patients had complete pituitary hormonal profile including; prolactin, LH, FSH, IGF-1, TSH, FT4, 9am cortisol, testosterone/oestrogen done. 17 out of 33 patients had pituitary hormonal dysfunction either at baseline or during follow up, with 5 having more than one axis affected. 36.3% of patients had a change in their serial pituitary hormone estimations, either developing abnormalities, or normalising previously abnormal hormones.
Conclusions
Pituitary hormonal dysfunction is common in patients with primary ESS. They should be referred for endocrine assessment to reduce the burden of morbidity and mortality.

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Management of Complicated Pit-1 staining Non-functioning Pituitary macroadenoma in Pregnancy

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Background
Incidence of non-functioning pituitary macroadenoma (NFPMA) is very rare in pregnancy. We describe a case of complicated non-functioning pituitary macroadenoma presented during pregnancy. 26 year old female at 21 weeks gestation presented to emergency services with worsening headaches, nausea and vomiting for 2-3 months. This was associated with transient double vision and confusion since 2 days. She was admitted to emergency department 3 weeks ago with vomiting and was discharged following rehydration. AMTS at assessment was 7/10. Neurology review revealed papilloedema but no other focal neurological deficit. Goldman perimetry revealed enlarged blind spot and left inferotemporal field defect. Foetal assessment was normal. Urgent MRI revealed a giant (3.4cm) sellar/suprasellar mass in keeping with pituitary macroadenoma with acute obstructive hydrocephalus and optic chiasm compression. High dose dexamethasone was commenced and right frontal external ventricular drain inserted. Pituitary profile revealed a prolactin of 1657mU/l (dilutional factor applied), in keeping with stalk effect and cortisol of 329 nmol/l, IgF-1 28.4 nmol/l, TSH-1.26 mU/l, FT4-13.9 pmol/l. She was reviewed by neurosurgery, endocrinology and obstetric teams. As pituitary macroadenoma was causing compression of optic chiasm and obstructive hydrocephalus, the patient underwent selective trans-sphenoidal intracapsular partial resection was done to prevent CSF leak as the tumor was extending into third ventricle. Post-operative MRI revealed good debulking with a small posterior residual was evident. Histology and immunohistochemistry revealed Synaptophysin was strongly positive and Pit-1 positive. Prolactin, GH, TSH, ACTH, LH, FSH, CK8/Cam5_2 was negative with Ki-67 index of 3%. Post-operatively, the patient developed pan-hypopituitarism and was established on DDAVP, Hydrocortisone and Levothyroxine. Repeat ophthalmological review revealed significant improvement in the visual fields. Cognitive function improved.

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P98

Hypopituitarism secondary to hydrocephalus associated with tectal plate tumour

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Case History
17 year old boy presented with a six week history of polyuria, polydipsia, headaches and easy fatiguability. Further investigations confirmed hypopituitarism with low early morning urine osmolality. MRI brain revealed soft tissue mass arising from tectal plate extending into cerebral aqueduct resulting in hydrocephalus with normal pituitary gland. Hydrocortisone, Levothyroxine and Desmopressin were started and urgent in-patient transfer to Neurosurgical unit in tertiary centre arranged.
Investigations
Na - 144 mmol/l (136-145), K – 4.2 mmol/l (3.5-5.1), creatinine – 90umol/l (62-106), calcium – 2.35 mmol/l (2.1-2.55), glucose – 2.5 mmol/l (3.0-6.0), HbA1C -30 mmol/mol, Free T4 – 9.7 pmol/l (12.6-21.0), TSH – 0.98 miu/l (0.51-4.3), prolactin – 838 mu/l (86-324), IGF-1 – 20.2 nmol/l (14.2-63.4), FSH – 1.8 iu/l, LH – 4.5 iu/l, 9 am cortisol – 179 nmol/l (133-537), urine osmolality – 123 mosm/kg (50-1400).
Management
Patient underwent endoscopic third ventriculostomy along with placement of Rackham reservoir and biopsy of the soft tissue mass simultaneously. Symptomatic improvement was noted and he was discharged home on adequate hormone replacement. Further MDT review with results of tumour biopsy has been arranged.
Conclusions
Tectal plate tumours can be a glioma, astrocytoma, medulloblastoma, germinoma, primitive Neuro-ectodermal tumour or metastasis. Thirty cases have been reported so far with 70-80% presenting with symptomatic obstructive hydrocephalus (by slowly plugging of the aqueduct of Sylvius). 25% had endocrinopathies mostly manifesting as precocious puberty, short stature or pan-hypopituitarism. Ventricular dilatation and increased intracranial pressure is hypothesized to be the cause for hypothalamic pituitary axis disturbance. Endoscopic ventriculostomy is preferred treatment of choice. Regular multidisciplinary follow up and monitoring is required to assess progress of the tumour and possible reversal of pituitary dysfunction when hydrocephalus has improved. Literature search reveals that this might be the first case of tectal plate tumour leading to hydrocephalus presenting as Diabetes Insipidus.

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P99

Retrospective audit of clinical, biochemical and radiological features of Pituitary apoplexy

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Background
Pituitary apoplexy is one of the rare endocrine emergencies. Most series indicate that incidence is between 2-7% based on clinical, surgical and histopathological evidence.[1–3] Usually presents with severe headaches that may be associated with nausea vomiting, ocular palsies, fever, photophobia. Predisposing factors are pre-existing pituitary conditions, hypertension, major surgery, anticoagulation therapy, pregnancy, radiotherapy. Appropriate endocrine, radiological, visual fields assessment needs to be done to deliver adequate treatment.
Methods
Data was collected from the existing Pituitary MDT database, radiology and neurosurgical database using the "apoplexy, bleeding, methaemoglobin, haemorrhage and infarct" in the pituitary. We used the electronic patient record, radiology resources and patient case notes to collect the data. Data analysis done by using Microsoft excel. 36 patients were collected based on the radiological criteria. We collected information on demographics, predisposing factors, clinical features, radiological and biochemical investigations, treatment.
Results
Demographics-Male-16/36, female-19/36, age-21-90 years with median-59 years. 28/36 patients presented as apoplexy of this 21/36 presented as emergency and 41% incidental finding.

1. *Previous history of pituitary disease 1/36 (30.6%) of this*NFPMA-26/36 (72.2%), Prolactinoma-3/36(8.3%), Acromegaly-1/36.
2. Presenting clinical features: Headache 86.6% (31/36), Vomiting 11/36, Fatigue 16/36, reduced labido 4/36, Visual Disturbance 7/36, Fever 2/36, Photophobia 4/36, Phonophobia 2/36. Abnormal Pupils 3/36, CN III Palsy 6/36, CN VI Palsy 4/36, CN III and VI Palsy 3/36.
3. Predisposing factors: Hypertension 15/36, Diabetes Mellitus /36, Intrapartum 0/36, Anti-Platelet Therapy 5/36, Dopamine Agonists 1/36, Radiotherapy 0
4. Biochemistry: a) Sodium-136.7+/-6 <125-3/36, 126 to 130-4/36, 131 to 135-3/36 >135-26/36 b) Pre-treatment cortisol: 401-677-3/36, 100-400-21/36, < 100-10/36. (one patient was on Prednisolone) c) Prolactin-<100-6/36, 101-500-22/36, >500-10/36. d) FT4-<9pmol/l-6/34, >9 pmol/l-28/34 (4 patients didn't get TFT's measured at admission) e)Short Synacthen test post apoplexy: 18/33-Adequate response, 11/33-Inadequate response. (3 patients missed the follow ups)

Radiology

MRI	100%
Findings on MRI	
Normal	8.3% (3/36)
Haemorrhage	83.3% (33/36)
Infarction	11.1% (4/36)
Microadenoma	16.7% (6/36)
Macroadenoma	66.7% (26/36)
Cavernous Sinus Invasion	27.8% (11/36)
Optic Chiasm Compression 100%	22.2% (9/36)

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P100

Conservative management of Cushing's in COVID times: A case series and meta-analysis

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We present a case series of patients admitted to our hospital with various manifestations of Cushing's. 71 male, known type 2 diabetes, hypertension referred for adrenal incidentaloma. Cushingoid features with non suppressed ACTH. Low dose dexamethasone test (LDSST): no suppression. 4 cm pituitary microadenoma (likely co-secretory as gonadotropins elevated). Offered IPSS and pituitary surgery. Declined the same due to fears of COVID opted for medical therapy with metyrapone. Patient monitored in clinic with metyrapone titrated to cortisol with follow ups for past 3 years. 81 male admitted with generalized weakness. Hypokalemia and hypocalcemia required monitoring on HDU. Cortisol >1750iU, and no suppression with LDSST. Calcitonin 130 ng/l ACTH 352ng/l. CT metastatic lung malignancy. MRI pituitary Normal. Liver biopsy: Metastatic small cell carcinoma (lung origin). Started on dexamethasone by oncology and planned for chemotherapy. Patient RIP due to sepsis and COVID. 62 male admitted with ?COVID. New diagnosis of diabetes, hypertension and worsening psychosis. Metabolic alkalosis with refractory hypokalemia and hypocalcemia. 24HR Urinary Cortisol 3536 nmol. LDSST: No suppression. ACTH 270 ng/l. MRI Pituitary normal, some lung lesions noted ?source of ACTH. Patient declined bronchoscopy, managed with combination of metyrapone with epleronone for life threatening electrolyte derangement and behavioural issues with good results. We did a meta-analysis of established literature comparing medical management of Cushing's with comparison of treatment options in terms of medications available and comparison of medical and surgical management of Cushing's. Eight electronic databases were searched from May-July 2021 with a total of 81 randomized controlled trials and cohort studies. A total of 5631 patients were compiled and we concluded that medical management of Cushing's particularly in global pandemic such as COVID may be reasonable. No meta-analysis on quality of life was done as lack of evidence, our case series did demonstrate a positive correlation.

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P101

Worst headache of my life

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Introduction
Pituitary apoplexy is a rare clinical syndrome secondary to abrupt haemorrhage or infarction of the pituitary gland. It complicates 2-12% of pituitary tumour, most commonly in the setting of non-functioning adenomas 1. We are reporting a case on the evolving apoplexy. A 28-year-old male with sudden onset stabbing type frontal headache at night. He described this as the worst headache in his life. CT scan of head at presentation showed a 1.9 m lesion in the pituitary with no bleed. MRI Head scan showed pituitary mass of 20 mm x 7 mm x 24 mm abutting the optic chiasm. Whilst

as an inpatient, he continued to have persistent frontal headaches. He was investigated for other causes of headache. He had a lumbar puncture which excluded subarachnoid haemorrhage. Baseline Pituitary function tests were normal cortisol = 661 nmol/l, prolactin = 76Miu/l and TSH was normal. Testosterone level was low at 8 nmol/l with low gonadotropins. On day 3 he developed polydipsia, polyuria and his serum sodium levels dropped from 140 mmol/l to 125 mmol/l, Urine sodium 43 mmol/l, serum osmolality 259, urine osmolality 196. He was placed on a fluid restriction of 1.5litres. On day 6th of admission, he had another acute episode of headache similar to previous but with increased sweating and narrowing of vision, which lasted for 2-3 hours. He was found to be hypotensive, with a sodium levels of 114 mmol/l. Repeat CT scan showed a high signal in the pituitary in keeping with pituitary apoplexy. He was diagnosed with secondary adrenal insufficiency. Commenced on IV hydrocortisone and hypertonic saline with improvement of sodium levels and hypotension. Visual field assessment was normal. He was referred to the Neurosurgical team and the pituitary MDT he was managed conservatively.
Conclusions
Pituitary apoplexy is a medical emergency and requires prompt recognition and treatment.

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P210

Management of cranial Diabetes Insipidus in a tertiary centre – clinical outcomes and patient perception of care

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There is growing recognition within Endocrinology physician and patient groups of morbidity and mortality in association with prescribing errors and dysnatraemia, in hospitalised patients with cranial diabetes insipidus (CDI). The aims of this study were firstly, to assess outcomes in hospitalised patients with CDI by review of electronic records from 2012-2021, and secondly, to assess the same patient cohort's perceptions of their care via telephone questionnaire. 109 patients were included (59 female), median age 42 (6-80) years. Median duration of CDI was 11(1-39) years. Aetiology of CDI included hypothalamic-pituitary tumours (46%), post-pituitary surgery (18%) and infiltrative disorders (16%). Route of desmopressin was oral in 83% of patients. There were 85 admissions (66% emergency) to OUH in 38 patients, median length of stay 3(1-16) days. Daily measurement of serum sodium was performed in 39% of admissions; hyponatraemia and hypernatraemia occurred in 44% and 15% of admissions respectively. Endocrine consultation was sought in 63% of admissions post-2018. 78 patients (71%) completed the questionnaire.45 patients (58%) self-reported one or more hospital admission since the diagnosis of CDI. Of these, 53% felt their medical team did not have a good understanding of the management of CDI during hospital admission. 24% reported delay in administration of desmopressin, while 44% reported confusion between CDI and diabetes mellitus, often leading to blood glucose monitoring. 33% reported difficulty sourcing desmopressin from their community pharmacy. 23% recalled a history of hyponatraemia, while 38% delayed or skipped a dose of desmopressin once weekly to allow aquaresis. Dysnatraemia is common in hospitalised patients with CDI. More than half of patients perceived their medical team's understanding of CDI to be poor when admitted with intercurrent illness. A coordinated approach, including education of non-specialist hospital staff, consideration of renaming of diabetes insipidus to avoid confusion, and early involvement by specialists, is needed to address this.

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P211

Digital transformation of a hyponatraemia toolkit: impact on clinical practice

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Hyponatraemia is associated with an increased morbidity and mortality. Despite having a hyponatraemia algorithm (pdf format) on our hospital intranet, it was rarely accessed and a wide variation in care was noticed. A novel digital hyponatraemia diagnostic toolkit (hyponatraemia.wordpress.com) for Foundation doctors (FDs) was introduced to assess our aims if it: A) increases the awareness of FDs to start investigating when serum Sodium is <130 mmol/l B) increases FDs confidence in managing hyponatraemia (self-rated scale 1 to 5) C) reduces variation in care by using the Bartter-Schwartz (BS) criteria to diagnose SIADH D) increases the minimum standard of care (MSOC) (Urine osmolality, urine sodium, Plasma osmolality requested within 24 hours of admission) E) reduces length of stay (LOS) in hospital A survey was sent to FDs before and after the digital toolkit to investigate aims A to C. The LOS and MSOC was assessed for the first 25 consecutive patients admitted with hyponatraemia (<130) in the month of October 2020 and re-assessed once the digital toolkit was launched. Out of 25 responses from FDs, 68% would investigate at a level less than 130 mmol/l , this increased to 100% after the digital toolkit. Mean (SD) confidence in managing hyponatraemia increased from 2.55 ($\pm$0.83) to 3.87 ($\pm$0.45); $P = 0.01$. 100% of FDs followed the BS criteria compared with 5% prior to the toolkit. A 60% increase in MSOC was noted after the toolkit. The mean LOS was 7.2 ($\pm$3.2) days and dropped to 4.6 ($\pm$2.4) after the toolkit ($P = 0.01$). This novel digital hyponatraemia toolkit increased FDs confidence and awareness in managing this common condition. Within a small group of patients, it improved the variation and efficiency in patient care. The referral rate to the endocrine team are currently being analysed. A larger multi-hospital study would help determine if these results are replicable.

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P212

Cabergoline treatment in human primary non-functioning pituitary adenomas

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Non-functioning pituitary adenomas (NFPAs) are the second most common subtype (15-43%) of all clinically presenting pituitary adenomas. Although the primary treatment of symptomatic NFPAs is surgery, gross total resection is achieved only in about 66% of the cases, and 20% of gross total resected tumours recur after 10 years. Despite recent advances in medical management of pituitary tumours, NFPAs remain the only subtype with no widely accepted pharmacological treatment. Expression of dopamine receptor type 2 (DRD2) in NFPAs suggests dopamine agonists as a potential treatment strategy. The DRD2 agonist cabergoline is already used as first-line treatment of prolactinomas to induce tumour shrinkage and reduce prolactin secretion. Here we aim to investigate the efficacy of cabergoline on human NFPA tissue. We assessed DRD2 expression levels via immunohistochemistry and qPCR in a large cohort of NFPAs ($n = 40$) and in few prolactinomas. Two different DRD2 isoforms, long (D2RL) and short (D2RS), are differently expressed, and cell viability varied according to subtype. In cabergoline-sensitive prolactinomas D2RS is the predominant isoform, while in NFPAs the D2RS shows similar expression levels to D2RL. In NFPAs we observed a significant decrease of cAMP production after cabergoline treatment (45% $\pm$7; $P < 0.0001$); however, viability after one-week cabergoline treatment showed only 4% ($\pm$0.7; $P < 0.0002$) reduction, compared to a 20% decrease in prolactinomas. Our data suggest that the difference in cabergoline responses between NFPAs and prolactinomas may be due to their distinct expression of D2DR isoforms. These isoforms differ by 29 amino acids in the third cytoplasmic loop, essential for G-protein binding. It has been shown that D2RL, but not D2RS, requires Ga_{i2}. The difference in D2R isoform expression could translate to distinct G-protein activation, ultimately leading to the contrasting viability results after cabergoline treatment. Taken together, these data will help inform future treatment strategies for patients with NFPAs.

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P213

The use of low dose tolvaptan for the treatment for hyponatraemia - a retrospective analysis of its efficacy and safety

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Aims
The lowest licensed dose of tolvaptan for treatment of hyponatraemia is 15 mg. There is little data on lower doses. Our study aimed to evaluate the safety of an initial dose of 7.5 mg tolvaptan.

Methods
We retrospectively reviewed data from a London teaching hospital over a 6-year period. All adults administered a first dose of 7.5 mg tolvaptan were included. Three different timeframes were reviewed: 4-12, 12-18 and 18-30 hours. We analysed response to a second dose of 7.5 mg or 15 mg tolvaptan.
Results
181 patients met the inclusion criteria. Regardless of pre-dose sodium levels, 7.5 mg tolvaptan resulted in a significant increase in sodium at all time intervals, with a mean increment at 4-12 hours of 4.54 mmol/l ($P < 0.0001$), rising to 6.1 mmol/l by 18-30 hours ($P < 0.0001$). 137 patients had blood taken between 4-12 hours, 8.7% had a rise of 10 mmol/l or more. 93 patients had a blood test between 18-30 hours, 19.4% had an unsafe rise. 34 patients had an over correction, 33 had a basal level of $\leq$127 mmol/l . There were no instances of osmotic demyelination. 95 of the patients were given a second dose of tolvaptan during their admission, 55 were given 7.5 mg and 45 had 15 mg. There was not a significant difference between the two doses in their increase to sodium. 83.6% of the patients administered 7.5 mg showed a smaller increase in sodium than after their first dose, with 1 case of overcorrection. 73.3% of the patients administered 15 mg showed a smaller increase in sodium than after their first 7.5 mg dose, with 2 patients overcorrecting.
Conclusion
This is the largest study reviewing the use of 7.5 mg tolvaptan for treatment of hyponatraemia. We recommend an initial dose of 7.5 mg with monitoring of sodium levels at 8 and 24 hours post administration. If a second dose is required, 7.5 mg is safer than 15 mg.

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P214

Pregnancy and neuroendocrine neoplasms

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Background
The incidence of neuroendocrine neoplasms (NENs) in younger populations ($<$ 50 years) is increasing and was 1.8 per 100,000 persons in 2011. There is limited data on NENs and pregnancy.
Methods
A retrospective analysis was performed on pregnant women with NENs managed in an ENETS Centre of Excellence. The objectives of the study were to describe the tumour characteristics, pregnancy outcomes, treatment and the tumour behaviour intra-pregnancy. The tumour behaviour was assessed through the comparison of images carried out at baseline pre/intra-pregnancy with the images performed post-pregnancy.
Results
A total of 15 women with 18 pregnancy encounters were included. All had well differentiated NENs. Majority 7(46.7%) had mid gut NENs. 15(83.3%) had successful pregnancy outcomes and the mean gestational age at delivery and birth weight were 36.7weeks 3.02kg respectively. 11 (61.1%) pregnancies proceeded the diagnosis of NENs. Of them, 10 (90.9%) had residual/metastatic disease at conception. Median time between the pre and post-natal imaging assessments was 13 months (range 6-25). At baseline, 2(20%) patients had progressive disease (PD) and both received Octreotide LAR throughout the antenatal/postnatal period. 5(50%) had PD at the end of the pregnancy including the 2 patients with PD at the time of conception. A total of 3 patients received Octreotide LAR during antenatal/postnatal period. Of them, 1 developed gestational diabetes while another had a preterm delivery with neonatal complications related to prematurity. 5 out of 18 (27.7%) pregnancies were diagnosed with NENs in the antenatal period. Among them, 3(60%) had metastatic disease and 1(20%) had PD on postpartum imaging compared with baseline. Furthermore, 2(11.1%) patients were discovered with NENs during the postpartum period.
Conclusion
Although most patients with NENs and pregnancy had favourable pregnancy outcomes, a significant proportion had progressive NENs at the end of the pregnancy.

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P215

Prevalence of cholelithiasis in somatostatin analogues treated Acromegaly patients

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Background
World Gastroenterology Organisation (WGO) quotes gallstones prevalence of 9-21%, incidence of 0.63/100 persons/year in Europe; 10-15% of UK population have gallstones (1). Acromegaly patients' prevalence is 8.3% and 35% developing incidental gallstones during somatostatin analogue (SSA) treatment (2).
Objective
To evaluate the prevalence of gallstones in SSA treated Acromegaly patients in University Hospitals of Leicester (UHL).
Methods
Retrospective case notes and electronic records' review of consecutive Acromegaly patients in UHL from 1957 to 2021 (UHL audit No 9300).
Results
$N = 132$ Acromegaly patients, 45/132 (35%) received SSA, male 30/45 (66%), female 15/45 (33%). Octreotide 22/45 (49%), Lanreotide 15/45 (33%), 8/45 (18%) received both. Of the 45 in SSA group, the gallstone prevalence is 6/45 (13%), 5/6 (83%) female. 30/45 (66%) SSA group had BMI of $\geq$25, 6/6 (100%) who had gallstones had BMI $\geq$25; 2/6 (33%) underwent cholecystectomy. 4/6 (66%) continued treatment, 2/6 (33%) SSA stopped due to Acromegaly remission. Mean duration of SSA: 45 SSA patients - 7.25 years; 6 gallstone patients on SSA 13 years. Of the 87 non-SSA group 5/87 (6%) had incidental gallstones, 4/5 (80%) female.
Discussion
Cholelithiasis is a recognized side effect of SSA. Possible mechanisms of SSA-induced cholelithiasis: a) delayed gallbladder emptying through inhibition of cholecystokinin release b) alteration of hepatic bile composition resulting in gallbladder stasis. Electronic Medicines Compendium (EMC) recommends ultrasound surveillance at baseline and at 6-12 monthly intervals. Our audit showed the cholelithiasis prevalence to be similar to that of background population and correlates to weight and female gender. Limitations are small number, retrospective study's inherent limitations and absent of baseline ultrasound.
Conclusion
1. The prevalence of gallstones in the SSA treated cohort remains similar to that of background population.
2. Routine surveillance scan for gallstones in SSA treated Acromegaly patients may not be necessary unless symptomatic.

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P216

Neuroendocrine Tumours (NETS): Telemedicine and patient satisfaction in the COVID-19 pandemic: A patient survey from a European Neuroendocrine Tumour Centre of Excellence

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Introduction
NETs are regarded as rare endocrine malignancies, which often present late. The COVID-19 pandemic may have affected this and patient care. The impact will have been felt in health service delivery and patient experiences. To understand NET patient perspectives and optimise care, we conducted a survey to review patient perception of: telemedicine-based care, delays to imaging, treatment, and the impact of COVID-19.
Method
70 NET patients treated between January and December 2020, were randomly selected from the NET database. Paper questionnaires, with a pre-paid return envelope, were sent out in April 2021. These consisted of 35 multi-choice questions, with four options (graded 0-3 for unhelpful to extremely helpful), yes-no questions (coded 1 or 2), and a free text area. Questions were grouped into 6 main sections: initial contact, physicians, delays for diagnostics and treatment, psychological support, experience of telemedicine (phone and video), and illness with COVID-19.

Results
47 out of 70 responses were received. 71 % of patients surveyed felt extremely well cared for by their NET physicians, 63 % being extremely satisfied with consultations. Only 34 % felt psychological support was extremely good, 25% felt it was very helpful. 36 % felt their anxiety levels had increased during the pandemic. 28% felt their imaging had been delayed. 2 % stated their treatment had been delayed. 60% liked the video/telephone follow-up. 77 % felt supported by their team. 2% of those surveyed tested positive for COVID-19. The free text highlighted somatostatin analogue therapy homecare provisions: positives and negatives, issues with self-injection, and how NET patients highly value their care.
Conclusion
This novel survey has confirmed that NET patients were able to adapt to changing service delivery and were happy to be managed through telemedicine. It highlighted the need to implement additional psychological support in the wake of the COVID pandemic.

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P217

Comparison of cardiovascular outcomes of radiotherapy vs non-radiotherapy cohort of Acromegaly patients

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Background
Radiotherapy is a third line treatment in Acromegaly. Pituitary radiotherapy (RT) is known to have cardiovascular complications (MI/IHD, CCF & CVA) due to radiation effects on normal pituitary and surrounding structures over and above the excess Growth hormone risk on metabolism (1).
Objective
To compare RT vs non-RT treated Acromegaly cohorts' cardiovascular (CV) outcomes in unselected consecutive Acromegaly patients.
Methodology
Retrospective case notes and electronic records' review consecutive Acromegaly patients with at least 1-year follow-up in University Hospitals of Leicester from 1957-2021 (UHL audit No:9300). Age-standardised IGF-1 levels were used to define remission status. PRISM software was used for statistics analysis.
Results
$n = 132$ (62 M: 70 F); mean follow up 17.8 yrs. Mean age 46.2 yrs (SD 13.4); 51:81::microadenomas:macrodenomas; 121/132 had transsphenoidal surgery; 53/132 had RT; 79/132 were in remission. 51% (27/53) of RT-group & 66% (52/79) of Non-RT were in remission. 63.6% increase in CV complications in RT-group ($P < 0.0001$) vs non-RT 40.5% ($P < 0.0001$) was noted. Diabetes, hypertension, hyperlipidaemia, OSA and dementia did not show meaningful difference.
Discussion
Diabetes, hypertension, hyperlipidaemia, IHD, MI, CCF and CVA increased substantially in entire Acromegaly cohort with marginal increased incidence of CV complications in RT-group compared to Non-RT despite no change in mean BMI at the latest assessment (28.6 vs 28.6). There was 6-fold increase CVA incidence in RT-group vs 2.5 fold in non-RT, similar to previously reported studies. This could be as a result of higher incidence of pituitary hormone deficiencies noted in RT vs non-RT group (4-fold in our audit), and potentially also from radiation-induced structural damage.
Conclusion
1. Conservative approach to pituitary RT in Acromegaly patients could be considered in order to prevent long term morbidity especially in patients with pre-existent CV risk factors.
2. To be extra vigilant of CV complications in RT treated Acromegaly patients.

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P218

Imaging screening for lung cancer required at diagnosis and at 6 months after established diagnosis of SIADH? A retrospective Audit of real-life clinical practice

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Background
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) secretion is the most common cause of hyponatremia in cancer patients. About 14% of hyponatremia in medical inpatients is due to underlying tumor-related conditions. We performed an audit to evaluate prevalence of lung malignancy in patients newly diagnosed with SIADH and to assess proportion of patients having radiological evidence of lung cancer through chest x ray and/or CT chest imaging six months after established biochemical diagnosis of SIADH.
Methods
A comprehensive retrospective review of case notes and the laboratory database was conducted for 47 patients (23 Males/24 Females, mean age 77.65 $\pm$ 13.49 years) diagnosed with SIADH in our Centre in 2019. Mean sodium level at diagnosis was 123.24 $\pm$ 5.12 mmol/l . A minimum of 6 months follow-up data were reviewed and radiological findings of lung malignancy through chest x ray and/or CT chest at baseline and 6 months after established diagnosis of SIADH were analysed.
Results
At SIADH diagnosis, 73% of patients had either CXR, CT Chest, or CT chest abdomen and pelvis at baseline. Radiological data suggested that eight patients (23%) had lung malignancy (new/old) and three patients (9%) had metastatic disease at baseline. At 6 months, one out of 12 patient (0.08%) who had the chest imaging developed new lung cancer.
Conclusion
A significant percentage of SIADH patients were positive lung malignancy in our cohort. Therefore, we suggest that screening these patients at SIADH diagnosis for lung cancer through radiological imaging seems to be a reasonable approach. Although further imaging studies at 6 months does not appear to add significantly. Our observations need to be confirmed and extended in larger cohorts.

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P219

Pituitary apoplexy- a retrospective analysis of clinical features, management and outcomes

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Introduction
The term "pituitary apoplexy" (PA) describes the appearance of abrupt hemorrhage and/or ischaemia of the constituents of sella turcica, usually in a pre-existing pituitary tumor. The presentation of this syndrome may be acute or subclinical.
Objective
This study aims to assess clinical, imaging and hormonal features and the outcomes following surgery or conservative treatment among pituitary adenoma patients presenting with PA.
Patients and Design
Retrospective analysis which included 36 case-records of patients with PA, evaluated during one year in Department of Pituitary and Neuroendocrine Pathology at the "C.I. Parhon" The National Institute of Endocrinology Bucharest, Romania.
Results
36 patients (19 men, 17 women) were identified. The mean-age at diagnosis was 49.2 years. Half of the patients presented an acute PA episode, whilst the other half had a-/oligosymptomatic intratumoral haemorrhage based on imaging evaluation. Only 25% of cases were previously known to have a pituitary adenoma (mainly non-functional adenoma). Most important symptoms of apoplexy in our patients were headache (44.4%), visual abnormalities (44.4%) and digestive manifestations (22.2%). 23 patients (63.8%) underwent surgery, while the rest were managed conservatively. 75% of the patients had remnant intrasellar mass after PA. Regardless of treatment choice, in 85.3% cases a tumor remnant was present after treatment. Corticotropic deficiency was the most common deficit in patients with classical PA (4/7 patients) while gonadotropic deficiency was frequent in subclinical cases (6 /9 patients). More than half (69.4%) remained with longterm hormone replacement therapy. 16 cases presented with visual manifestations and 11 of them underwent surgery. 9 of the operated patients and all cases with conservative treatment had improvement in vision.

Conclusions
A multidisciplinary approach is needed when symptoms or signs of ischaemia in pituitary adenomas appear. The visual recovery in these patients is notable, but the outcome of pituitary function is less encouraging.

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P220

Multiple Cell Line Pituitary Adenoma associated with PIT-1 and TPIT lineage cells resulting in acromegaly with ACTH dependent Cushing's: a case report

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Introduction
Anterior pituitary cells are characterised by functional lineages based on the expression pattern of transcription factors. Functional differentiation in the form of pituitary adenomas co-secreting ACTH and growth hormone is very rare. We report a case of multiple cell line pituitary adenoma resulting in acromegaly and ACTH dependent Cushing's.
Case
A 52-year-old woman of Ghanian origin (BMI of 57.5 kg/m^2) presented with progressive unexplained weight gain, snoring, dental changes and enlargement of hands and feet. Her past medical history included hypertension, rheumatoid arthritis, sciatica, multinodular goitre and cataracts. The family history was insignificant. Blood tests showed elevated IGF-1, LH, FSH, prolactin, serum calcium, PTH with normal thyroid function and gut peptide hormone levels. An LDDST with CRH test revealed failure of cortisol suppression with an ACTH level of 44ng/l post CRH suggestive of ACTH dependent Cushing's. Her growth hormone failed to suppress below 0.4 ng/ml on OGTT suggestive of co-existing acromegaly. A T2-weighted MRI brain with dynamic contrast imaging identified a pituitary lesion on the right side of the midline. IPSS was not conclusive. DOTATATE PET scan was normal and MEN-1 screen was negative. A neck sestamibi scan confirmed a right sided parathyroid adenoma. After trans-sphenoidal resection of the pituitary adenoma immunostaining was positive for synaptophysin, chromogranin, CK8/18, ACTH, TPIT with low proliferation rate for ki-67 and negative for prolactin, PIT1 and SF1. The overall appearances were most suggestive of a corticotroph adenoma however clinical expression of prolactin and growth hormone in addition to ACTH therefore remained unexplained.
Discussion
This case demonstrates a multiple cell line pituitary adenoma causing acromegaly with Cushing's disease. A trans lineage expression of transcription factors as the underlying mechanism of this unique functional differentiation may explain the co-secretion of ACTH and growth hormone.
Keywords: Pituitary adenoma, Transcriptional factor, Acromegaly, GHoma, Cushing's disease, ACTH dependant Cushing's

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P221

The usefulness of measuring neurone specific enolase in patients seen in the Endocrine Clinic

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Introduction
There is a clinical need to develop better biomarkers for the monitoring of patients with neuroendocrine tumours (NETs), including for patients with multiple endocrine neoplasia (MEN). Chromogranins are widely used, as are individual hormones for specific syndromes. Neurone specific enolase (NSE), however, is measured less commonly and its utility is debatable.
Aims
To assess the value of measuring NSE in the clinical management of patients seen in Endocrinology.
Methods
Our electronic hospital results reporting system was searched for all NSE results from between 1/3/2016 to 1/3/2021 with the following fields: patient name, ID, request reason, clinician, location and result. Incomplete data were collated manually. Clinic letters were then screened manually to determine if NSE results influenced clinical plans.
Results
223 NSE reports were identified covering 103 patients (range 1-6 reports per patient). Most were performed on patients with MEN (142, 63.7%) or those undergoing investigation for MEN (17, 7.6%). 92.4% of NSE requests were from Endocrinology. It was not possible to analyse 33/223 samples due to haemolysis, sample processing errors or incorrect samples being received. 30/190 (15.8%) reports were abnormal, 6 being in patients with non-endocrine tumours. The remaining 24 reports covered 19 patients, 12 who had confirmed MEN. Abnormal NSE results ranged from 15.1-138.2μg/l, with all but 2 results being less than twice the upper limit of normal (15 & 16.3μg/l). NSE results, whether normal or abnormal, did not change the clinical management plan for any patient. In 2 patients where the NSE was especially high (>60μg/l), gastrin and chromogranins were also raised and were more clinically relevant, which influenced management.
Discussion
NSE does not seem to be a useful marker to measure in patients seen in our Endocrine Department. Reducing NSE test requests could result in time and cost savings without having an impact on patient care.

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P222

SDHD missense pathogenic variants: not always benign

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Pathogenic variants in the SDHx genes are responsible for ~20% of familial Phaeochromocytoma/Paraganglioma (PPGL) tumours. Metastatic disease is lower in SDHD in comparison to SDHA, B and C mutations. Although the genotype-phenotype relationship is not well established it is considered that truncating SDHD pathogenic variants have a higher risk of causing disease in comparison to missense variants. We present two cases of metastatic paraganglioma in patients with heterozygous c.242C$>$T (p.Pro81Leu) missense SDHD pathogenic variants. Patient 1 (aged 82) had multiple head and neck paragangliomas (left glomus jugulare and bilateral carotid body tumours) resected between 1969 and 1983. In 1988, metastatic deposits were identified in the liver which were treated with therapeutic MIBG. She had been under regular surveillance since (serial imaging and biochemistry). In 2020, in view of no recurrent disease and clinical stability with non-elevated plasma metanephrines, she was discharged from tertiary care. Patient 2 (aged 54): At the age of 18, a left vagal paraganglioma was resected. Subsequently he developed contralateral Jugular PGL. He was treated with stereotactic radiotherapy followed by gamma-knife radiosurgery in 2005. A small right sided carotid body PGL was also noted and remained stable in size over the years. Gallium-DOTATATE-avid left anterior pelvic bone metastasis were detected in 2017 and he received 4 cycles of Lutetium-177 PRRT (Peptide Receptor Radionuclide Therapy). He remains under regular surveillance for his stable disease. The above patients with the SDHD p.Pro81Leu missense pathogenic variant developed metastatic disease detected >15 years after their initial diagnosis of HNPGL. They represent 7% of our total cases (n$=$ 27) with the same mutation (93% without metastases). We conclude that although there is lower reported risk of penetrance and metastatic disease in *SDHD* p.Pro81Leu pathogenic variant carriers compared to other *SDHD* variants, regular surveillance is required until 80 years of age.

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P223

Generation of normative data on serum insulin-like growth factor I (IGF-I) in healthy school children of a north indian city

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Context
To diagnose and monitor GH-related disorders, serum IGF-I is a cornerstone, but Indian ethnicity based data, following consensus criteria for establishment of normative data are not available.

Objectives
To generate normative IGF-I data for chronological age, bone age (BA) [Greulich & Pyle] and Tanner stage for both genders.
Setting and Participants
We conducted a cross-sectional epidemiological study for children (age 5-18 years) from the north Indian city of Chandigarh including 2191 apparently normal subjects (1141 males; 1050 females). With robust exclusion criteria, 1746 subjects (males = 889 and females = 857) were available.
Outcome Measures
Serum IGF-I using the Immunodiagnostic Systems (IDS) iSYS assay (ng/mL) were measured and normative data for 2.5th, 5th, 10th ,25th, 50th (median), 75th, 90th, 95th and 97.5th centiles were generated.
Results
Age-and gender-specific serum IGF-I normative data generated from a uniquely large cohort reflected various patterns. In age-specific data, females had IGF-I median peak at 13 years (393.9) [14 BA years (448.53)], and males had median peak at 16 years (372.01) [15 BA years (397.3)]. Females had earlier rise & peak and higher IGF-I values. In Tanner-specific data ($n = 1735$), females ($n = 855$) had median peak in stage IV (410.14) while for males ($n = 880$) median peak was in stage III (371.2) with maximum difference noticed between stage II and III in both genders. When reviewed published literature, Caucasian females had IGF-I median peak at 15 years (300.1) and Tanner stage III (382.8) and males had median peak at 15 years (318.3) and Tanner stage IV (439).
Conclusions
The normative data on serum IGF-I are ethnicity-specific and it will improve the diagnostic utility of IGF-I in evaluation and management of growth disorders. Using both age-and Tanner stage-specific normative data simultaneously can improve diagnostic work-up for growth disorders.

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P224

Three cases of metastatic spinal cord compression secondary to malignant pheochromocytoma and paraganglioma

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Approximately 15-20% of phaeochromocytomas and paragangliomas (PPGL) are metastatic. Metastatic spinal cord compression (MSCC) has been reported infrequently. We present three cases of MSCC secondary to metastatic PPGLs. MSCC can occur in patients with PPGLs and should be considered in patients with either spinal symptoms or spinal metastases on imaging. Our series has shown radiotherapy followed by therapeutic MIBG to be effective in treating spinal metastases. Each case should be discussed with a multidisciplinary team comprising a spinal surgeon, nuclear medicine physician, radiologist, endocrinologist and medical and clinical oncologists. Furthermore, dexamethasone can precipitate PPGL crises so enhanced vigilance for this is required in patients with MSCC.

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P225

Utility of prolactin measurement in inferior petrosal sinus samples when investigating ACTH dependent cushing's

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Introduction
The use of Inferior Petrosal Sinus Sampling (IPSS) to differentiate between central and ectopic ACTH dependent Cushing's, although requires expertise, is widely available. The value of adding prolactin measurement to that of ACTH to improve IPSS diagnostic accuracy remains controversial. We evaluated the impact of adding prolactin measurement to IPSS procedures at a large academic center.
Methods
Leftover samples from patients who were investigated by IPSS procedure for differentiation of ACTH source were stored at -70°C until analysis. ACTH had been measured and results reported. Retrospective measurement of prolactin was performed on the saved sample aliquots using Cobas 4000 (Roche Diagnostics, IA, USA). Prolactin normalized ACTH IPSS peripheral ratios >0.8 indicated central Cushing's and <0.6 indicated ectopic source of ACTH. Previously reported IPSS studies were reevaluated following prolactin normalization of ACTH.
Results
Patients ($n = 10$) with ACTH dependent Cushing's and who had undergone IPSS were entered into the study. Prolactin levels in IPSS samples ranged from 38 mIU/l to 12,978 mIU/l. Although left and right inferior petrosal ACTH values were significantly different ($P = 0.03$) suggesting lateralization, prolactin normalized ACTH levels were not ($P = 0.37$). Patients ($n = 8$) were reported as having central ACTH production. One patient had ectopic ACTH production, whereas one patient was difficult to cannulate and thus to assess. In this patient, although ACTH data suggested a questionable pituitary source for ACTH, the patient was classified as having ectopic ACTH syndrome following prolactin normalization of ACTH. Subsequent clinical findings were consistent with ectopic ACTH syndrome.
Conclusions
Although the addition of prolactin to the analysis of IPSS ACTH provided a reassurance for ACTH ratio calculations as well as an aid in difficult catheterization studies, tumour lateralization became less obvious when using prolactin normalized ACTH levels. A larger study is required to confirm those findings.

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	Case 1	Case 2	Case 3
Patient characteristics	57, male, SDHB, metastatic paraganglioma, referred for consideration of metiodobenzylguanidine (MIBG) treatment (progressive disease).	63, female, no genetic mutation, diagnosis following initial presentation with COVID-19 infection and incidental adrenal mass.	62, male, no genetic mutation, metastatic phaeochromocytoma treated with left nephrectomy and adrenalectomy, liver metastatectomy, and lung ablation. Referred for second opinion (progressive disease).
Spinal symptoms	Back ache.	None	None
Plasma metanephrines (<510.0 pmol/l)	318.7	1051.0	202.0
Plasma normetanephrines (<1180.0 pmol/l)	1327.0	>30000.0	18026.0
Plasma 3-methoxytyramine (<180.0 pmol/l)	<75.0	12540.0	311.6
Imaging	Right-sided L3 paraspinal mass with impending cord compression. MIBG and Ga-68 DotaPET avid. Widespread skeletal metastases and enlarged retroperitoneal mass.	Right adrenal phaechromocytoma, with left adrenal, spinal and pelvic metastases on MIBG. Grade 1B spinal cord compression at L2/3.	Multiple lung and liver lesions, and T3 metastasis on MIBG. Multiple spinal lesions with Grade 3 cord compression at T3 on MR spine.
Treatment and progress	Radiotherapy 20 Gy in 5# to L3 and MIBG therapy. Partial response. Normal mobility.	Radiotherapy 20 Gy in 5# to L2/3 and MIBG therapy (2 cycles, developed pancytopaenia).	Single fraction radiotherapy and MIBG therapy. Improved appearance of T3 and skeletal metastases.

P226

Complete third nerve oculomotor nerve palsy as initial presentation of pituitary tuberculosis

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Introduction
Pituitary tuberculosis (TB) is a rare form of intracranial TB and remains a diagnostic challenge in the absence of systemic TB. A limited number of cases has been reported in the literature.
Case
A 47-year-old south Asian man presented to the accident and emergency department with complete isolated left third nerve palsy which had developed gradually over the course of a week. Brain magnetic resonance imagining (MRI) revealed a 15 mm inflammatory sellar and suprasellar pituitary mass extending cranially to the optic chiasm and laterally to the cavernous sinuses. Endocrine investigations showed secondary hypothyroidism, secondary adrenal insufficiency and secondary hypogonadism and hormone replacement therapy was commenced. The patient underwent a pituitary biopsy and the histological analysis revealed non-caseating granulomas and multinucleated giant cells. Pituitary and CSF tests for acid-fast bacilli (AFB) including AFB stain and PCR were negative. Further immunohistochemical work up showed positivity for Langerin and suggested V600E BRAF mutation with leading to a likely differential diagnosis of Langerhans cell histiocytosis (LCH) or Erdheim Chester disease. An increased glucocorticoid dose resulted in limited radiological improvement of the pituitary inflammatory changes. Whole body Positron emission tomography (PET) to assess for possible systemic disease involvement showed increased metabolic activity in the left hemithyroid and FNA was suggestive of a malignancy. A diagnostic left hemithyroidecomty revealed a follicular carcinoma. Repeat PET prior to starting steroid-sparing immunosuppression showed increased uptake in a left level IV lymphnode and subsequent biopsies revealed necrotising granulomatous lymphadenitis suspicious for TB. Initial TB PCR was negative, but culture from a repeat lymph node aspirate confirmed fully sensitive TB. Antitubercular treatment was commenced and resulted in full clinical recovery.
Conclusion
Pituitary tuberculosis is rare and difficult to diagnose. Therefore, a high index of clinical suspicion is required. Accurate diagnosis is essential to start prompt, curative antimicrobial treatment.

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P227

Ectopic Cushing's syndrome: challenging the stereotype

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Ectopic Cushing's syndrome (CS) is commonly caused by malignancy, often behaves aggressively and may not clinically manifest with features of hypercortisolism due to its rapid course and associated cachexia. This may mislead clinicians into discounting the diagnosis in patients with more indolent features of CS. We present a 41 year old woman with an 8 year history of Cushingoid features with associated hypertension, obesity and Type 2 Diabetes. Investigations confirmed CS with two elevated urinary free cortisol assessments (UFC) (934 and 906nmol/24hr respectively) and a failed overnight dexamethasone suppression test (221nmol/l). An ACTH of 39.1 ng/l confirmed ACTH-dependence and secondary hypothyroidism (TSH 1.68mIU/l, free T4 8.2pmol/l) suggested a pituitary source. Corticotrophin releasing hormone (CRH) testing was indeterminate with basal to peak increases of $>50\%$ for ACTH (24.1 to 86.5 ng/l) but $<20\%$ for cortisol (783 to 806 nmol/l). Subsequent contrast pituitary MRI showed a possible right sided microadenoma and metyrapone and thromboprophylaxis were started. Inferior petrosal sinus sampling (IPSS) favoured an ectopic source, with a central:peripheral ACTH ratio of <2 prior to CRH and <3 post CRH. A prolactin-normalised central:peripheral ACTH ratio of 0.4, also suggesting an ectopic source. An FDG-PET scan revealed a 12mm right maxillary sinus polyp with intense FDG avidity (SUVmax 11.9). This is consistent with a rare case of ectopic ACTH secretion from the paranasal sinuses and the patient has been referred for surgery. This case highlights the diagnostic challenge presented by CS, and emphasises the importance of thorough investigation to delineate ectopic and pituitary sources. It challenges the stereotype that ectopic CS always results from an aggressive malignant process and may instead present in a slowly progressive manner. It is essential that these cases are correctly diagnosed to avoid unnecessary surgery.

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P228

Rhabdomyosarcoma in Carney complex - Is there an association

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Carney complex is a rare autosomal dominant syndrome characterized by multiple pigmented lesions on the mucosae and skin, cardiac myxoma, endocrine and non-endocrine tumours. It is caused by mutations of the PRKAR1A gene on chromosome 17q. We present a 24-year-old gentleman with Carney's complex PRKAR1A gene positive. He has a strong family history of Carney complex- He also has a sister and 3 half- brothers who were also affected. One of his half-brothers has primary adrenal failure which is not a recognised feature of Carney's. He had adrenal insufficiency followed by removal of right ventricular myxoma, acromegaly of which he wasn't keen on surgery, microlithiasis of the testes and multiple skin freckles He was admitted to hospital recently following a fall which resulted in neck pain and difficulty in mobilising. His initial CT of the cervical spine showed pathological fracture/dislocation through the base of the odontoid peg with an extensive destructive tumour centred on the right ethmoid sinus, invading the right cribriform plate with likely frontal lobe invasion as well as invasion of the extraconal right orbit. His FDG-PET CT scan showed significant tracer avidity on the right nasal/orbital region with widespread bony lesions. He had a biopsy which showed lesional cells diffusely positive for desmin, myogenin, myo D1 and vimentin consistent with alveolar rhabdomyosarcoma. He was referred to the oncology team for radiotherapy to the cervical spine and chemotherapy. He continues to be under regular follow up under the local endocrinology team and oncology team. A number of tumours and malignancies have been reported in Carney's Complex, however, to our knowledge, no cases of rhabdomyosarcoma were previously reported in this condition. While rhabdomyosarcoma is known to be associated with a number of gene mutations, PRKAR1A is not known to be one of them.

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P229

Case report: pituitary metastasis and Its diagnostic complexity

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Background
Pituitary metastasis (PM) is a rare occurrence in malignancy, associated with poor prognosis. Only 7% of patients are symptomatic. High index of suspicion and prompt investigation are essential. We report a case of PM, highlighting challenges in diagnosis and management.
Case Report
Sixty-six year old male was referred to endocrinology due to headaches and hyponatremia. He had metastatic colorectal carcinoma, treated with bowel, liver and lung resections and chemotherapy. Clinical examination was unremarkable and he was euvolemic. Baseline investigations suggested SIADH (serum sodium (Na) 121 mmol/l , plasma osmolality 253 mmol/kg, urine osmolality 31 8mmol/kg and urine sodium 45 mmol/l). CT Head was normal. Further investigation supported provisional diagnosis of adrenal insufficiency (9am cortisol 97 nmol/l) and hydrocortisone was added to management with fluid restriction. Bloods later returned with borderline satisfactory cortisol response (471 nmol/l , new assay) on short synacthen test (SST) and normal ACTH (11.1 ng/l). MRI head and CT thorax, abdomen and pelvis (including adrenals) were unremarkable. Hydrocortisone was stopped and patient discharged. Two days later, he presented with symptomatic hyponatremia (Na 122 mmol/l). Hydrocortisone was restarted and Na levels normalised. Anterior pituitary hormone profile revealed panhypopituitarism and MRI Pituitary showed PM (6-7 mm lesion in proximal pituitary stalk). Dexamethasone and levothyroxine was started. MDT review deemed him for palliation only. One month later he passed away.
Conclusion
PM should be considered as a differential for hyponatremia due to adrenal insufficiency in patients with metastatic cancer. Our case highlights the

complexities of diagnosing secondary adrenal insufficiency of recent onset as SST may show misleading borderline normal response. High clinical suspicion and early scrutiny with full pituitary hormone profile and imaging can aid in timely diagnosis of PM.

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P230

Immune check point inhibitor induced hypophysitis with normal pituitary imaging

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We present a 60-year-old man who was referred to endocrine clinic with fatigue and a random cortisol of 136nmol/l . He had clear renal cell carcinoma and had right radical nephrectomy 7 years ago. Surveillance scans revealed involvement of mediastinal lymph nodes, pancreas and small bowel and he has pancreatic and small bowel resection in four years ago. He had recurrence a year ago and received Ipilimumab and Nivolumab. Biochemistry revealed low fT4 and inappropriately normal TSH, undetectable prolactin but normal gonadal and growth hormone axes. A clinical diagnosis of immune check point inhibitor hypophysitis was made. He was commenced on replacement hydrocortisone followed by Levothyroxine. MRI pituitary was unremarkable. Low basal cortisol, undetectable ACTH and no significant rise after synacthen administration confirmed loss of pituitary adrenal axis. Patient was taught steroid 'sick day rules' and doing well two years after initial diagnosis. Immune check point inhibitors are a novel immunotherapy for several cancers. Endocrine adverse effects include hypophysitis, thyroid dysfunction, primary adrenal insufficiency and rarely autoimmune diabetes mellitus. Immune checkpoint inhibitors associated hypophysitis can cause irreversible hypopituitarism, requiring long-term hormone replacement. As in our case, a normal pituitary MRI does not rule out hypophysitis. Pituitary biopsy is gold standard for diagnosis but is not usually required nor is it practical. Also, ACTH/TSH/ADH deficiency is more common in hypophysitis in contrast to neoplastic or structural lesions where GH/LH/FSH deficiency is more common. Clinicians must be mindful of possibility of hypophysitis or primary adrenal insufficiency and have a low threshold of investigations in patients receiving immune check point inhibitors who present with non-specific symptoms.

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P231

A challenging adrenal incidentaloma

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Case History
69 years old gentleman was referred to endocrinology for investigation of a benign appearing left incidental adrenal adenoma (1cm) after being investigated for abdominal pain. He had a past medical history of an abdominal aortic aneurysm (AAA), type 2 diabetes mellitus and hypertension.
Investigations
Initial endocrine investigations revealed normal 24h urinary free cortisol levels (twice), metanephrines and ARR. His overnight dexamethasone suppression test was abnormal (370 nmol/l – NR <50). The vascular surgeons were keen to undertake endovascular repair of his AAA. There were no stigmata of Cushing's syndrome and together with unconvincing biochemical results, surgery was undertaken. His low dose dexamethasone suppression test failed to suppress his cortisol (135 nmol/l) with a baseline ACTH of 52.3 ng/l (NR 1.6 – 63.3). Moreover, his midnight cortisol was elevated (107 nmol/l). A pituitary MRI scan demonstrated a 4mm microadenoma. His repeated urinary free cortisol levels were abnormal (128 and 187 nmol/24h – NR 1-124). The patient declined pituitary surgery, and was commenced on Metyrapone titrating up to 1.5g BD. 11 months later, he agreed to have surgery. IPSS then confirmed Cushing's Disease: left petrosal ACTH sampling showed a peak concentration of 1,203 ng/l and the right petrosal one was 1,165 ng/l (NR 1.6 – 63.3). The ratio favoured left sided hypersecretion. A repeat pituitary MRI scan, 24 months after initial scan, showed that the lesion had increased in size and had proteinaceous content. He is scheduled for explorative surgery.
Conclusion
We present a diagnostically challenging case of Cushing's Disease, referred initially as adrenal incidentaloma. He had no clinical features of hypercortisolaemia and with unconvincing biochemistry, he underwent vascular surgery that was deemed necessary. Subsequent investigations confirmed pituitary source rather than ectopic or adrenal. Pituitary surgery has now been scheduled.

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P232

Dramatic resolution of a pituitary macroadenoma: non-functioning or prolactin-secreting?

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Background
Non-functioning pituitary tumours can be associated with a modestly elevated prolactin. Response to dopamine agonist therapy in such cases is unusual. Large macroprolactinomas are associated with much higher prolactin levels and respond well to dopamine agonists.
Case
We report a 41-year-old man with a pituitary macroadenoma associated with an elevated prolactin of around 2000mIU/l who developed marked resolution in his pituitary MRI images radiologically reported as "consistent with post-operative changes". The patient was in fact on cabergoline treatment and had never had pituitary surgery. Five years previously, he presented with complaints of reduced libido and erectile dysfunction. He had no history of visual problems and no headache. Hormonal parameters were as followings: prolactin 2170 (normal range 86-324) mIU/l, FSH 2.32 mIU/mL, LH 1.84 mIU/mL, testosterone 2.39 (normal range 8.6-29) nmol/l . Pituitary MRI confirmed a pituitary macroadenoma measuring 33 x 26 x 23 mm in diameter. He was commenced on cabergoline and because of inadequate response, dose was gradually increased to 500 mcg six times weekly. A follow-up pituitary MRI showed a resolution of the pituitary tumour which now measured 7 x 7 mm in axial plane (compared to 24.6 x 22.7 mm a year previously). His serum prolactin dropped to 251.6 mIU/l; serum testosterone increased 6.77 nmol/l with an improvement in sperm count.
Discussion
Anatomical response to dopamine agonist therapy in prolactinomas can be dramatic. The case presented is unusual as it probably represents a very good response to cabergoline in a non-functioning pituitary tumour, or a slow response in a partially resistant prolactinoma.

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Reproductive Endocrinology

P102

Differentially glycosylated FSHR ligands as potential modulators of FSHR quaternary complexes and FSHR-dependent signalling

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The G protein-coupled receptor, follicle-stimulating hormone receptor (FSHR), is essential for reproduction. A key drug target of IVF, understanding the mechanisms modulating FSHR functions remains of high importance. The endogenous ligand of the FSHR, FSH, is a heterodimeric glycoprotein hormone with two predominant glycoforms identified. Partially glycosylated FSH21 has faster binding kinetics to the FSHR and more potent at activating cAMP-dependent signal pathways, in comparison to fully glycosylated FSH24. An important mechanism of regulating GPCR function is the formation of dimers and oligomers. The FSHR can self-associate, yet how FSH glycosylation regulates FSHR oligomerization remains unknown. The aim of this study was to determine if modulation of FSHR oligomers mediated the differential signalling displayed by FSH glycoforms. Using a modified super-resolution imaging technique (PD-PALM) to assess FSHR complexes, HEK293 cells expressing FSHR were treated $\pm$ 30ng/ml eFSH, FSH21, FSH24 or a FSHR biased agonist; eLHdg. eFSH and FSH21 rapidly dissociated FSHR oligomers into monomers at 2-minute treatment ($P < 0.001$), and pentamers at 5- and 15-minutes. FSH24 displayed slower kinetics, dissociating FSHR oligomers at 5-minutes ($P < 0.01$). In contrast, eLHdg enhanced FSHR oligomerisation into predominantly tetramers ($P < 0.01$)

and trimers ($P < 0.05$) at 5- and 15-minutes, respectively. Analysis of cAMP production by glosensor and Cre-luciferase reporter gene assays showed higher cAMP production by eFSH and FSH21, suggesting monomers/lower-order oligomers favour cAMP production. We next investigated the concentration-dependent effects of FSH glycoforms on FSHR oligomerization. Interestingly, at 5-minutes FSH24 induced rapid FSHR oligomer formation followed by FSH21 at 15-minutes. Only low-level cAMP production was observed with all ligand treatments, with significant increases in cAMP at 15 minutes by eFSH and FSH21. These data suggest functional specificity of FSH glycoforms at different concentrations may be mediated by FSHR oligomer rearrangements. Thus, highlighting potential novel avenues for therapeutic targeting of the FSHR to improve IVF outcomes.

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P103

Maternal fetuin-A (AHSG) serum levels are altered in pregnancies complicated by gestational diabetes and are associated with pathological fetal growth

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Background
Gestational diabetes mellitus (GDM) is associated with increased rates of large-for-gestational-age (LGA) or small-for-gestational-age (SGA) infants. Currently, it is not possible to predict which women with GDM are at risk of delivering LGA or SGA infants. Fetuin-A, (α 2-Heremans Schmid glycoprotein; AHSG), a glycoprotein associated with insulin resistance is altered in GDM maternal serum. It is unclear if levels are related to altered fetal growth. This study aimed to establish whether maternal serum fetuin-A has the potential to predict pathological fetal growth in pregnancies complicated by GDM.
Methods
Serum was collected from women with and without GDM between 26-32 weeks' gestation. Women were tracked to delivery, and fetal sex and birthweight centiles recorded. Serum extracellular vesicles (EVs) were isolated by size exclusion chromatography (SEC) and characterised by electron microscopy (shape), nanoparticle tracking analysis (NTA; size/concentration) and Western blotting (EV-enriched proteins). Levels of fetuin A in total serum, EV-enriched and EV-depleted fractions were assessed by Western blotting and ELISA.
Results
EVs were detected in early SEC fractions but absent from later fractions. Fetuin-A was not detected in EVs but was present in total serum and in EV-depleted fractions. Women with GDM ($n = 23$) had significantly lower levels of fetuin-A compared to non-GDM pregnancies ($n = 25$; $P = 0.0089$). Fetuin-A was not changed in women with GDM that delivered LGA babies ($n = 7$) but was significantly increased in women that delivered SGA compared to appropriate-for-gestational-age (AGA) infants, in both GDM ($n = 4$; $P < 0.0232$) and non-GDM patients ($n = 6$; $P = 0.0097$).
Conclusions
Fetuin-A is present in maternal serum but is not contained in EVs. Levels of serum fetuin-A are reduced in pregnancies complicated by GDM compared to uncomplicated pregnancies. Increased fetuin-A in SGA pregnancies, suggests that maternal fetuin-A levels may be important for predicting which pregnancies are at risk of delivering SGA infants, irrespective of GDM status.

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P104

An exploration of the association between CAG repeat status and mortality in men

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Introduction
The androgen receptor (AR) mediates the peripheral effects of testosterone. The main mechanism of action for the AR is direct regulation of gene transcription. Available evidence suggests that the number of CAG repeats in exon-1 of the AR gene is negatively correlated with transcriptional activity of the AR and that CAG repeat number links to mortality rate in T2DM men. The aim of this analysis was to determine the association between CAG repeat number and all cause mortality in a non-T2DM cohort.
Methods
Men aged between 40 and 79 years were recruited from primary care registers for participation in the UK arm of the European Male Aging Study. Baseline assessment included sex hormone levels and also CAG repeat determination. They were followed prospectively for up to 18 years. Cox proportional hazards model was used to determine the association between CAG repeat number/mortality with the results expressed as hazard ratios (HR) and 95% confidence interval (CI).
Results
312 men contributed data to the analysis. The mean age at baseline was 59.5 years. At follow up 85 of the 312 (27%) men had died. The range of CAG repeat length varied between 14 and 39, with the highest proportion of CAG repeat number at 19 repeats (14.1%). Using men with CAG repeat numbers of 22-23 as a reference group, and after adjustment for age at recruitment, total testosterone level and also index of multiple deprivation, men with a lower number of CAG repeats (< 22) had a higher likelihood of dying in the follow-up period (HR 1.50; 95% CI 0.78, 2.89) as did men with higher number of repeats (> 23) (HR = 1.31; 95% CI 0.62, 2.76).
Conclusions
Our data suggest that CAG repeat number may influence the risk of mortality in men. Further larger studies are required to confirm these findings.

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P105

Abstract withdrawn

P106

Pregnancies in women with Turner Syndrome: A retrospective multicentre UK study

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Background
Limited contemporary data exist with which to counsel women with Turner Syndrome (TS) with regards to risks associated with pregnancy. We conducted a multicentre UK retrospective cohort study to determine the characteristics and outcomes of pregnancy in women with TS.
Method
Retrospective cohort 20-year (2000-2020) study including 16 UK tertiary referral maternity units. Data were collated from case notes review, and maternal outcomes, obstetric and neonatal complications recorded. We included all livebirth, miscarriages, and terminations of pregnancy.
Results
81 women with TS and pregnancy were identified. Overall, 54/127 (42.5%) pregnancies were by egg donation (OD); and 22/31 (71%) in women with 45, X karyotype. 89/103, 86.4% pregnancies were planned. Only 9/31 (29%) of pregnancies in the 45, X group were spontaneous, compared with 53/66 (80.3%) in the mosaic group 45, X/46, XX ($P < 0.0001$). Women with mosaic TS (45, X/46, XX) were younger at their first pregnancy by 5.5-8.5 years compared to other groups ($P < 0.001$), and significantly more likely to have a spontaneous menarche (75.8% vs 50% or less, $P = 0.008$). There were 17 miscarriages, three terminations of pregnancy, two intrauterine deaths and 107 live births. There were two cases of maternal aortic dissection (2%), both 45, X, bicuspid aortic valve and OD pregnancies; one of whom died. Another woman required aortic root replacement within six months of delivery. 10/104 (7.7%) births were preterm and 22/96 (22.9%) were small for gestational age ($< 10^{th}$ centile). The elective caesarean section rate was 72/107 (67.3%). Only 69/127 (54%) women where data were available had undergone cardiovascular imaging within 24 months of conceiving

Conclusions
Pregnancy in TS is associated with major maternal cardiovascular risks. Assisted pregnancy is commonplace. Women with TS should undergo detailed and thorough cardiovascular assessment and counselling prior to assisted or spontaneous pregnancy and be managed by a specialist team.

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P107

A randomised controlled trial on the effect of very-low-calorie diet (VLCD) vs. an energy deficit diet, in women with the polycystic ovary syndrome (PCOS) – remission PCOS

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PCOS is the most common endocrine disorder affecting the women of reproductive age group and weight loss is the mainstay of management of PCOS. We performed an open-label randomised controlled trial to compare the effects of a conventional energy deficit approach (-600 kcal/day of the total energy requirements) vs. a very low-calorie diet (VLCD: 800 kcal/day) on free androgen index (FAI), body weight, and metabolic markers in women with PCOS. Forty-one eligible patients were randomly assigned to a VLCD diet (800 kcal/day provided with gradual food reintroduction over the next 8 weeks) (n = 21) or conventional energy deficit (n = 20) over the same period. Anthropometric characteristics and metabolic markers were assessed at baseline and at 8- and 16-week follow-up. Here, we report the results of the 8-week follow-up. Paired and unpaired t-tests were used to compare differences within- and between-groups, respectively. Nine participants in the VLCD group and 12 participants in the energy deficit arm completed the 8-week follow-up. After 8 weeks both groups experienced weight loss, however, this was significantly higher in the VLCD arm (-11.4 vs -4.2 kg, $P < 0.0001$). There was also a significant reduction in FAI in the VLCD group as compared to the energy deficit group (-37% vs -7.7%, $P = 0.04$). In the VLCD arm, 22% of women (n = 2), but none of the energy deficit arm, had biochemical remission of PCOS (FAI < 4). There was a significant within-group increase in the SHBG ($P = 0.01$) and reductions in total cholesterol ($P = 0.008$) and HbA1c ($P = 0.04$) in the VLCD arm, but not in the energy deficit arm. One serious side effect of abdominal pain and cholecystitis was reported in the same participant. Our findings suggest that VLCD is superior to the energy deficit approach in PCOS and can cause significant weight reduction, improvement in hyperandrogenaemia and biochemical remission of PCOS.

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P108

HIIT'ing or MISS'ing the optimal management of Polycystic Ovary syndrome: A systematic review and meta-analysis of high-versus moderate-intensity exercise prescription

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Introduction
Polycystic Ovary syndrome (PCOS) is a metabolic disorder associated with increased cardiovascular disease risk. Exercise is an effective treatment strategy to manage symptoms and reduce long-term health risk. High-intensity interval training (HIIT) has been suggested as a more efficient exercise mode in PCOS; however, it is not clear whether HIIT is superior to moderate intensity steady state exercise (MISS).
Methods
We synthesized available data through a systematic review and meta-analysis to compare the effectiveness of isolated HIIT and MISS exercise interventions. Our primary outcome measures were cardiorespiratory fitness and insulin resistance, measured using O_{2max} and HOMA-IR respectively.
Results
A total of 16 studies were included. Moderate-quality evidence from 16 studies identified significant improvements in O_{2max} following MISS (Δ = 1.081 ml/kg/min, $P < 0.001$, n = 194), but not HIIT (Δ = 0.641 ml/kg/min, $P = 0.128$ n = 28). Neither HIIT nor MISS improved HOMA-IR [Δ = -0.257, $P = 0.374$, n = 60] and [Δ = -0.341, $P = 0.078$, n = 159], respectively).
Discussion
A significant improvement in O_{2max} was evident following MISS, but not HIIT exercise in women with PCOS. This contrasts with previous literature in healthy and clinical cohorts that report superior benefits of HIIT. Therefore, based on available moderate-quality evidence, HIIT exercise does not provide superior outcomes in O_{2max}compared with MISS, although larger high-quality interventions are needed to fully address this. Additional dietary/pharmacological interventions may be required in conjunction with exercise to improve insulin sensitivity.

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P109

The relationship between polycystic ovarian syndrome and fractures: A Mendelian randomization study using the UK Biobank

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Background
Polycystic ovary syndrome (PCOS) is believed to be a primeval condition with the earliest hints of its existence found in ancient Egyptian literature. Despite its negative impact on fertility, it has emerged as the most common endocrine disorder in women of reproductive age, creating what is called the PCOS paradox. We hypothesized that this phenomenon can be explained by testosterone-mediated high bone mineral density (BMD) in women with PCOS, providing a survival advantage in harsh ancient environments.
Methods
Using the mendelian randomization (MR) analysis, we evaluated the association of genetic risk of excess testosterone in PCOS with BMD and fractures. The MR analysis was performed using linear regression analysis with the weighted genetic risk score as an independent variable adjusting for age, body mass index (BMI), and population eigenvectors. Horizontal pleiotropy in the MR analysis was tested using MR-Egger regression analysis.
Results
The study consisted of 2,21,086 Caucasian women with a mean age of 56.7 $\pm$ 7.9 years, mean BMI of 27.0 $\pm$ 5.1 kg/m^2 and a mean BMD of 0.50 $\pm$11 g/cm^2. The study participants reported 24,797 (11%) fractures during their lifetime. The regression analysis showed that one standard deviation increase in the genetic risk for high testosterone levels in PCOS was associated with significantly higher BMD and a significantly reduced risk of fractures.
Conclusions
In PCOS, genetic predisposition to high testosterone levels is associated with high BMD and reduced risk of fractures. This could have offered a survival benefit in ancient environments and explains why this disorder has persisted in human evolution despite resulting in sub/infertility.

Table 1 Association of weighted genetic risk score for testosterone levels in PCOS with BMD and fractures.

Phenotype	Effect Estimate	P-value
Bone mineral density Beta (SE)	0.0007 ($\pm$0.0002)	0.001
Fractures OR (96%CL)	0.97 (0.96, 0.99)	0.003

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P110

Clinical characteristics associated with testosterone prescribing in men in primary care

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Background
Testosterone replacement therapy (TRT) is widely used for the treatment of symptomatic hypogonadism in men. However, data on prescription behaviours of TRT are limited. The objective of this study was to investigate clinical characteristics associated with the likelihood of being prescribed TRT by general practitioners (GPs) in North West London (NWL).
Methods
We carried out a retrospective cohort study using Discover database of GP-registered patients in NWL between 2015-2019. We identified 20,299 men aged ^{3}18 years who had a serum total testosterone measurement (TT) and without prior TRT prescription records, and determined whether TRT was subsequently commenced, and analysed clinical characteristics associated with hypogonadism that may influence TRT prescription.
Results
Of all men having TT measurement, 19,583 (96.4%) were not commenced on TRT (Group A) and 716 (3.5%) men were commenced on TRT (Group B). Men prescribed TRT (Group B) were older with higher mean body mass index (BMI), and higher risks of hypertension, depression, type 2 diabetes and ischaemic heart disease (IHD); conversely, men in Group B had lower mean pre-treatment TT and were less likely to have prostate cancer. Over twenty four percent of men with TT $<$ 8nmol/l and low libido were not prescribed TRT.
Conclusions
Our study suggests that 3.5% of men in primary care with a single TT measurement had subsequent commencement of TRT. We highlight several comorbidities may influence the decisions made by GPs when initiating TRT. Clearer guidance for clinicians with unified TT cut offs may help to improve the consistency of treatment of men with hypogonadism.

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P111

An investigation of androgen-responsive non-coding RNAs in boys with atypical genitalia without genetic variants in the androgen receptor (AR)

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Introduction
Transcriptome analysis of peripheral blood mononuclear cells (PBMC) RNA has identified a set of androgen-responsive non-coding RNAs.
Aim
To quantify the androgen-responsive gene expression and investigate its relationship to the testosterone (T) rise following hCG stimulation in boys with no genetic evidence of androgen insensitivity.
Methods
Boys with suspected DSD who were evaluated at the Royal Hospital for Children, Glasgow from 2018 to 2021 were included. Information on clinical, biochemical and genetic assessment was obtained from clinical records. PBMC RNA was collected before and after hCG stimulation of the testes on day 4(D4) and day 22(D22) and gene expression was quantified using QuantStudio™ 3D Digital PCR.
Results
Ten XY boys with atypical genitalia, a median age of 0.8yrs(0.5,3.4) and no detected *AR* variants were included. The median baseline and peak T was 0.5nmol/l(0.5,6.8) and 21.7nmol/l(1.2,42.1), respectively. Within this group, there was one patient who did not show a T response to hCG at all on D4 and a minimal response on D22(1.2nmol/l). The median fold change in *SNORD5*and *RNY5* on D4 in this patient was 0.09 and 0.05, respectively. The median fold change for the two genes on D22 was 0.14 and 0.04, respectively. In the rest of the cohort, the median post-hCG T on D4andD22 was 16 nmol/l(2.5,42) and 25 nmol/l(17,37), respectively. In this group, the median fold change in *SNORD5*expression on D4andD22 was 4.0(0.25,14) and 1.2(0.1,5.6), respectively. The median fold change in *RNY5*expression on D4andD22 was 1.0(0.1,38) and 0.5(0.2,7.7), respectively.
Conclusions
Expression levels of *RNY5* and *SNORD5* can be quantified accurately and show androgen dependency. Further research in genetically confirmed cases of androgen insensitivity plus those with no response to hCG stimulation is required to determine the diagnostic role of non-coding RNAs in XYDSD.

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P112

What is the prevalence and pattern of cancers in Turner syndrome? A single centre cohort study

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Background
Previous population studies suggest cancer morbidity is different in Turner syndrome (TS) compared to the background female population. Whilst gonadoblastoma is well recognized in TS with Y chromosome material, studies have suggested increased prevalence of skin tumours and meningioma but reduced incidence of breast cancer.
Methods
Retrospective analysis of an adult TS clinic patient database identified women who developed cancer. Tumour type, age at onset, mode of presentation and karyotype were collected. McMillan-NCRAS cancer database was used for comparison of prevalence and types of cancer in the background female population; 4.44%, breast, colorectal cancer and melanoma were the most common types of cancer.
Results
Among 156 women with TS, mean age 46.1 ($\pm$15.3 years), 9 (5.8%) had a recorded cancer diagnosis. The types of cancer were; bilateral gonadoblastoma (46, XY/45, X karyotype), type 1 gastric neuroendocrine tumour (NET), appendiceal NET, gastrointestinal stromal tumour, POEM syndrome, synovial sarcoma, cervical cancer, medulloblastoma and aplastic anaemia. Mean age at cancer diagnosis was 37.2$\pm$18.8years and 4/9 cancers were detected incidentally. Five women had a 45, X karyotype. Three received growth hormone treatment and all except one were on oestrogen replacement therapy.
Conclusions
We confirm the previous observations that women with TS do not appear to be at overall increased risk of common malignancies within the background female population. Our small cohort showed a spectrum of unusual malignancies, which were frequently incidentally detected. The slightly increased prevalence of cancer in our cohort might be related to regular monitoring of these women due to TS per se and selected small sample size. All clinicians managing women with TS should consider the possibility of non-TS related tumours as a differential diagnosis for unexplained symptoms or unexpected radiological abnormalities.

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P113

PCOS SEVa: High prevalence anxiety and body dysmorphia in women with PCOS in the UK and India

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Introduction
National Institute of Health and Care Excellence (NICE) recommends screening for emotional wellbeing as part of consultations for polycystic ovary syndrome (PCOS).
Aim
We evaluated several dimensions of emotional wellbeing in people attending PCOS consultation in the UK and India.
Methods
All people attending reproductive endocrine clinic for PCOS at three centres: Queen Elizabeth Hospital Birmingham, UK; Apollo Hospitals, in Navi Mumbai, India; and MS Ramaiah Medical College, Bengaluru, India from October 2020 to June 2021 were invited to complete a survey before attending the clinic. This survey had questions on demographics, Hospital Anxiety and Depression Scale (HADS; score 8-10 borderline; score $\geq$11 cases of anxiety and depression, respectively), Body Image Concern Inventory (BICI; score $\geq$72 suggestive of body dysmorphic disorder, BDD), Beliefs About Obese Persons Scale (BAOP; higher score suggestive of weight bias), and Female Sexual Function Index (FSFI; higher score suggestive of psychosexual dysfunction). Comparison between women of the two countries was made with Mann-Whitney U test.
Results
A total of 109 women (43 UK and 66 India) completed the survey. The prevalence of anxiety and depression were 46.8% (51.2% UK vs 47.0% India; $P = 0.402$) and 11.0% (12.2% UK vs 10.6% India, $P = 0.937$), respectively, with no significant difference between the two groups. Overall, 24.8% had BDD with higher prevalence in the UK women (39.5% UK vs 15.2% India; $P = 0.005$). Participants had higher scores for BAOP (overall: 30.5/48 (25.0-36.0)) with higher scores for UK women (UK: 32.5 (27.25-38.0); vs India: 29.0 (24.25-33.0); $P = 0.033$). The overall scores for FSFI were towards the upper end of the scale (22.3/36 (8.4-26.7)) with no significant difference between the two groups (UK: 23.15 (15.08-26.73); vs India: 20.9 (6.8-26.8); $P = 0.204$).
Conclusions
High prevalence of emotional illbeing with PCOS both in UK and India suggest a need to improve screening and management for this globally.

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P114

PCOS pearls - gathering perceptions and opinions from lived experiences of people with polycystic ovary syndrome

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Introduction
Existing educational resources for polycystic ovary syndrome (PCOS) have limited inclusion of patient perspectives. We invited people with PCOS to share their lived experiences to understand their perception and opinion on the current standard of care.
Methodology
Women aged 18-60 years with PCOS were invited to complete an online survey in April and May 2021. The survey had open questions focused on people's lived experiences with PCOS. Participants had the option to share their views either as written text or as voice note audio recording(s) on WhatsApp. The data from audio were transcribed verbatim. Data were coded by thematic inductive method using NVivo 12 initially by two study members independently. These codes were then reviewed by two senior study members to identify common themes.
Results
43 of 45 participants had a formal diagnosis of PCOS, the remaining two had suspected PCOS which was under active investigation. Four participants opted to share their views as voice note recordings; one of them could not be contacted as they had incorrectly inputted their phone number. Overall, five common themes emerged: symptoms (504 references by 42 participants), patient journey 421 references by 42 participants), knowledge (197 references by 40 participants), peer-to-peer advice (162 references by 41 participants), and impact of PCOS on social aspects of life (42 references by 19 participants). Within these themes, emotional wellbeing, attitudes towards healthcare professionals, knowledge of signs and symptoms, being involved in care, and societal expectations of women were the most discussed topics.
Conclusions
PCOS affects the everyday lives of those with the condition, with many feeling dissatisfied with the clinical support they currently receive. We propose involving people with PCOS to co-create educational resources informed by lived experiences which will help those newly diagnosed to gain a more comprehensive and true-to-life understanding of the condition.

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P115

Disentangling Turner syndrome and Leri-Weill Dyschondrosteosis; the importance of genetic assessment in the management of Turner Syndrome

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Leri-Weill Dyschondrosteosis (LWD) is a skeletal dysplasia resulting in short stature and mesomelic limb-shortening; Madelung deformity of the wrist is often present. Mutation or deletion of the *SHOX* gene is the underlying cause of LWD. *SHOX* plays a role in regulating proliferation and maturation of chondrocytes. It is located in the pseudoautosomal region of the sex chromosomes (Xp22.3/Yp11.3); males and females usually have 2 functioning copies. Turner syndrome (TS) affects approximately 1 in 2500 girls and haploinsufficiency of *SHOX*causes the short stature associated with TS; moreover Madelung deformity is sometimes seen. SHOX deletions may additionally be associated with proportionate 'idiopathic' short stature. The overlapping skeletal phenotypes can cause diagnostic uncertainty. Molecular and cytogenetic analysis can be required in order to distinguish LWD and TS. We present 3 cases which demonstrate the diagnostic challenges of differentiating these conditions.

1. Adult female with a diagnosis of mosaic TS made in childhood. Further investigation demonstrated a normal karyotype and a *SHOX*mutation consistent with LWD.
2. Teenage female under investigation for short stature and suspected skeletal dysplasia. Found to have mosaic TS with a complex structural rearrangement of the second X with significant reproductive implications.
3. Adult female presenting with Madelung deformity of the wrist. Karyotype revealed a diagnosis of mosaic TS with deletion of *SHOX* on the second X. Correct diagnosis is important as it has implications for both management and genetic and reproductive counselling. Referral to Clinical Genetics should be considered for patients with features of either condition.

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P116

A rare case report of spontaneous pregnancy in long standing premature ovarian insufficiency secondary to chemotherapy

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A 37-year-old woman presented to ED with abdominal bloating and pain. Ultrasound abdomen showed a viable single intrauterine pregnancy at 24 weeks of gestation. Patient was surprised of the diagnosis as she had longstanding premature ovarian insufficiency (POI). She had stage 3B Hodgkin's disease (HD) diagnosed at 14 years of age when she had BEAM chemotherapy (Carmustine, Etoposide, Cytarabine and Melphalan) followed by autograft bone marrow transplant for recurrent disease four years later. She had been in remission but developed POI at the age of 20 years and had been on hormonal replacement therapy (HRT) for 15 years. She had an uncomplicated pregnancy and was induced at 40 weeks due to reduced fetal movements. She had an emergency caesarean section for fetal distress and delivered a healthy baby. HD mainly affects young adults. Although it is one of the most curable cancers, POI in premenopausal women is a serious long-term sequel of chemotherapy. The incidence of infertility is dependent on the type of chemotherapy, radiotherapy and age of the woman. It should be remembered that there is a rare possibility of

ovulation occurrence. Young women embarking on treatment for cancers should be referred to fertility experts for discussion about future fertility options. Spontaneous conception in women with POI secondary to chemotherapy is rare but possible. Women who do not wish to become pregnant must be offered contraception as HRT does not offer contraception.

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P117

Spontaneous adrenal haemorrhage and adrenal deficiency during third trimester – successful delivery with conservative management: A case report

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A 33 year old white European patient presented at 32 weeks gestation with a three day history of severe epigastric pain radiating to left flank with vomiting. She had pre-existing hypertension, controlled with labetalol. On admission, her BP dropped from 170/100mmHg to 90/70mmHg. Abdominal examination revealed epigastric tenderness without peritonism. There were no Cushingoid features. An abdominal ultrasound scan was normal. An MRI scan showed a bulky left adrenal gland, with appearances of recent haemorrhage; the right adrenal was normal. Of note, no adrenal abnormality was seen in an MRCP 5 years previously. Inflammatory markers were raised, but platelet count normal; amylase 69IU/l; plasma sodium 130 mmol/l , potassium 4.5 mmols/l; normal renal profile; urine sodium 55 mmol/l; thrombophilia screen negative. A 9 am plasma cortisol was very low, 40 nmol/l, with undetectable ACTH; adrenal antibodies negative. A 24-hour urine metanephrine profile was unremarkable: metanephrine $<$ 56 nmol/l, normetanephrine 2076 nmol/24 hours, and 3-methoxytyramine 1025nmol. Plasma metanephrine profile was also normal: metadrenaline $<$ 37.5 pmol/l, normetadrenaline 419.7 pmol/l, 3-methoxytyramine $<$ 75pmol/l. Echocardiography was normal. The clinical picture suggested suppression of the adrenal axis by a cortisol-producing adrenal tumour, but with spontaneous haemorrhage into it. The biochemical findings predated any obstetric use of betamethasone. She was commenced on PO hydrocortisone 25 mg per day and remained well throughout gestation. Hydrocortisone 100 mg IM was given at vaginal delivery. There were no neonatal or perinatal complications. Our case represents a rare presentation of probable Cushing's syndrome in pregnancy, which is usually due to an adrenal adenoma. We hypothesise that our patient may have had secondary haemorrhagic transformation following ischaemic infarction of the adenoma. Further MRI scanning and endocrine tests are planned post-partum.

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P233

***In vitro* effects of dihydrotestosterone (DHT) on gonadotropin receptor function and steroidogenesis in human granulosa lutein cells**

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Polycystic ovary syndrome (PCOS) is a multifactorial, complex endocrine disorder affecting a significant proportion of the global population. Hyperandrogenism is a key feature of PCOS patients. Aberrant secretion and/or action of gonadotropins have been implicated in PCOS, but, to date, we have only limited knowledge of how these factors may interact in the aetiology of PCOS. We hypothesised that excess androgens may cause aberrant gonadotropin activity and therefore sought to examine the effect of androgen treatment on gonadotropin receptor signalling and function. Granulosa lutein cells (GLC) from women without PCOS were pre-treated with 10nm DHT *in vitro* for 24 hours prior to luteinizing hormone (LH) treatment. LH receptor (LHCGR) gene expression, downstream signalling and steroid synthesis were evaluated by R-qPCR, cyclic AMP (cAMP) assay, immunofluorescence, and Western blotting. DHT augmented the cAMP response to LH (up to 15-fold change). Increased generation of pERk 1/2 in response to LH was also observed with the addition of DHT. These changes occurred without an increase in LHCGR expression but DHT treatment increased androgen receptor (AR) gene expression. AR expression was, in turn, downregulated by LH treatment *in vitro*, indicating a functionally significant relationship between these two key receptors. In conclusion, androgens directly contribute to reprogramming LHCGR signalling and function in GLCs and this interaction is relevant to understanding the aetiology of PCOS.

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P234

Reproductive health disturbance in the era of the COVID-19 pandemic

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Background
The combined effect of the COVID-19 pandemic and associated restrictions have adversely affected population mental health. Periods of psychological distress can induce menstrual dysfunction. We previously demonstrated a significant disruption in women's reproductive health during the first 6 months of the pandemic. The present study investigates longer term reproductive and mental health disturbances.
Materials and Methods
An online survey was distributed through social media in April 2021. The survey included measures of depression (PHQ-9), anxiety (GAD-7) and sleep quality (Pittsburgh Sleep Quality Index). All women of reproductive age were invited to participate.
Results
1335 women responded to the survey. Median age was 34 years (range 29-38). 966 (77%) recorded their menstrual cycles. 581(56%) reported an overall change in their menstrual cycle since the beginning of the pandemic. There was no change in the median cycle length (28 days (28-30)) or days of menses (5 (4-5)), but there was a wider variability in the minimum ($P < 0.0001$) and maximum ($P < 0.0001$) cycle length. There was a significant increase in menorrhagia ($P < 0.0001$), dysmenorrhoea ($P < 0.0001$) and missed periods ($P < 0.0001$) compared to pre-pandemic. 64% of women reported worsening pre-menstrual symptoms. 54% had a reduction in their libido. Rates of severe depression, anxiety and poor sleep were more than double those from large scale representative community samples. Poor sleep quality was an independent predictor of overall change in menstrual cycle (OR = 1.11, 95%CI 1.05-1.18), and missed periods (OR = 1.11, 95%CI 1.03-1.19) during the pandemic. Increased anxiety was an independent risk factor for change from non-painful to painful periods (OR = 1.06, 95%CI 1.01-1.11) and worsening of pre-menstrual symptoms (OR = 1.06, 95%CI 1.01-1.07) during the pandemic.
Conclusion
The COVID-19 pandemic continues to bear a significant impact on female reproductive health. Increased levels of psychological distress and poor sleep are associated with menstrual cycle disruption.

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P235

Wilms' Tumour-1 (WT1) regulates proliferation, apoptosis and endocrine function in a model of human granulosa cells

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Background
The Wilms' Tumour-1 (WT1) transcription factor is a critical regulator of embryonic gonadogenesis, but is also expressed by granulosa cells (GCs) in preantral follicles in the ovary after birth. Evidence from animal models suggests an important role for WT1 in regulating GC steroidogenesis and apoptosis. However, the role of WT1 in human GC biology has not been extensively explored.
Aim
To investigate the role of WT1 in regulating human GC function, proliferation and apoptosis.
Methods
Human KGN granulosa tumour cells were transfected with anti-WT1 or scrambled (control) siRNAs. Gene expression was measured using RT-qPCR. Proliferation was assessed using phosphorylated histone H3 immunohistochemistry, and apoptosis by cleaved caspase-3 and cleaved PARP immunoblotting.

FSH treatments (10nM, 24h) were performed on serum-starved KGNs.
Results
Expression of the proliferation marker *CCND1* was reduced ~64% in WT1-KD cells vs controls ($P = 0.016$), concomitant with a reduction in the proportion of proliferating cells from 8.08% ± 0.97% (controls) to 5.21% ± 0.46% (WT1-KD; $P < 0.026$). Expression of pro-apoptotic gene *BAX1* was increased ~80% in WT1-KD cells vs controls ($P = 0.032$), and sensitivity to apoptotic stimuli was enhanced, demonstrated by 2.4-fold increases in cleaved caspase-3 and cleaved PARP in WT1-KD KGNs (both $P = 0.029$). In contrast to data from rodent and bovine models, WT1-depletion in KGNs was associated with repression of *CYP11A1* (~30% reduction vs controls, $P = 0.032$) while other steroidogenic genes remained unchanged. Depletion of WT1 also dysregulated *FSHR* expression (3.6-fold increase in WT1-KD cells vs control, $P = 0.016$) and enhanced FSH-mediated upregulation of *CYP19A1* by ~2.2-fold vs controls ($P = 0.029$).
Conclusion
These data identify WT1 as a potential regulator of human GC proliferation, survival and function, and reveal possible species-specific differences in the regulation of steroidogenic genes by WT1. As *WT1* mutations have been associated with premature ovarian failure, this work may provide insight into the molecular basis of female infertility.

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P236

Increased levels of testosterone associated with polycystic ovary syndrome (PCOS) negatively affect *HOXA10* and integrin *β3* expression in endometrial cells and embryo attachment using a trophoblast cell spheroid model

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PCOS is a reproductive endocrine disorder that affects up to 10% of women of a reproductive age, with 70-80% of patients defined as infertile. There are many different symptoms that could impact fertility in women with PCOS such as anovulation, hyperandrogenism and insulin resistance. A trophoblast (BeWo cell) spheroid attachment assay was used as an *in vitro* model of embryo implantation to examine the effect of testosterone on the receptivity of endometrial (Ishikawa cell) monolayers. Attachment of BeWo spheroids to Ishikawa cell monolayers was significantly reduced following pre-treatment of Ishikawa cells with 10nM testosterone for 24h (33% compared to 80% with untreated Ishikawa cells; $P < 0.0001$, $n = 3$). Flutamide (an androgen receptor antagonist, 1μM) added simultaneously with testosterone reversed the effect of treatment with testosterone alone, returning attachment rates to control levels (75%; $p > 0.05$ compared to untreated cells, $n = 3$). The transcription factor HOXA10 and the cell surface adhesion receptor αVβ3 have previously been shown to play key roles in implantation. Testosterone treatment significantly decreased the expression of *HOXA10* ($P < 0.001$, $n = 4$) and integrin β*3* ($P < 0.002$, $n = 4$) in Ishikawa cells detected by qPCR. Immunocytochemistry showed a significant reduction in αVβ3 protein expression in testosterone-treated ishikawa cells ($P < 0.05$, $n = 2$, >300 cells analysed per condition). Co-treatment of flutamide and testosterone rescued the levels of *HOXA10* and *β3* gene expression ($p > 0.05$ compared to untreated cells, $n = 3$) and αVβ3 protein expression ($p > 0.05$ compared to untreated cells; $n = 2$, >150 cells analysed). These data suggest that the hyperandrogenism observed in women with PCOS results in reduced endometrial receptivity through the decreased expression of *HOXA10* gene and αVβ3 protein and this may in part be responsible for infertility in these individuals.

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P237

Impact of pharmacological Interventions on androgen hormones in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials

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Context
Polycystic ovary syndrome (PCOS) is a complex endocrine disease that affects women of reproductive age and characterised by biochemical and clinical androgen excess.
Aim
To review the available literature on the effectiveness of the various pharmacological interventions on androgen hormones in women with PCOS.
Data source
We searched PubMed, MEDLINE, Scopus, Embase, Cochrane library and the Web of Science in April 2020 and updated the search in March 2021.
Data synthesis
Two reviewers selected eligible studies and extracted data, and the review is reported according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).
Results
of 814 randomised clinical trials (RCTs) located in the search, 92 met the eligibility criteria. There were significant reductions in total testosterone with *metformin vs placebo* (SMD:-0.33; 95% CI-0.49 to-0.17, $P < 0.0001$, moderate grade evidence) and *dexamethasone vs placebo* (MD:-0.86 nmol/l ; 95% CI:-1.34 to-0.39, $P = 0.0004$, very low-grade evidence). Significant reductions in the free testosterone with *sitagliptin vs placebo* (SMD: -0.47; 95% CI: -0.97 to 0.04, $P = 0.07$, very low-grade evidence), in dehydroepiandrosterone sulphate (DHEAS) with *flutamide vs finasteride* (MD: -0.37 μg/dL; 95% CI: -0.05 to -0.58, $P = 0.02$, very low-grade evidence), in luteinising hormone (LH) with *simvastatin + OCP vs OCP* (MD: -2.02 IU/l; 95% CI: -3.52 to -0.52, $p = 0.008$, very low-grade evidence), in follicular stimulating hormone (FSH) with *rosiglitazone vs placebo* (MD:-0.32; 95% CI: -0.61 to -0.02, $P = 0.04$, very low-grade evidence) and a significant increase in sex hormone-binding globulin (SHBG) with *oral contraceptive pill (OCP) (35 μg EE/2 mg CPA) vs placebo* (MD: 103.30 nmol/l ; 95% CI: 55.54 to 151.05,$P < 0.0001$, very low-grade evidence) were observed.
Conclusion
metformin, dexamethasone, flutamide, OCP, and rosiglitazone have significantly reduced androgen hormones in women with PCOS.

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P238

Clinical utility of free androgen index (FAI) in the assessment of PCOS

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Background
Free androgen index (FAI) is used to estimate free testosterone concentrations in patients undergoing investigation for polycystic ovarian syndrome (PCOS). However, it's not widely used for diagnostic purpose due to lack of consensus in the literature. We present an appraisal of biochemical data from patients referred to a hyperandrogenaemia clinic with a view to establish an in-house cut-off for the diagnosis of hyperandrogenaemia in PCOS.
Method
Clinical and biochemical data were extracted from patient records ($n = 220$ from 2012-2020). Patient were categorised as (i) non-PCOS (Group 1), (ii) PCOS (hyperandrogenaemia) (Group 2) or (iii) PCOS (no hyperandrogenaemia) (Group 3) based on the Rotterdam criteria (2003). Hyperandrogenaemia was defined by a patient having ≥1 of the following: testosterone >1.9nmol/l , androstenedione >8.5nmol/l (both measured by LC-MS/MS) or FAI >4.5%.
Results
Patients were categorised as: Group 1 ($n = 38$), Group 2 ($n = 132$) and Group 3 ($n = 46$). Mean testosterone, androstenedione and FAI were 1.0 nmol/l , 3.8 nmol/l and 1.9% (Group 1); 2.2 nmol/l , 8.0 nmol/l and 6.8% (Group 2) and, 1.1 nmol/l , 4.6 nmol/l and 2.5% (Group 3). Testosterone and androstenedione were significantly different when Group 2 was compared to Groups 1 ($P = <0.0001$) and 3 ($P = <0.0001$). No significant difference was observed between Group 2 and Group 3 ($P = 0.05$). A significant difference was observed in FAI between all 3 groups ($P = <0.02$, all comparisons).
Conclusions
FAI was significantly different between all clinical groups and much lower than the frequently used cut-off of >4.5% currently used to identify

hyperandrogenaemia. We propose that a lower FAI cut-off of 2.5% is adopted to help identify hyperandrogenaemia in patients undergoing investigation for PCOS.

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P239

The rate of progression of atherosclerosis in menopause is associated with levels of circulating amyloid beta 1-40

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Background
Cardiovascular disease remains the leading cause of death worldwide, affecting both sexes. Awareness and prevention practices aiming to control cardiovascular risk in women remain inadequate. On the other hand, circulating amyloid β 1-40 (Aβ1-40) is a proatherogenic peptide, closely linked with the process of aging. We aimed to evaluate the possible association between the progression of atherosclerosis in postmenopausal women and the role of Aβ1-40 peptide, as well as its time-related pattern of change, in this population with substantial unrecognized CV-risk beyond traditional risk factors.
Methods
This prospective study of 152 postmenopausal women free of cardiovascular disease (CVD), aimed to assess carotid atherosclerosis, by using high-resolution ultrasonography and levels of Aβ1-40. Evaluation was performed at baseline and after a median follow-up of 28.2 months.
Results
Levels of Aβ1-40 at baseline associated with higher sum of maximal wall thickness in all carotid sites (sumWT) but also higher carotid bulb intima-media thickness (cbIMT) (p-value <0.05, all cases). Aβ1-40 levels increased with the progress of time, and were also linked with declining renal function (p-value <0.05, all cases). A pattern of accelerated progression of atherosclerosis was evident in women with increasing or persistently high levels of Aβ1-40, after adjusting for baseline values, renal function and traditional CV-risk factors. The pattern of atherosclerotic changes was evident in cbIMT, sumWT and maximum carotid wall thickness.
Conclusion
The progression of subclinical carotid atherosclerosis in otherwise healthy postmenopausal women is associated with increasing or persistently high levels of Aβ1-40, irrespectively of its baseline levels. The results of this study provide insights into a link between Aβ1-40 and the progression of atherosclerosis in menopause. If these findings are confirmed by larger observational studies, then Aβ1-40 might serve as an atherosclerosis biomarker in women without clinically overt CVD.

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P240

Effect of pharmacological interventions on lipid profiles and C-reactive protein in polycystic ovary syndrome: a systematic review and meta-analysis

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Context
Polycystic ovary syndrome (PCOS) is a heterogeneous condition affecting women of reproductive age. It is associated with dyslipidaemia and elevated plasma C-reactive protein (CRP), which increase the risks of cardiovascular disease (CVD).
Objective
To review the existing evidence on the effects of different pharmacological interventions on lipid profiles of women with PCOS.
Data sources
We searched PubMed, MEDLINE, Scopus, Embase, Cochrane Library, and Web of Science in April 2020 and updated the results in March 2021.
Study selection
The study included randomised controlled trials (RCTs) and follows the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).
Data extraction
Two independent researchers extracted data and assessed for risk of bias using the Cochrane risk of bias tool. Covidence systematic review software was used for blinded screening and study selection.
Data synthesis
In 29 randomised controlled trials (RCTs), there were significant reductions in triglycerides with atorvastatin vs placebo (MD: -0.21 mmol/l ; 95% CI: -0.39, -0.03, $I^2 = 0\%$, moderate grade evidence). Significant reductions were seen for LDL-C with metformin vs placebo (SMD:-0.41;95%CI:-0.85, 0.02,$I^2 = 59\%$, low grade evidence). Significant reductions were seen for total cholesterol with saxagliptin vs metformin (MD:-0.15 mmol/l ; 95% CI: -0.23, -0.08, $I^2 = 0\%$, very low grade evidence). HDL-C was significantly reduced for saxagliptin vs metformin (MD: -0.11 mmol/l ; 95%CI: -0.15, -0.06, $I^2 = 7\%$, very low grade evidence). Significant reductions in C-reactive protein (CRP) were seen for atorvastatin vs placebo (MD:-1.51 mmol/l ;95%CI:-3.26-0.24, $I^2 = 75\%$, very low-grade evidence).
Conclusion
There were significant reductions in the lipid parameters when metformin, atorvastatin, rosiglitazone and pioglitazone were compared with placebo or other agents. There was also a significant reduction of CRP with atorvastatin.

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P241

Efficacy and safety of androgens in transgender medicine

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Androgen therapy is the mainstay of treatment in female to male (FtM) transgender persons to increase testosterone levels, suppress oestrogens and treat gender dysphoria. Testosterone is widely used for male hypogonadism, but is comparatively under-investigated in FtM transgender persons. The aim of our study was to identify treatment and safety outcomes associated with testosterone use in transgender medicine. A literature search was conducted in PubMed/Medline, as well as EMBASE, using MeSH terms. A total of 260 records were identified. Forty-eight studies were suitable for final analysis. Androgens in FtM transgender people are effective to lower voice frequency, increase facial hair-growth, and increase hematocrit and hemoglobin levels to adult male reference ranges. Similarly, body uneasiness and sexual desire have been shown to improve after androgen use. A 1.2-fold to 3.7-fold higher rate of myocardial infarction has been reported retrospectively compared to cisgender women. Blood pressure, glycaemic control and body mass index remained unchanged in FtM transgender people. However, total cholesterol levels may increase above recommended targets following testosterone treatment. Androgens in FtM transgender persons have positive physical effects, but it is important to highlight cardio-metabolic risk factors. Studies on mortality require prospective evaluation with longer participant follow-up periods. Randomised control trials, longer follow-up periods and studies involving older participants may further improve the management FtM transgender people.

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P242

Assessing emotional wellbeing in women with PCOS living in the UK and Indian community: the Blue Morpho Survey

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Aim
To study differences in various aspects of emotional wellbeing among women with PCOS living in the UK and India.
Methods
Women with PCOS were invited to complete an online survey between September and October 2020 in the UK and May and June 2021 in India. The survey included Hospital Anxiety and Depression Scale (HADS; score ≥ 11 cases of anxiety and depression, respectively), Body Image Concern Inventory (BICI; score ≥ 72 suggestive of body dysmorphic disorder, BDD), Beliefs About Obese Persons Scale (BAOP; higher score suggestive of weight bias) and Female Sexual Function Index (FSFI; higher score suggestive of psychosexual dysfunction). The Mann-Whitney U test was used to make comparisons between women from both countries.
Results
A total of 758 women, living in the UK ($n = 344$) and India ($n = 414$) completed the survey. The prevalence of anxiety and depression were 62.1% overall, with higher prevalence in Indian women (56.4% UK vs 66.9% India; $P = 0.003$) and 25.6% (20.6% UK vs 29.7% India, $P = 0.001$). Overall, 36.5% had BDD with a significantly higher prevalence in the UK women (47.7% UK vs 27.3% India; $P = 0.000$). UK women had higher scores for BAOP compared to Indian women (overall: 30/48 (25.0-35.0); UK: 32.0 (27.0-35.0) vs India: 29.0 (23.0-34.0); $P = 0.000$). A similar trend was seen for psychosexual dysfunction (overall scores for FSFI: 21.0/36 (8.4-26.5); UK: 23.30 (10.75-28.00); vs India: 19.85 (7.83-25.5); $P = 0.000$).
Conclusion
A differential impact on emotional wellbeing with PCOS in the two countries suggest other factors such as socioeconomic status, deprivation and education which may play a role. Future studies are needed to explore this further.

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P243

The effect of exogenous kisspeptin administration in a novel mouse model of hypothalamic amenorrhoea

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Kisspeptin is integral to hypothalamo-pituitary-gonadal (HPG) axis function and overall fertility. Functional deficiency of GnRH/lH secretion in the central reproductive disease, hypothalamic amenorrhoea (HA), indicates diminished kisspeptin signalling. Clinical trials have shown kisspeptin to be a viable therapeutic intervention. However, repeated administration led to the development of tachyphylaxis and so is likely a problem for future implementation. Indeed, elevated LH responsiveness suggests increased Kiss1R expression, increasing the pathway's susceptibility to desensitisation through heightened sensitivity. Together suggesting that improved understanding of the Kiss1-Kiss1R system in HA is necessary to devise an effective long-term treatment strategy. Thus, we aimed to create a novel model of HA in mice, based on body weight reduction induced by chronic caloric restriction, and conduct preliminary investigations into kisspeptin responsiveness and gene expression. Following 60% caloric restriction, mice displayed acyclicity and reduced body weight and fat mass. Upon kisspeptin stimulation, LH responses were elevated. Concomitantly, *Kiss1R* expression was upregulated. These data replicate the human HA phenotype in a mouse models, displaying increased LH responsiveness in mice following chronic calorie restriction. This model has the potential to inform future therapeutic regimens, possibly with dose titrating, to restore HPG axis function and fertility in women with HA.

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P244

Service evaluation of patients referred for PCOS - Are we doing enough to diagnose and manage them well?

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Introduction
Polycystic ovary syndrome (PCOS) is a complex endocrine disorder of uncertain aetiology, affects 1 in 10 reproductive women and has broad spectrum risks related to reproductive, cardiometabolic and psychosocial health. The wide overlap with other hyperandrogenemic conditions, complexity of PCOS spectrum, and inconsistencies in investigation and management potentially can result in risks of delay in diagnosis and management.
Aim
To evaluate the diagnosis of PCOS and subsequent management.
Method
Retrospective observational data analysis of patients presenting with hyperandrogenaemia in endocrine service (544 patients from 2012 to 2020). 219 (56.1%) patients confirmed to have PCOS based on the Rotterdam criteria were included.
Results
62.7% reported oligomenorrhoea. Hirsutism was reported in 66.2%, Acne in 21.5%, male pattern alopecia in 14.4% and acanthosis nigricans in 1.5%. The BMI was not recorded for majority (53%), 73% were in overweight/obese range of the ones recorded. 20% did report fertility issues. Biochemical hyperandrogenemia was present in 132 patients. Mean testosterone, androstenedione and free androgen index (FAI) were 2.2 nmol/l , 8.0 nmol/l and 6.8% in patients with biochemical hyperandrogenemia and 1.1n mol/l , 4.6 nmol/l and 2.5% in other PCOS patients with no biochemical hyperandrogenemia. Pelvic USS was performed in 69.2% of patients, 41.2% had findings suggestive of PCOS; ovary enlargement or presence of multiple peripheral follicles or cysts. Combined oral contraceptive pills were used only in 16.5% and Metformin in 46.9%. Mechanical hair removal (20.2%), laser therapy (11.6%), Vaniqa cream (6.6%) and spironolactone (4%) were used for hirsutism.
Conclusion
Variations in clinical and biochemical profiles reflect the complex heterogeneous nature of PCOS. Having different diagnostic criteria, biochemical assay and cut off values further poses diagnostic challenge. The treatment options are limited; lacks robust evidence and uptake of these treatments amongst patients are very inconsistent. Timely diagnosis, robust assessment for cardio metabolic risk factors and individualised care are vital.

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P245

COVID19 in Turner Syndrome; results of a self-completed website survey

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Background
Girls and women with Turner Syndrome (TS) are commonly estrogen deficient, and may also be affected by conditions that have been suggested as increasing risk for severe infection with COVID.

Objective
To determine the self-reported experience of COVID19 in girls/women with Turner syndrome
Design
Anonymous self-completed website survey (UK TSSS) and analysis of submitted data
Population
49 people; 10 on behalf of their child, 26 for themselves, 1 on behalf of a patient (where reported), mean age 29y (5-48). Reported karyotype; 45, X (18), mosaic (8), other (3).
Main Outcome Measures
Clinical features of COVID infection and severity. Characteristics of Turner Syndrome in those affected by COVID, pre-existing drug therapy and proportion in high-risk groups.
Results
The commonest initial features were tiredness ($n = 22$, severe in 8), and muscle aches ($n = 17$). Specific symptoms were noted; fever/high temperature (9), loss of smell/taste (12), headache (21) and least commonly - cough (8). 19 women described anxiety as a major feature (severe in 4). Only 1 infection was scored as severe, requiring hospitalisation for severe breathing problems and requiring oxygen. No patient required ITU. Contact with hospital was the mode of infection in 3/9. Eight reported previous cardiac surgery. 7 had hypertension, 4 diabetes mellitus (3/4 insulin) and 12 primary hypothyroidism. Medication included vitamin D (14), HRT/OCP (27) anxiety medication (6). 10/26 had received flu-vaccine.
Conclusions
In this self-reported survey of COVID19 infection in TS, severity was mild in all but one, which may be related to their relatively young age. Notwithstanding significant pre-existing morbidity in many patients, only one patient required hospitalisation, and none required assisted ventilation. Anxiety was significant for many, with associated increased social isolation. Despite the increased morbidity associated with respiratory disease and infection reported in TS, this small survey was relatively reassuring in terms of COVID19.

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P246

The Impact of COVID-19 on Endocrine Treatments from a patient perspective - effect on parenteral testosterone

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Introduction
The COVID-19 pandemic has had a huge impact on the delivery of health services. Here we review the patient perspective, on rapid changes in treatment delivery of testosterone preparations instituted in the first wave of the pandemic.
Methods
49 hypogonadal male patients were identified as attenders to the Endocrine unit for Nebido™ injection. They were temporarily switched to testosterone gel to rapidly comply with COVID rules. 8 weeks after the switch these patients were sent a postal questionnaire to assess patient satisfaction and preference. The survey consisted of 18 questions including: details of the new treatment, administration satisfaction, side effects and preference of location of treatment administration. The questions included multiple choice satisfaction ratings, yes or no answers and free text areas.
Results
51% of patients responded to the survey. Patients were satisfied with the information provided need for treatment change, administration satisfaction was much lower. 61.9% of patients reported numerous issues and difficulties around using the gel and most felt less than satisfied with their new treatment. Patients reported difficulty using the gel and found it time consuming and inconvenient to apply. A few patients expressed concern regarding the risk of transference on to children. The most common reported side effect was fatigue. There was no correlation between the side effects experienced and the patients underlying indication for treatment. Other local side effects included burning of the skin, itching and painful rashes.
Conclusion
The survey results found that although patients were happy to continue using the gel if a second wave were to occur, 96% of respondents would rather switch back to receiving their injection in hospital as opposed to using the gel once it was safe to do so. Many have now switched back and community teams have enabled this to happen efficiently in the domiciliary setting.

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P247

A case of reversible congenital hypogonadotropic hypogonadism

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Case
A 21 year old gentleman presented to endocrine clinic with failure to develop secondary sexual characteristics. He had no growth since age 16, nor any change in voice, body hair or muscle or genital growth. Examination was in keeping with pubertal staging Tanner stage II. His right testicular volume was 5ml and left testicular volume 4ml. He had normal sense of smell. Investigations demonstrated low testosterone at 1.6 nmol/l (10-30). Results showed hypogonadotropic hypogonadism with inappropriately normal LH at 0.9 U/l (0.6-9) and FSH at 1.2 U/l (1-10). His remaining pituitary hormones were normal. His diagnosis was thought to be either Kallman syndrome with normosmia or congenital hypogonadotropic hypogonadism. He was commenced on testosterone replacement. For a period of time he was also using additional testosterone replacement purchased at his gym, but this was stopped following advice in clinic. His repeat testosterone was normal and his symptoms improved, with improved energy levels, increasing muscle bulk and facial and pubic hair, and deepening voice. He continued on testosterone replacement and progressed though pubertal stages. Following this his partner became pregnant. His testicular volume was reassessed and right volume was 20 ml, with left being 12 ml. His repeat gonadotrophins showed normal testosterone level with detectable FSH and LH. He underwent a semen analysis and had a low but detectable sperm count. Following this his testosterone treatment was stopped. Following cessation of testosterone replacement his testosterone level remains normal (12.2 nmol/l), and he has normal sexual characteristics, erectile function and libido.
Discussion
This demonstrates a case of reversible congenital hypogonadotropic hypogonadism, with recovery of fertility following treatment, and recovery of reproductive axis following cessation of testosterone replacement. This raises the question of whether trialling withdrawal of treatment with monitoring of results would be beneficial in a subgroup of patients.

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Thyroid

P118

Cost-effectiveness analysis of liothyronine for the management of treatment unresponsive hypothyroidism based on latest evidence

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Introduction
Between 5-10% of patients with hypothyroidism treated with levothyroxine (T4) continue to experience profound symptoms, despite achieving free T4/thyroid stimulating hormone concentrations within reference range. Liothyronine is sometimes added to levothyroxine, but its use is controversial due to uncertainties in clinical/cost effectiveness.
Methods
An economic model was developed to estimate the incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS in the UK. Health utilities were obtained from a survey of symptomatic hypothyroid patients. EQ-5D-5L profiles were converted to EQ-5D-5L index values (utilities, a preference-weighted measure of patients' health evaluation) based on the UK EQ-5D-5L/3L cross walk value set. A survey of clinicians provided estimates of healthcare resource use/treatment efficacy.
Results
37% of people responding to the survey reported severe problems in performing usual activities of everyday living. 22% reported severe anxiety/depression symptoms. Mean utility was 0.53 (the UK population norm for the EQ-5D-3L, for the age category of 45-54 years is 0.85) (SD 0.25), decreasing to 0.80 (0.26) for category 55-64 years. The mean (SD, minimum, maximum) EQ-VAS score was 49.3 (17.2, 5.0, 90.0)(100 indicates optimal health). The model indicated that at £11,881/QALY gained, the incremental cost effectiveness ratio fell below the cost-effectiveness threshold of £20,000/QALY operating in the NHS, and was stable to modelling assumptions. The probability of liothyronine/levothyroxine combination therapy being cost effective at this threshold was 0.56. The estimated value of eliminating the uncertainty surrounding the decision problem (£3.64m

per year in UK) significantly exceeds the plausible costs of a clinical trial.
Conclusions
Liothyronine/levothyroxine combination therapy may represent a cost-effective treatment option for patients remaining symptomatic with levothyroxine alone. A definitive clinical trial is necessary to confirm clinical effectiveness, and would be justified given the value of the information gained far exceeds the cost.
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P119

Conundrum of Thyroid Function Tests
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This case highlights the lessons learnt from a patient who was diagnosed 37 years following presentation with abnormal Thyroid Function Tests (TFTs). Mrs ID had a subtotal thyroidectomy in 1983 for thyrotoxicosis and was started on levothyroxine. She was referred to endocrine services in 2003, and was noted to have a small goitre and abnormal TFTs. Follow up consultations concentrated on thyroxine dose adjustment and querying compliance. She had a background of COPD, CVA (2018), Folate and B12 Deficiency and a sister with hypothyroidism. She had a 47 pack-years smoking history. We reviewed her in 2017 (Aged 64 years). She looked anxious, BMI of 16.9 and history of 11kg weight loss (2003-2017). Clinical examination was normal except ?left temporal visual field defect. Following initial consultation, baseline bloods (including albumin) were normal. TFTs (2003-2019) showed persistently elevated fT4 (30-66 pmol/l), with non-suppressed TSH (20-60 Mu/l). Coeliac screen was negative. Chest X-ray was normal. Formal absorption test ruled out issues with compliance/absorption. Interference assay was negative. Her visual field defect led to a pituitary profile, showing normal cortisol, borderline raised IGF-1 (26.4nmol/l) and raised prolactin (710Mu/l). MRI pituitary revealed a 4mm left sided adenoma. Formal visual field testing returned normal. Simultaneously, α-subunit and SHBG were normal. At this juncture, thyrotropin releasing hormone stimulation test showed a normal prolactin response with persistently raised TSH (>100). Reviewing the entire picture, a requested genetic analysis reported "all previously reported pathogenic variants in the thyroid hormone receptor β (THR β) gene have been detected in hormone binding domain (exon 7, 8, 9 and 10)" confirming the diagnosis of thyroid hormone resistance. The challenge lies ahead of explaining the diagnosis to the patient, 16 years following her initial referral to the hospital services. Methodical approach to atypical TFTs is must in every endocrine clinic.
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P120

Service review on the use of TRAB antibodies for patients with hyperthyroidism
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Background
Recent evidence favours the use of TRAB in patients with hyperthyroidism (a) at presentation to identify the aetiology and predict outcomes (b) at the time of withdrawal of medical therapy to predict remission and (c) during pregnancy. However, If TRAB is not requested at an appropriate time, it may not help, may mislead or add to cost.
Aim
To review the current process of requesting TRAB in line with available evidence and identify areas for service improvement.
Patients and methods
The proportion of patients, who had a request for TRAB, amongst new patients with hyperthyroidism between 01-07-2020 and 31-12-2020, was estimated. Hospital record of 56 patients with TRAB requests were reviewed retrospectively for demographics, details of hyperthyroidism, timing of TRAB request and clinical decisions made on the basis of the result.
Results
Only 126/505 (24.9%) newly diagnosed patients with hyperthyroidism had TRAB antibodies checked. 56 patients studied, had a mean age 49 years, 71.5% were females, mean T4 24.9pmol/l, T3 7.1pmol/l, 23.2% were smokers. TRAB was positive in 46% and was requested to (a) identify the aetiology in 44(79%) patients (b) to guide treatment withdrawal in 5(9%) patients and (c) to make management decisions during pregnancy in 7(12.5%) patients. Of those in group (a) in 32% patients the result was unhelpful due to incorrect timing of request. The initial result was used to guide long term treatment planning in only 4(9%) patients.
Conclusions
TRAB antibodies were checked only in a quarter of the patients with hyperthyroidism. They were mainly requested to identify aetiology but request was often incorrectly timed. TRAB was infrequently requested to guide therapeutic decisions or treatment withdrawal. Recommendations: A new well-structured care-pathway for requesting TRAB antibodies in specialist care and an auto-request mechanism for hyperthyroid samples received from primary care are needed.
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P121

Thionamide-associated hepatitis: A forever clinical conundrum
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A 37-year healthy man initially presented to primary care with weight loss and palpitations and diagnosed to have thyrotoxicosis based on thyroid function tests (TFT) – TSH (<0.05; $n = 0.27$-4.20μIU/l), FT4 (59.8; $n = 12$-22 pmol/l), and FT3 (32; $n = 3.1$-6.8pmol/l) . CBZ was started and 4-weeks later was seen in the Endocrine clinic where Graves' disease was confirmed based on a goitre and positive antiTSH receptor antibody. However, we noted new abnormal liver function tests (LFT) with an elevated Alkaline-Phosphatase (ALP:296; $n = 30$-130 U/l) but normal Alanine transaminase (ALT), GammaGT and bilirubin. CBZ was continued pending further liver tests. 2-weeks later, his TFT's improved, but with the progression of hepatitis with now both ALP and ALT rising to 320 U/l and 78 ($n = 0$-41U/l) respectively. Ultrasound liver did not show any abnormalities and liver autoimmune screen was negative. Based on temporal association with CBZ initiation; a diagnosis of Thionamide-induced hepatitis was made. CBZ was discontinued but radioiodine (RAI) treatment or surgery could not be offered since he was the principal carer of his infant. Hence, PTU was started with a warning that his hepatitis could worsen but fortunately, his hepatitis did not worsen and remains on PTU 200 mg/day with guarded monitoring of LFTs.
Discussion
Thionamide-induced hepatotoxicity has an overall incidence of $<0.5\%$ and liver failure at 1:10000 adults. Their mechanisms are slightly different: CBZ causes dose-dependent intracannalicular cholestasis whereas PTU is associated with idiosyncratic hepatocellular damage. This case poses two interesting comments: firstly, what treatment options could be offered if PTU caused similar hepatotoxicity and both RAI and surgery were contraindicated? Secondly, it highlights the importance of checking baseline LFTs before initiation of ATDs, regular monitoring and improving awareness amongst prescribers.
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P122

A family with euthyroid hyperthyroxinaemia
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Background
Euthyroid hyperthyroxinaemia can present a diagnostic challenge. Abnormalities in the binding proteins of thyroid hormones can cause this discordant picture of thyroid function tests, with thyroxine binding globulin being the protein most commonly affected. Familial dysalbuminaemic hyperthyroxinaemia is a rarer cause, and is an autosomal dominant condition which can present with euthyroid hyperthyroxinaemia. This condition is associated with a mutation in albumin which causes an increased affinity to thyroxine (T4) and triiodothyronine (T3) and hence interference in immunoassays.
Case
A 34 year old woman and her 65 year old mother were referred to endocrine clinic with an unusual pattern of thyroid function tests. They had no symptoms of thyroid dysfunction and neither woman had a goitre. The daughter had a

normal thyroid stimulating hormone (TSH) with raised free T4 of 32 pmol/l (9 to 21), and the mother had a normal TSH with raised free T4 between 23 pmol/l and 25.5 pmol/l for the preceding 6 years. The sex hormone binding globulin was normal in both women. TSH was normal across multiple different platforms, however raised free T4 was reproduced on Roche and Siemens platforms, but not with an Abbott platform. The Abbott platform demonstrated normal TSH and normal free T4 for both mother and daughter. Results were unchanged following testing with blocking tube to remove heterophilic antibodies that could potentially cause interference. Familial dysalbuminaemic hyperthyroxinaemia was suggested as a likely diagnosis to explain thyroid function results, with an alternative diagnosis being a transthyretin mutation as opposed to albumin mutation. Serum has been sent for a radioligand binding assay and results are awaited.

Discussion

Knowledge of the potential causes of euthyroid hyperthyroxinaemia is important, as it has the potential to prevent unnecessary treatment of hyperthyroidism.

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P123

The impact of intraoperative elements on postoperative hypoparathyroidism in patients after total thyroidectomy

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Background

The surgical technique and the extent of thyroidectomy are related to parathyroid injury and hypoparathyroidism.

Methods and results

We retrospectively analyzed the files of 552 patients who underwent thyroidectomy in our surgery department between 2015-2017 with the aim to assess the incidence and impact of intraoperative features that may predispose to postoperative hypoparathyroidism (PoSH).

Results

171 (30.97%) patients, 153 women (89.5%), median (IQR) age 49(22) years developed PoSH (88.37% transient). The intraoperative features studied in these PoSH patients were: cervical neck dissection and lymphadenectomy (15.2%), surgeon reported difficult thyroidectomy (8.3%), the presence of retrosternal goiter (7%), no parathyroid gland identification (6.8%) and re- operative thyroid surgery (2.3%). Median age was higher in PoSH patients with surgeon reported difficult thyroidectomy [62(7.5) vs 48 (22.75) years, $P = 0.007$]. Surprisingly, median postoperative calcemia was higher in patients with reported difficult surgery [8.2(0.2) vs. 7.9(0.6) mg/dl, $P = 0.043$]. Although patients with no intraoperative parathyroid gland identification had a higher prevalence of inadvertent excision of parathyroid tissue (20% vs 2.2%, $P = 0.037$), the median postoperative serum calcium level was higher in these patients [8.25 (0.25) vs. 7.9 (0.67) mg/dl, $P = 0.001$]. Our data showed that when cervical neck dissection and lymphadenectomy was necessary it was associated with a higher median surgery duration [152 (70) vs. 127 (53) min, $P = 0.007$] and a higher median serum calcium decrease [1.8 (0.85) vs. 1.6 (0.67) mg/dl, $P = 0.048$]. Postoperative and long-term biological parameters (calcemia, PTH, 25-hydroxyvitamine D, phosphatemia) were similar in PoSH patients regardless the presence of retrosternal goiter or the need for re- operative thyroid surgery.

Conclusions

Our data, that needs further validation in large trials, showed that in PoSH patients intaoperative features, of which in particular cervical neck dissection and lymphadenectomy, must be carefully monitored.

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P124

Two Unusual Cases of Subacute Thyroiditis (SAT) and management

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Subacute thyroiditis (SAT) is a self-limited inflammatory condition of the thyroid characterised by a clinical course of hyperthyroidism, hypothyroidism, and then return to normal thyroid function. The inflammation is thought to be triggered by a viral infection and is usually treated with anti-inflammatory medications and steroids. Recurrences can uncommonly occur and could be difficult to manage. There are some promising reports of the role of Colchicine in managing recurrent SAT. Here we report two SAT case scenarios where colchicine was found useful. Case 1: A 28-year-old female athlete who presented with hyperthyroidism caused by 4th recurrence of SAT. Previously she was managed with tapering Prednisolone therapy and remained on a small dose of Prednisolone for a long time since the 3rd recurrence before weaned off slowly; however, she had the 4th recurrence within 4 months. She was restarted on a tapering course of Prednisolone, and based on some recent evidence, Colchicine was started. She hasn't shown any sign of recurrence since. Case 2: A 47-year-old female who developed fever, tachycardia and thyroid tenderness eight months after SARS-CoV-2 infection. Laboratory tests and nuclear imaging were indicative of subacute thyroiditis. She had initial response to high dose of prednisolone however it relapsed after stopped. She had persistent tachycardia which was thought to be due to pericarditis. She was started on Colchicine for this, but only took it for two weeks due to intolerance. However, she did complete a second course of prednisolone and is currently euthyroid. Our cases have demonstrated that Colchicine, as an anti-inflammatory agent, may provide a steroid-sparing method in managing difficult SAT and prevent recurrence. In addition, increasing reports have shown SAT as a part of systemic inflammation caused by SARS-CoV-2 virus. Colchicine could be a treatment choice in this scenario. Further large study is required.

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P125

Catastrophic complication related to uncontrolled thyrotoxicosis

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Presentation

A 32-year-old woman was brought to the Emergency Department following an out-of-hospital cardiac arrest. CPR was started by a neighbour and on arrival, she was found to be in ventricular fibrillation (VF). She received 4 DC-shocks and reverted to atrial fibrillation with fast ventricular rate and staged a full cognitive and haemodynamic recovery. She had a 10-year history of Graves' thyrotoxicosis for which she was on Carbimazole but remained uncontrolled due to non-compliance related to ongoing mental health and social issues. She was admitted to the Intensive Care Unit and was stabilised with Propylthiouracil, Lugol's iodine, hydrocortisone and beta blockers. A definite diagnosis of thyroid storm was difficult in view of the post-cardiac arrest state and mental health background.

Investigations

Echocardiogram demonstrated a floppy prolapsed anterior mitral valve and moderate mitral regurgitation, dilated left ventricle (LV) with preserved LV function. Cardiac MR showed no evidence of scarring and coronary arteries were patent on CT angiogram.

Follow up

She remained stable and was euthyroid on block and replacement therapy, beta-blockers and anticoagulants.

Discussion

(a) Why did she have VF?: Single mitral leaflet prolapse and uncontrolled hyperthyroidism on their own have rarely been linked to VF although the latter is known to lower its threshold. Since structural cardiac pathology and channelopathy were excluded, the multidisciplinary opinion was that VF may have resulted from a combination of uncontrolled thyrotoxicosis and mitral valve prolapse (b) Management plan: The consensus is to proceed with mitral valve replacement, followed by cardiac re-assessment for ICD implantation. During this time stable euthyroidism would be maintained to lower the threshold of VF. Once the cardiac condition is stable, definitive therapy for thyrotoxicosis would be radioiodine administration, is in keeping with patient's choice.

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P126

Conversion of Hypothyroidism to hyperthyroidism: a rare but not an uncommon phenomenon

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Background
Graves' disease and Hashimoto's thyroiditis are the most common autoimmune thyroid conditions. Hyperthyroidism following hypothyroidism is a rare phenomenon. Hypothyroidism was once thought to be a permanent state requiring lifelong replacement therapy but we have noted that there are increasing numbers of cases which are against this postulation. We would like to report 3 cases initially diagnosed with hypothyroidism and referred to us following development of hyperthyroidism in recent times.
Case 1
84-year-old lady with clinical and biochemical hypothyroidism in 2017, initiated on levothyroxine therapy, presented with hyperthyroid symptoms in 2020 confirmed by laboratory testing and strongly positive TSH receptor antibody.
Case 2
66-year-old lady, diagnosed with hypothyroidism in 1998, was initiated on thyroxine developed hyperthyroid symptoms in 2018 leading to stopping levothyroxine therapy. She was treated with Carbimazole for 18-months following which she developed hypothyroidism needing Levothyroxine.
Case 3
51-year-old lady was diagnosed and treated as hypothyroidism from 2015. She developed hyperthyroidism and ophthalmopathy in 2018. She then had Carbimazole therapy, followed by near-total-thyroidectomy in 2019.
Conclusions
The pathophysiology behind the fluctuating thyroid biochemistry is poorly understood. One involves switching of TSH-receptor-blocking-antibodies (TSAb) and TSH-receptor-stimulating-antibodies (TBAb) resulting in hypothyroid and hyperthyroid phase respectively, causing a push-pull effect. Second is initial autoimmune thyroid damage causing underactivity of thyroid followed by the recovery phase where the stimulating antibodies would lead to a hyperactive state. Conversion of hypothyroidism to hyperthyroidism may not be as rare as we have previously thought. The underlying mechanism is still not clear, needing more research in this area. Having this knowledge and awareness will guide the clinicians to suspect the fluctuation in the condition earlier, stop thyroxine timely and counsel patients better about the potential uncertain natural course of the disease.

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P127

Can a person with long standing hypothyroidism develop thyrotoxicosis despite stopping thyroxine?

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A 65-year-old lady who was known to hypothyroidism and was treated with Levothyroxine 100microgram once daily for more than 20 years presented to the endocrine clinic with symptoms and signs of thyrotoxicosis. Apart from Levothyroxine, she was taking over-the-counter multivitamins and Vitamin D. Visual fields were full to confrontation and there was no goitre. Thyrotoxicosis was confirmed biochemically and levothyroxine was stopped. Despite being off Levothyroxine for more than a few months, she remained clinically and biochemically thyrotoxic. TPO antibodies were positive and ultrasound thyroid showed coarse echotexture of thyroid gland suggesting chronic thyroiditis. She was treated with antithyroid drugs and became euthyroid. Hoshimotos and Graves' disease are the two most common autoimmune thyroid problems. Conversion from thyrotoxic to hypothyroid state is common but vice versa is relatively rare. The exact aetiology is unknown but may involve autoimmune mechanisms. It is thought to be due to either switching of blocking TSH receptor antibodies (TRAb) to stimulating ones or predominant effect of TPO antibodies over stimulating TRAb when both antibodies (TPO and TSH receptor antibodies) are present. Clinicians should be mindful that patients with hypothyroidism can become thyrotoxic years down the line and hence regular monitoring of TFTs is required. Also, many such patients will require long term block and replacement antithyroid drugs to ensure fluctuations between stimulating and blocking antibodies does not significantly affect thyroid functional status or thyroid eye disease.

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P128

A case of Transient Neonatal Thyrotoxicosis born to mother with Graves' Disease

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Neonatal autoimmune hyperthyroidism is rare but potentially fatal condition. It occurs in 1-5% of infants born to pregnant mothers with Graves' disease (GD). We present a case of transient neonatal thyrotoxicosis born to pregnant women with GD and high TSH Receptor antibodies. 42 years pregnant lady was referred to Antenatal Endocrine clinic at Walsall Manor Hospital in 15th week of pregnancy with symptoms of Thyrotoxicosis. She has GD and was taking Propylthiourcil 100 mg twice a day. Her bloods showed supressed TSH with Free T4 60pmol/l. Propylthiouracil was switched to carbimazole 30 mg once daily. Carbimazole dose was uptitrated to 50 mg daily with close monitoring of 1-2 weekly Thyroid functions (TFT's). Her TSH Receptor Antibody was 39.8IU/l (very high) when tested at 20 weeks of gestation. Examination revealed a large Goitre with no nodules. She has significant Proptosis but no active Thyroid Eye Disease. Neonatal alert was raised and Obstetricians were advised to monitor foetus due to high Maternal TSH receptor antibody levels. She delivered healthy baby via Caesarean at 39 weeks of Gestation. Baby's TFT's at 48 hours revealed TSH: 13 miu/l with fT4: 23.1pmol/l. TFT's at Day 4 revealed TSH 2.3 miu/l with Ft4: 33.4pmol/l. Baby remained well but TFT's at day 8 indicated worsening Thyrotoxicosis with suppressed TSH and Ft4 54.7pmol/l. Hence Carbimazole was commenced as per Infant's body weight which swiftly resolved thyrotoxicosis and carbimazole weaned off completely at 4th week. Although neonatal GD is usually self-limited, it can be severe, life-threatening. Maternal GD is most common cause of neonatal hyperthyroidism. It is important to monitor baby when TSH receptor antibody is 5 times or more in pregnant women with GD. The higher the maternal stimulatory TSHR-Ab during the third trimester, the greater is the likelihood of neonatal GD.

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P129

COVID 19 Related Thyroiditis

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During the past year and a half during the Covid pandemic it has been noted that cases of abnormal thyroid functions post Covid infection rises and few case report published related to thyroiditis. For this we want to present one of our own patient who had Covid 19 infection in January 2020 with good recovery and after that she had symptoms of hyperthyroidism including palpitation weight loss and heat intolerance. It was confirmed with undetectable TSH and high T4 of 30. She was previously diagnosed with Grave's disease in 2012 treated successfully with medical treatment and in remission since then. Recent TBii was normal, her thyroid uptake scan show low uptake and repeat bloods shows normalization of T4 and suppress TSH. Diagnosis of thyroiditis made. In Conclusions patients with Covid 19 infection shows manifestation of sick euthyroid syndrome and we have to be aware of the possibility of acute and sub-acute thyroiditis.

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P248

Radioactive Iodine Therapy in Benign Thyroid Disease – results from implementing 2007 RCP Guidelines

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Aim
To evaluate the outcomes of radioactive iodine therapy (RAI) in benign thyroid disease following implementation of 2007 Royal College of Physicians (RCP) guidelines in a large NHS foundation trust.
Method
The medical records of patients referred for RAI therapy at Sheffield Teaching Hospitals (UK) between 2013 and 2015 were retrospectively reviewed. Patient data was collected from patients' notes and electronic documents system. The data recorded included pre-treatment patient characteristics, RAI activity dose

and patient outcomes for a 1-year period.
Results
Data was analysed from 194 patients who received RAI therapy for Graves' disease ($n = 144$), toxic multinodular goitre ($n = 38$) and toxic adenoma ($n = 13$). 95% of patients received treatment activity within RCP guidance range, the remainder being adjusted for specific clinical reasons. At 1 year, 71.6% were hypothyroid, 21.2% were euthyroid and 7.2% remained hyperthyroid, resulting in a cure rate of 92.8%. Cure rate for Graves' disease was 94.4% ($n = 144$), toxic multinodular goitre 82.9% ($n = 35$) and toxic adenoma 100% ($n = 13$). For patients rendered hypothyroid, 83.4% occurred within 18 weeks of treatment, and 91% within 6 months. 2% of patients developed thyroid eye disease after RAI treatment.
Conclusion
The implementation of RCP guidelines on radioactive iodine therapy resulted in effective and safe treatment of benign thyroid disease. The majority of patients treated with these guidelines were hypothyroid at 1-year post-treatment.

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P249

Pulse methylprednisolone as preparation for thyroidectomy for drug-resistant amiodarone-induced thyrotoxicosis

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Background
Amiodarone-induced thyrotoxicosis is sometimes extremely difficult to treat necessitating emergency thyroidectomy with perioperative risks including possible thyroid storm. We obtained near normalization of free T3 (FT3) by pulse Methylprednisolone prior to thyroidectomy for drug-resistant Amiodarone-induced thyrotoxicosis.
Case Description
A 56 year old man (BMI 29.7 kg/m^2), with history atrial flutter/fibrillation, episodes of fast AF~200/minute, after unsuccessful ablation therapy, presented with severe Amiodarone-induced thyrotoxicosis, unresponsive to high dose oral Thiamazole (40 mg/day). On admission his FT3 was 24.59 pg/ml (ref. range 2.0-4.4), free T4 (FT4) $>$ 7.77 ng/dl (ref. range 0.93-1.7), TSH $<$ 0.005 uIU/ml. All anti-thyroid antibodies were negative. Thyroid ultrasound revealed normal size thyroid without focal lesions. He initially responded to high dose intravenous Thiamazole (40 mg tds), Lithium Carbonate (250 mg tds) and oral Prednisolone (60 mg od) i.e. after 11 days his FT3 was 5.4 pg/ml, FT4 4.96 ng/dl, but after change to oral thiamazole (20 mg tds), there was a rebound increase of FT3 (to 9.6 pg/ml), and FT4 (to 6.14 ng/dl). Re-administration of intravenous Thiamazole prevented an increase in FT3, but there was further increase in FT4 ($>$ 7.77 ng/dl). On 24th day of admission he was therefore referred for emergency thyroidectomy. Administration of 500 mg of intravenous Methylprednisolone (on a background of oral Prednisolone) within 48 hours resulted in a decrease in FT3 from 9.53 pg/ml to 6.03 pg/ml (2.0-4.4) i.e. only 37% above upper reference range. Following administration of two units of fresh frozen plasma (in order to enhance further thyroid hormone binding) he underwent successful total thyroidectomy (9 days post-surgery: TSH 0.005 uIU/ml, FT3 0.99 pg/ml, FT4 1.16 ng/dl).
Conclusions
Pulse intravenous Methylprednisolone may be a useful adjunct therapy for preparation for thyroidectomy in cases of drug-resistant Amiodarone-induced thyrotoxicosis.

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P250

A case of autoimmune hyperthyroidism in pregnancy after COVID-19 vaccine

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A 36-year-old lady presented at 26-weeks gestation with symptoms of palpitations, anxiety, tremors, and breathlessness. She had received the 1st dose of the mRNA vaccine (Pfizer) for Covid-19 a month prior and her symptoms started a couple of weeks after the vaccine. She was a gravida 4 para 2 with gestational diabetes diagnosed during previous pregnancies and also early on in the current pregnancy requiring insulin treatment maintaining excellent antenatal glycaemic control. She also has pregnancy induced hypertension treated with Labetalol. There is no family history of thyroid disorder. She is an ex-smoker. This pregnancy has been otherwise uneventful specifically without any hyperemesis. Clinical examination demonstrated features of thyrotoxicosis with tremors of the outstretched hands, tachycardia and she did have a diffuse goitre more prominent on the right side with a bruit on auscultation. The investigations confirmed thyrotoxic state with TSH $<$ 0.01 mU/l, free T4 59 pmol/l and free T3 $>$ 30 pmol/l . Anti-TSH receptor antibodies were significantly elevated at 41.8 IU/l (ref $<$1.0) supporting the aetiology of thyrotoxicosis being Graves' disease. After 2 weeks of Carbimazole 30 mg /day there was mild symptom relief and fT4 improving slightly to 43 pmol/l . The Carbimazole was increased to 40 mg and the Labetalol continued. There are recent literature reports of sub-acute thyroiditis and Graves' disease that develop shortly after mRNA Covid-19 vaccination. Our case illustrates a potential association of Graves's disease occurring after the m-RNA vaccine for Covid-19. Vaccine adjuvants have been shown to trigger a pathogenic immune response that can lead to a range of autoimmune diseases, including thyroid disorders. These are well recognised in the literature but less commonly perceived in routine clinical practice and requires a high index of suspicion especially as newer vaccines are also on the horizon for SARS-Cov-2.

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P251

Iodine deficiency causing goitre and deranged thyroid function

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Background
Iodine deficiency is a well known cause of goitre and abnormal thyroid function but is rare in patients born in the UK. Iodine is primarily found in fish and dairy products and patients who avoid these foods may be at risk of iodine deficiency.
Case
A 22 year old gentleman was referred to endocrine clinic with an unusual pattern of thyroid function tests (TFTs). He had a goitre on examination. He had a background of irritable bowel syndrome and had minimal fish, fruit and vegetables and no dairy, bread or nuts in his diet. He had a normal TSH at 3.8 mU/l (0.2 to 4.5), low free T4 at 7 pmol/l (9 to 21) with raised free T3 at 5.7 pmol/l (2.5 to 4.9). The unusual pattern was confirmed at a second laboratory with a different immunoassay. Results were additionally confirmed following post-blocking tube, to remove antibody interference. Samples were sent to Addenbrooke's laboratory for analysis and iodine deficiency was suggested as a possible cause. He underwent an ultrasound of thyroid which demonstrated mild global enlargement of the thyroid with reduced echogenicity and hypervascularity throughout. Opinion was appearances were abnormal but nonspecific. He was given dietary advice regarding sources of iodine and commenced Forceval. 2 months later his thyroid function had normalised. He stopped taking his Forceval but had recurrence of fatigue so recommenced his Forceval with symptoms resolving. His thyroid function has remained normal with adequate iodine supplementation.
Discussion
Iodine deficiency, whilst uncommon in the UK, can be a cause of abnormal thyroid function and goitre. Although it is rare, it should be considered in unusual patterns of TFTs, particularly in patients who have restrictive diets or dietary intolerances. Thyroid function can be normalised with dietary advice and supplementation if required.

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P252

? Toxic nodule or Thyroid Carcinoma

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Introduction
Risk of thyroid cancer is 17-32% in cold nodules and <1 % in hot nodules. Hot nodules are usually associated with Thyrotoxicosis. Patients with thyroid carcinoma are usually euthyroid but may be associated with hypothyroidism. We report 3 patients with hyperthyroidism and associated thyroid carcinoma.
Case 1
A 17 years old lady presented with a lump in the neck and examination revealed prominent nodule on the right. TFTs were suggestive of hyperthyroidism and she achieved euthyroidism within 6 weeks of treatment with carbimazole. USS showed U3 right Thyroid nodule along with multiple benign cystic nodules. FNA reported as appearances consistent with thyroid neoplasm. She underwent right thyroid lobectomy and histology confirmed papillary thyroid carcinoma and also hurtle cell adenoma.
Case 2
A 58 years old lady was found to have subclinical hyperthyroidism when she presented with history of feeling generally unwell and significant weight loss. She had no symptoms of hyperthyroidism but examination revealed multinodular goitre with a prominent nodule in the right and USS showed nodules consistent with (U3) and (U4) and FNA was suggestive of follicular lesion. She underwent total thyroidectomy and histology confirmed Multinodular goitre and 2 papillary micro carcinomas (follicular Variant).
Case 3
A 72 who was on levothyroxine for hypothyroidism previously complained of hoarse voice and night sweats and was found to have subclinical hypothyroidism on the blood test. On examination thyroid gland was felt bulky, USS showed multiple nodules and one of them was consistent with U3. FNA is consistent with follicular lesion and she is currently awaiting surgery.
Discussion
Thyroid nodules are present in 75% of population and only about 1-5% are malignant. We present our patients t to highlight the importance of performing USS in women who presents with goitre and associated hyperthyroidism but with a prominent nodule on examination.

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P253

A case of Pituitary hyperplasia in patient with Graves' disease over treated with carbimazole lead to severe hypothyroidism

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Pituitary hyperplasia is a relatively common condition that occurs in both physiological and pathological states. Pregnancy is the most common condition associated with physiological pituitary enlargement, associated primarily with lactotroph hyperplasia. Pathological hyperplasia has been shown to be associated with end organ insufficiency from primary gonadal insufficiency, primary adrenal insufficiency, and primary hypothyroidism. We present the case of a 33-year-old male with profound primary hypothyroidism following treatment of Graves' disease with Carbimazole treatment and secondary pituitary hyperplasia that resolved after thyroid hormone supplementation (175 mcg/day) in addition to Carbimazole (40 mg daily) treatment. Our patient is a 33-year-old Caucasian male presented with symptoms of hyperthyroidism due to Graves' disease and he was treated with carbimazole. A few months later he presented with symptoms of severe headache, lack of energy, exhausted and symptoms of low libido and sex drive. Repeat Thyroid function test, revealed a thyroid stimulating hormone (TSH) >150 mU/l (NR, 0.35-5.5) FT4 4 (NR, 9-23 pmol/l), free T3, 2.2 (NR 3.5-6.5 pmol/l), Thyroid stimulating inhibiting immunoglobulin (TBII) 5 IU/l, cortisol 334 nmol, serum testosterone 1.7 nmol/l , LH 1.3 IU/l, FSH 1.5 IU/l, and serum prolactin 546 (45-375 mIU/l). MRI of the pituitary revealed an enlarged pituitary gland with suprasellar extension without optic nerve involvement. Repeat MRI Scan of the pituitary gland a few months later revealed normal structure of pituitary gland.
Conclusion
Pituitary hyperplasia in primary hypothyroidism is not uncommon and close follow up of patient with hyperthyroidism is very important to avoid patient from developing a severe hypothyroidism while in medical treatment.

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P254

Assessment of the efficacy of follicular phase thyroid hormone concentrations in predicting an endometriosis diagnosis

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Endometriosis is a common gynaecological condition caused by the abnormal growth of endometrial-like tissue outside the uterus. There are currently no biomarkers validated for non-invasive diagnosis and the exact aetiology is unknown; however, the association between endometriosis and thyroid dysfunction has recently been reported. We aimed to investigate the value of thyroid hormone testing in predicting the odds of an endometriosis diagnosis. Retrospective data was taken from normo-ovulatory women who undertook a Hertility Health at-home blood test to measure free thyroxine (FT4) and thyroid-stimulating hormone (TSH) among other reproductive hormones. Via a virtual questionnaire, cases ($n = 17$) had a self-reported diagnosis of endometriosis whilst controls ($n = 208$) confirmed that they had not been diagnosed. Exclusion criteria for both cohorts included diagnoses of polycystic ovary syndrome, primary ovarian insufficiency, fibroids, pelvic inflammatory disease and fallopian tube blockage. Capillary blood sampling was performed on day 3 of the menstrual cycle; serum FT4 and TSH concentrations were measured using enzyme immunoassays. Multivariate logistic regression and ROC curves were used to assess whether FT4 or TSH concentrations were associated with an endometriosis diagnosis. Thyroid hormone measurements were log-transformed prior to analysis. P values, adjusted odds ratios [OR] and areas under ROC curves [AUC] have been reported. A multivariate logistic regression model which included TSH concentration, age, exercise frequency, recreational drug use, smoking status and BMI was found to be statistically significant ($P = 0.0016$, OR [1.80], AUC [0.94]). Similarly, statistical significance was found when FT4 was incorporated in a logistic regression model with the same demographic covariates ($P = 0.0089$, OR [0.01], AUC [0.89]). These data suggest that TSH or FT4 concentrations in combination with the demographic variables described above may have some predictive value in assessing the likelihood of an endometriosis diagnosis in normo-ovulatory women. However, more data is required to evaluate the accuracy and clinical impact of this model.

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P255

Graves' thyrotoxicosis complicated by mental health disorder and twin pregnancy

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We present a case of a young female, who was diagnosed with Graves' thyrotoxicosis in 2019 with very high TSH Receptor antibody. She had a goitre and mild thyroid ophthalmopathy and was commenced on carbimazole. She was followed up in the Endocrine Clinic and carbimazole was titrated according to the clinical and biochemical picture. Her past medical history included epilepsy, generalised anxiety, and emotionally unstable personality disorder. She had difficult social circumstances with four young children, worsening anxiety and continued to smoke cigarettes. She did not attend numerous clinic appointments and was not diligent with repeat thyroid function tests. In March 2020, her carbimazole dose was increased due to worsening thyroid function and thyrotoxic symptoms. She was also experiencing obstructive symptoms from the goitre. The patient admitted to poor adherence with medication and was therefore given a dosette box. Coincidentally, in the same month she was found to be pregnant with MCMA twin pregnancy. The patient was keen to have thyroidectomy due to ongoing symptoms, swallowing difficulty and poor tolerance to carbimazole due to vomiting. She was admitted to Watford General Hospital for pre-operative optimisation of thyrotoxicosis, planned inpatient thyroidectomy and termination of pregnancy (TOP). She was started on high dose propylthiouracil (PTU) and Lugol's iodine was considered if the patient consented to TOP. Euthyroidism was achieved with high dose PTU and Lugol's iodine was not required. She had a successful TOP and thyroidectomy. In early pregnancy, patients can present with gestational thyrotoxicosis, which can worsen the pre-existing Graves' biochemistry. This is an interesting and complex case involving the multi-disciplinary team. Management of thyrotoxicosis was laborious due to poor compliance, intolerance to high doses of carbimazole, complex social circumstances and unstable decision-making due to patient's mental health disorder. This situation was further complicated by the unplanned pregnancy.

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P256

Audit of Liothyronine Prescribing at the University Hospitals of Leicester (UHL) NHS Trust

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Introduction
Levothyroxine is the first choice treatment for patients with hypothyroidism However, some people would continue to have symptoms of thyroid disease despite biochemical control on levothyroxine. Others might be intolerant to levothyroxine.
Aim
The aim of this audit is to evaluate UHL endocrinology practice against local and national guidelines with regards to prescribing and monitoring of liothyronine treatment in 2019.

- Retrospective data collection
- Period from January 2019 to January 2020
- List of patients was provided by UHL pharmacy
- Electronic database search
- Improvement in symptoms of tiredness, dizziness and lack of sleep was reported by 17 of 21 patients after starting liothyronine.
- Well-being was assessed using Quality of Life (QoL) questionnaire in 13 of 21 patients using SF-36. Only 2 patients had their post-treatment outcome documented on subsequent clinic follow up.
- Bone health was assessed using Dual Energy X-ray Absorptiometry (DEXA) scan in 3 of 21 patients. Two had osteopenia and one had osteoporosis.

Conclusion
1) There is a small cohort of patients with hypothyroidism in Leicestershire who clinically improve on liothyronine compared with conventional replacement.
2) No biochemical evidence of over-replacement in liothyronine-naïve patients started on treatment at UHL
3) There was biochemical evidence of over-replacement in patients established on liothyronine prior to UHL referral.
4) We need formal quantitative documentation of SF-36 scores after treatment.
5) We need to be more proactive at looking for evidence complications like osteoporosis/osteopenia and atrial fibrillation.

Table 1: demographic and patient information

Demographics	Total number = 21
Age	23 – 85 years (average = 53 years)
Sex	Female = 20, male = 1
LT3 treatment	
LT3 was Initiated in clinic	5
Already on LT3	16
Sole LT3	4
Combined LT4/lT3	17
LT3 discontinuation	
Attempted	5
Not attempted	16
LT3 dose	5 - 70 mg (average = 15.2 mg)
LT4 dose	50 - 325 mg (average = 114.7 mg)

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P257

Hashimoto's Encephalopathy: organic psychosis vs catatonic schizophrenia

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32 year old female with no prior past medical problems presented to hospital with a two week history of rapid onset delusional psychosis with religious themes, paranoid ideas and rapidly developing into catatonia. There was no previous history of psychiatric disorders. On physical examination the Glasgow Coma Score (GCS) was 15 and she was responding to visual hallucinations; speaking to imaginary person and reported seeing objects. She was afebrile and bedside observations were within normal range. Systemic examination was grossly normal except bilateral brisk reflexes were elicited. Soon after admission her GCS started to deteriorate and she became catatonic, mumbling words and maintaining spontaneous eye movements (V2 E4 M3). Initial investigations including full blood count, renal function, liver function, CRP and ESR were within normal range. Her thyroid function results demonstrated an elevated TSH 46mU/l (0.27-4.2), Free T4 10 pmol/l (12-22), Free T3 4.0 pmol/l (3.1-6.8), antiTPO antibodies present in elevated concentrations >999.9 IU/l (0-5.5). The remainder of the pituitary profile was within normal range. MRI of brain, CT CAP and ultrasound of abdomen were reported as normal. Lumbar puncture had normal cell count and protein and glucose. NMDA antibodies were negative. Subsequent focused neurological assessment found sustained ankle clonus and bilaterally extensor planters. Diagnosis of Hashimoto's Encephalopathy was made and she was commenced on methylprednisolone, thyroxine and lorazepam after consultation with neurology and psychiatry teams. Her symptoms improved dramatically within 2 weeks of treatment and was able to be discharged home with outpatient follow up. Hashimoto's Encephalopathy is a rare syndrome associated with autoimmune thyroiditis, first reported in 1966 and remains an important differential in patients with psychosis and needs prompt recognition for appropriate treatment to be commenced.

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P258

Case Study: Profound iatrogenic hypothyroidism in early pregnancy secondary to propylthiouracil

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A 36-year-old woman was admitted with newly diagnosed Grave's disease due to significant symptoms. Blood results revealed fT4 83.2 (pmol/l) TSH <0.01 (mIU/l), and TSH Receptor Antibody 4.56 (0-0.4 U/l)). She was commenced on Propylthiouracil (PTU) thrice daily alongside Propranolol. She had a blood test in 4 months' time, when she was 5 weeks pregnant. Blood results suggested profound hypothyroidism with fT4 4.7 (pmol/l) and TSH 82.02 (mIU/l), and she was commenced on 75 mcg Levothyroxine/day. She and her partner were counselled on the potential adverse effects of hypothyroidism during early pregnancy, and they decided to continue with the pregnancy. At 9 weeks gestation, the patient reported palpitations and tremors, and was tachycardic on examination. Blood tests revealed fT4 20.4 (pmol/l) and TSH 0.06 (mIU/l). Levothyroxine was stopped and she was re-commenced on 50 mg PTU/day due to sustained symptoms. PTU was stopped at 15 weeks gestation as TFTs were within normal limits and she remained clinically euthyroid. Anomaly scan at 20 weeks reported no congenital abnormalities, foetal goitre or tachycardia. The patient underwent an elective C-section at 39 weeks for a history of previous C-sections. No intrapartum or postpartum complications were noted. APGAR score was 9,10,10, and the baby's birth weight was 3860g (82.8 centile). At a clinic review at 9 months post-partum, the patient was clinically euthyroid with TFTs within normal limits. At 16 months post-partum, she reported no developmental or behavioural concerns with her baby. As hypothyroidism was detected early in the pregnancy, this allowed for prompt initiation of treatment with thyroxine, which may have contributed to the positive outcome. Clinicians and midwives should be aware of the importance of pre-conception counselling and TFT monitoring prior to pregnancy in patients with known thyroid disease.

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Nursing Practice

P130

Assessing the effectiveness of the endocrine specialist nurses (ESN) hydrocortisone education video created during covid-19 pandemic

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Background
During Covid-19 pandemic, we recognised the importance of optimising adrenal insufficient patients' ability to manage adrenal crisis and seek medical intervention thereby reducing the need for more intensive support. Evidence suggests omission of steroids during an adrenal crisis is a medical emergency and can be fatal. Research by National Reporting Learning System (2020) identified 4 deaths, 4 admissions to critical care, 320 incidents relating to steroid replacement. ESN's were unable to facilitate face to face education, an education video lasting

12 minutes was created for patients to access online. Video registered more than 4K views. Video included information - how to manage steroids during illness/stress and demonstrates how/when to administer emergency steroid injection.
Method
Randomly selected 150 adrenal insufficiency patients at Liverpool University Hospital. Using a mixed methodology approach, created a feedback questionnaire assessing patient's knowledge base and suggestions to improve service. A retrospective audit analysed both qualitative and quantitative data.
Results
Received 56 responses over a 4 month period. 62% found video extremely helpful, 27% very helpful and 11% helpful. 90% information delivered; as much as they wanted, 5% more than and 5% not as much. 96%-video easily comprehendible. 91% previously received information – 60% via ESN's, 32% via medical team, 5% from other source. Approximately 63.5% were fully aware of all symptoms of low cortisol. 41 % felt more confident about managing illness, 48% little more confident. 91% would administer the emergency steroid injection if they developed adrenal crisis symptoms. 93% already possess the emergency injection. Overall, 86% disclosed written responses to video – all positive.
Conclusions
91% of patients' would administer the emergency steroid injection, potentially reducing need for more intensive support /fatality. Aim of this initiative is to reach and support a larger number of patients in avoiding adrenal crisis and improving steroid management.

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P131

The value of dual energy X-ray absorptiometry (DXA) scan in patients at low risk of fragility fracture

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Background
University Hospitals Birmingham NHS Foundation Trust offers a comprehensive bone health assessment, through the Fracture Liaison Service (FLS), to individuals who sustain fragility fracture/s. Patients requiring assessment are identified daily through admissions from Accident and Emergency and Trauma and Orthopaedics. A bone density scan is requested for further investigations according to the FRAX tool to identify more accurately their fracture risk and to help define the management plan (ROS, 2019). However, the FRAX tool is a guide, and NICE guidance (2017) states that the tool can underestimate fracture risk. Therefore, for those patients considered to be low risk but with additional risk factors, DXA scan is arranged to better estimate their future fracture risk.
Aim
To assess the value of bone density scans in patients classed as low risk of sustaining a future fracture.
Methodology
A retrospective audit was completed using the FLS database for those who received a DXA scan (01 Jan 2020 – 18 June 2021) and were classed as low risk at baseline FRAX.
Findings
Between 01 Jan 2020 to 18 June 2021 a total of 137 patients received a bone density scan. Of the 137 patients, only 1 showed osteoporosis (NICE criteria for a T score $<$ -2.5) and 23 had osteopenia (T score -1.0 - - 2.5). These 136 patients required no further management, therefore supports the recommendation from FRAX for lifestyle advice only.
Conclusions
We found that patients classed as low risk by baseline FRAX, regardless of additional risk factors, do not require a bone density scan as the result does not change the management plan. Low risk patients rarely show osteoporosis on DXA and therefore emphasising lifestyle advice is important without the need for radiological intervention. This reduces demand for DXA scans and additional patient hospital appointments.

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P132

Systematic review of behavioural change interventions for the prevention of adrenal crisis in adults with primary adrenal insufficiency – An infographic interpretation

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Background
The incidence of adrenal crisis remains constant, despite the introduction of behavioural interventions to educate and empower patients. To increase the success of future behaviour change interventions, theoretically informed and empirically supported behaviour change frameworks are available. The current review aimed to identify and evaluate available evidence of interventions used to prevent adrenal crisis in people with primary adrenal insufficiency to inform future intervention development.
Methods
We performed a search of 10 databases and trial registries up to October 2020 for studies about adults $\geq$ 18-years-old with primary adrenal insufficiency, taking glucocorticoid replacement, and exposed to a behavioural intervention. Risk of bias in each study was assessed using the AXIS and Mixed Method Appraisal Tools. Findings were reported narratively. Intervention components were described using the TiDIER checklist. The behaviour change techniques employed in each intervention were synthesised and then mapped to behaviour change techniques taxonomy, theoretical domains framework, and Capabilities-Opportunities-Motivation-Behaviour (COM-B) model.
Results
Seven European studies (1999 – 2020) were included. One study focused on patients with primary adrenal insufficiency, and the remaining studies focused on both primary and secondary adrenal insufficiency. Patient education was the focus of all interventions to improve patient knowledge and self-management. Most studies did not measure their intervention's effectiveness. All studies utilised the same two behaviour change techniques, 'instruction on how to perform a behaviour' and 'pharmacological support'. Six out of 14 theoretical domains were not targeted. Study quality was moderate to high. There were no randomised controlled trials.
Conclusions
The systematic review showed that most studies examining behavioural interventions developed to improve knowledge and self-management and prevent adrenal crisis, did not measure their effectiveness. Interventions targeted limited theoretical domains and behaviour change techniques. Effectiveness of interventions require testing in randomised controlled trials. The review extends knowledge and informs development of future behavioural interventions.

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P133

Development of interventions to prevent adrenal crisis – How can application of behaviour change theory and intervention frameworks inform practice?

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Background
Behavioural interventions have been developed to empower patients with adrenal insufficiency and prevent adrenal crisis. Behavioural theory, such as the theoretical domains framework, can inform future intervention development. The current systematic review aims to describe what techniques have been employed in previous interventions and highlight neglected behavioural barriers that could be targeted in future interventions.
Methods
We performed a systematic review to identify studies in which a behavioural intervention was used to prevent adrenal crisis in patients with primary adrenal insufficiency. Data about the interventions were extracted by two reviewers and described narratively. Intervention components were described using the 'better

reporting of interventions' (TiDIER) checklist. Active components of the interventions were described using the behaviour change techniques (BCTs) taxonomy (v1). The techniques employed were then mapped onto the barriers and facilitators they were best suited to using the 14 theoretical domains described in the Theoretical Domains Framework and the capabilities-opportunities-motivation-behaviour (COM-B) model.
Results
We identified seven observational studies, no RCTs. Studies assessed their intervention's effectiveness on adrenal crises ($n = 4$), and changes in patient knowledge ($n = 4$). Assessment of knowledge was inconsistent across studies and improvement in knowledge and self-management was reported in only three studies. Mean number of BCT's per intervention was 6 (3-8). The most frequently targeted domains were 'knowledge', social influence', and 'emotion'. Seven of the theoretical domains were not targeted in any studies, including 'beliefs about capabilities', 'reinforcement', 'intentions',' goals', 'social professional role and identity', 'memory, attention and decision processes' and 'behavioural regulation'.
Conclusions
Studies describing behavioural interventions to prevent adrenal crises are limited in number and rigor. Future interventions could target neglected barriers, eg, patients' ability to regulate their behaviour and goals. Linkages between domains and BCTs offer some suggestions forward, which must be tailored to meet the needs of diverse groups of patients.

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Late Breaking

LB1

Effect of Dolutegravir on adrenal function in HIV patients on ARVs using serum and salivary cortisol assay

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Background
The use of Dolutegravir (DTG) in the treatment of patients with HIV has been associated with reports of unexpected excess weight gain. The present study aimed to investigate the effect of DTG on the adrenal cortisol levels of HIV patients initiated on antiretroviral therapy (ART).
Methods
Adult patients ($\geq$18 years) newly initiated on ART were recruited into two groups (n-100 participants in each group). One group was initiated on a DTG-based regimen and compared to an age and sex-matched group initiated on non-DTG-based ART, between July 2020 and July 2021. A third non-HIV infected age- and sex-matched group of adults ($n = 100$) was used as the negative control. Serum cortisol was measured at baseline, after 30 mins and after 1-hour post-stimulation with 250 mg of synthetic ACTH. Salivary cortisol was also measured. The serum and salivary cortisol levels of the two groups were compared using a chi-square test.
Results
The mean basal serum cortisol in the DTG based ART regimen group was similar to that in the non-DTG based ART regimen group (323.79$\pm$9.06 mmol/l vs 318.94$\pm$10.37 mmol, respectively), $P = 0.338$. Basal salivary cortisol (8 am) was also similar between the DTG-based and non-DTG-based groups: (1.57$\pm$0.09 nmol vs 1.68$\pm$0.15nmol, respectively), $P = 0.224$. After stimulation with 250 mg of synthetic ACTH, there was no statistically significant difference in the serum and salivary cortisol levels of the two groups. Normal adrenal function was observed in 63.5%, and 65.8% of the population on DTG, non-DTG groups respectively $P = 0.776$ and adrenal hyperfunction in13.4%,12.7% respectively ($P = 0.537$).
Conclusion
This study has demonstrated that DTG does not cause adrenal dysfunction in adult patients with HIV and it can be deduced that metabolic side effects reported from the use of DTG may not be from excess cortisol. There is the need to conduct large scale multicenter studies.

10.1530/endoabs.77.LB1

LB2

Derivatisation for separation and detection of estrogens by ion mobility-mass spectrometry

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Estrogens are sex steroids with both protective or adverse roles in health and disease. For example, in pulmonary arterial hypertension, some estrogen metabolites are pro-angiogenic while others are anti-angiogenic. Measuring estrogenic profiles is challenging since many estrogens are isomeric and isobaric. Normally estrogen isomers are separated using liquid chromatography (LC) prior to mass spectrometry (MS), revealing overall quantities, but not molecular distributions in complex tissues. MS imaging (MSI) is a novel approach that visualises the localisation of metabolites on a tissue surface, but alone cannot distinguish isomers. Therefore, orthogonal separation is required. Here we hypothesise this could be achieved by ion mobility spectrometry (IMS) after derivatisation. In IMS, molecules are separated based on 3D shape, size, and charge, denoted as collision cross section (CCS). We assessed separation of a panel of estrogens using IMS, both intact and following shape modification by derivatisation with 1-(2,4-dinitro-5-fluorophenyl)-4,4- dimethylpiperazinium iodide (MPPZ), dansyl chloride (dansyl), and 1-(2,4-dinitro-5-fluorophenyl)-4-methylpiperazine (PPZ). IMS analyses were conducted on a Waters Synapt G2-Si and a Select Series cyclic IMS (cIMS). nderivatized estrogens could not be separated by IMS, where the minimum CCS difference necessary for separation was ~8 Å^2. Separation of some isomers was achieved using PPZ and dansyl derivatisation (hydroxyestrones, hydroxyestradiols). For hydroxyestradiols (11βOHE2, 16βOHE2, 16αOHE2), CCS values increased upon derivatisation with PPZ, from 168.60, 170.63, 172.19 Å^2 to 229.67, 242.45, 251.29 Å^2, respectively, allowing full separation. Separation of underivatised estrogens was achieved by cIMS with multiple passes, e.g., the hydroxyestradiols (2OHE2, 4OHE2, 16αOHE2) were separated in negative ion mode with 13 passes. Furthermore, the overlapping mass +2 isotopologue of estrone was separated from 17β-estradiol using 20 passes. Thus, we have demonstrated that IMS/cIMS offer an alternative separation which can be used in conjunction with LC or MSI, improving selectivity and allowing sampling without chromatography.

10.1530/endoabs.77.LB2

LB3

The importance of high-volume specialist centres. An audit of bilateral adrenal vein catheterization success rates

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Background
Adrenal vein sampling (AVS) is the gold-standard for localizing the site of autonomous aldosterone production in patients with primary aldosteronism (PA). The procedure is technically challenging with a reported success rate of 50-95%.
Aim
To audit the success rate of AVS at a regional referral unit.
Standards
No set standard exists. 80% success rate was taken as the minimum acceptable standard for a tertiary referral centre. This is the published, pooled average success rate from high-volume centres internationally.
Method
Patients who underwent AVS at our regional referral centre in 2019 were identified from the Radiology Information System (RIS) and their pathology results reviewed. AVS was deemed successful when the cortisol levels from both adrenal vein samples were at least double that of the sample taken from the low inferior vena cava. Samples were obtained sequentially with no ACTH stimulation via a femoral venous approach.
Results
35 patients with a biochemical diagnosis of PA, aged between 35-74 years, underwent AVS. 33/35 (94%) AVS were successful. There were no major complications. The median fluoroscopy time was 11.1 min [3 min – 51 min]. The audit was repeated in 2020. 29 patients aged between 25-72 years underwent AVS in 2020. AVS was successful in 28/29 (96.6%) with no major complications. The median fluoroscopy time was 7.3 min [2.9 min – 22.9 min], which was significantly lower compared to the previous year ($P = 0.02$).
Conclusions
This audit shows that adequate experience and exposure of the operator is crucial in achieving optimal outcomes. AVS in our centre was performed by a single operator carrying out at least two AVS procedures per month. As with specialist surgery where better outcomes are achieved in high-volume centres, we suggest

that AVS should only be carried out in selected high-volume centres by experienced operators.

10.1530/endoabs.77.LB3

LB4

Not your regular incidentaloma

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Adrenal Leiomyomas are very rare tumours. 20 cases have been reported to date. Their management remains difficult and challenging. They tend to present with flank or abdominal pain and have very little biochemical activity, if any.

Case presentation

We present a case of a young 44 year old female. She was referred to Endocrinology services with a history of 2 weeks abdominal pain. She underwent an ultrasound organised in primary care which was suspicious for left upper quadrant mass. Except left sided abdominal pain and palpable mass, she looked well with normal blood pressure and no features of Cushings. CT abdomen identified a large left sided supra-renal mass (17 cm) in close association to the kidney. An Overnight dexamethasone suppression test, plasma metanephrines, aldosterone renin ratio as well as her urine steroid profile was normal. Tumour markers were not elevated. She was referred to adrenal MDT. The working diagnosis was of Adrenal carcinoma. She underwent radical left adrenalectomy and nephrectomy. Histopathology was consistent with a diagnosis of leiomyoma.

Clinical discussion

Adrenal leiomyomas are rare tumours of the adrenal gland. They originate from the smooth muscles of adrenal vein. On imaging these tumours have a heterogeneous pattern making it difficult to ascertain the nature of the mass. Literature search provides evidence supporting biochemical activity in these tumours. Such as “slight elevation of epinephrine and norepinephrine in left adrenal and left renal vein" Another example is elevated blood metaneprines.

Conclusion

Not all adrenal masses are malignant. Non-functioning large masses are almost always considered to be sinister until proven otherwise. Adrenal leomyomas are rare, non-functional, benign tumours needing no further imaging after removal. Adrenal biopsy carries the risk of tumour seeding. The question remains if tumour biopsy would change surgical management in case of benign tumours but does the risk outweigh the benefit.

10.1530/endoabs.77.LB4

LB5

A rare presentation of malignant paraganglioma

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Malignant paraganglioma causing skull metastasis is rare. We describe a 49-year-old male who gives a history of a mass on the vertex of the scalp, noticed a year before presentation and which grew rapidly from 1 cm to 5 cm. His past medical history is significant for hypertension (treated with Amlodipine), and back pain and headache on a regular basis. On MRI the mass measured 5.7 cm craniocaudal, by 7 cm AP and 6.9 cm transverse. Additionally, multiple additional focal areas of bony abnormality (skull base, mandible and upper cervical spine) were present. Multiple myeloma screen was negative, but bone marrow aspirate revealed likely paraganglioma. A CT trunk showed multiple metastasis to ribs and a destructing metastasis to T9 vertebrae as well as a soft tissue mass in the left hemi-pelvis measuring 6.3 cm by 4.2 cm. A PET-CT scan showed extensive uptake in bone and soft tissue disease including lesions within the liver and possible infiltration around the kidneys. Plasma metanephrines were significantly raised: normetanephrine was 47538 pmol/l (<1180) and plasma 3-methoxytyramine measured 675 pmol/l (<180). A rib biopsy result was consistent with bone marrow infiltration by metastatic paraganglioma and Ki67 of 13.1%. The diagnosis of malignant paraganglioma with diffuse metastases was concluded and he was treated with radiotherapy for T9 vertebrae for impending cord compression and also started on Phenoxybenzamine and Propranolol as alpha and beta blockade respectively. He was started on Temozolomide and is being considered for PRRT. Repeat PET-CT showed decreased FDG uptake in previously described bone lesions. Genetic analysis confirms mutation of SDHB gene. This case shows the importance of considering malignant paraganglioma or phaeochromocytoma as a differential diagnosis of bone metastasis including skull, as well as measuring plasma metanephrines before considering biopsy of suspicious soft tissue masses.

10.1530/endoabs.77.LB5

LB6

An unusually small but symptomatic Phaeochromocytoma

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Phaeochromocytomas show a positive correlation between tumour size, metanephrines level and symptoms. Small tumours (<1 cm) are usually asymptomatic and are picked up through hereditary screening or surveillance of previous tumours. We present a 72-year-old gentleman who was referred to the Endocrinology service with symptoms of palpitations, sweating, dizziness and hypertension for several years. He was investigated for palpitations but no cardiac arrhythmias were present. Plasma metanephrine was mildly elevated at 559 pmol/l (<510 pmol/l). Serial measurement of plasma metanephrine remained mildly raised levels, with highest recorded level of 730 pmol/l. Chromogranin B showed a sequential increase from from 137 pmol/l (<149 pmol/l) to 252 pmol/l. CT adrenals revealed a 9 mm left adrenal nodule with a precontrast attenuation of 19HU, and a relative and absolute washout of 43% and 55% respectively. The nodule showed avid uptake on MIBG scan. In view of these findings, the patient was referred for laparoscopic adrenalectomy which confirmed the presence of a pheochromocytoma. This case shows that a phaeochromocytoma may give rise to troublesome symptoms despite its small size and mildly raised metanephrines. Follow-up with sequential plasma metanephrines and Chromogranin B helped establish the correct diagnosis and treatment for small phaeochromocytoma.

10.1530/endoabs.77.LB6

LB7

Vitamin D deficiency in female healthcare workers during a pandemic

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One of the most significant health measures implemented during the COVID-19 pandemic has been extended periods of lockdown. Vitamin D is essential for many biological functions including pregnancy and bone health and modulate the immune system. Many studies also suggested a beneficial effect of replenished stores of vitamin D (25(OH)D >50 nmol/l) against severe and long term COVID-19 and self-supplementation is recommended by the government. Here we report on the vitamin D status in a cohort of HCW during the 3rd UK lockdown. Vitamin D metabolites 25(OH)D and $24,25(OH)_2D$ were measured simultaneously by LCMS and $1,25(OH)_2D$ was measured by immunoassay on a cohort of HCW in January 2021. Of the 83 female HCW (42.3 ± 10.5 years; 94% white), only 45.8% were 25(OH)D replete, 36.1% were insufficient (25-49 nmol/l) and 18.1.0% were deficient (<25 nmol/l) With 54% having 25(OH)D <50 nmol/l, HCW were recommended to take D3 supplements as per NICE guidance. After 8 weeks, 25(OH)D increased significantly (+32.5 nmol/l on average, $P < 0.001$). Only 1.2% of HCW were still deficient and 80.7% were now replete. Concomitantly, $24,25(OH)_2D$ increased significantly ($P < 0.001$) and $1,25(OH)_2D$ also increased by 10.2 pmol/l on average ($P = 0.003$). Serum 25(OH)D concentrations are at their lowest in winter with expected prevalence of deficiency of 10% in Caucasian women. We observed a high proportion of 25(OH)D deficient HCW (18%). Pandemic restrictions in the UK have aggravated the vitamin D status of female healthcare workers which may have caused supplementary health problems including higher pregnancy risks. Stronger recommendations on vitamin D supplementation should be offered to the population and women during episodes of lockdown.

10.1530/endoabs.77.LB7

LB8

An atypical case of hypercalcaemia extending into adulthood in a patient with Williams-Beuren Syndrome

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A 33 year old man with Williams-Beuren Syndrome (WBS) was admitted following the finding of symptomatic hypercalcaemia (calcium 3.12 mmol/l (2.2-2.6)). Infantile hypercalcaemia is characteristic of WBS, however almost always, calcium levels return to the normal range by ~12 months of age. The patient also had an acute kidney injury (eGFR 39ml/min/1.73^2, creatinine 178 mmol/l (59-104)), secondary to hypercalcaemia. The patient complained of polydipsia. Past medical history included features typical of WBS such as supra-valvular aortic stenosis, pulmonary stenosis hypertension, intellectual disability and previous endocarditis. Medications included warfarin and bisoprolol. The hypercalcaemia was initially considered to be secondary to excessive calcium ingestion, as the patient drank 4-6 pints of milk per day. However, following a reduction in intake to 1 pint per day, calcium levels measured 2.98 mmol/l, prompting further investigations. Hyperparathyroidism and excess vitamin D were ruled out as potential causes with PTH 2.2 pmol/l (1.9-6.4) and 25OH Vitamin D 31 nmol/l (>50). There were no clinical or radiological features suggestive of a malignant or granulomatous cause. A trial of cinacalcet (30 mg BD) failed to resolve the hypercalcaemia (calcium 3.06 mmol/l), therefore this was discontinued. The patient was commenced on IV pamidronate (60 mg). Six weeks following the infusion, the hypercalcaemia had returned to the reference range (calcium 2.54 mmol/l). On-going monitoring delineated further hypercalcaemia ten months post-infusion (calcium 2.84 mmol/l). Therefore, the patient required another pamidronate infusion, which once again lowered calcium levels. The frequency of pamidronate infusions since has been on a 6-12 monthly basis. Renal function has recovered following the correction of his hypercalcaemia (eGFR 68 and creatinine 109). The continuing management plan for this patient includes long term calcium and vitamin D monitoring and pamidronate infusions as required. In patients with WBS, consideration should be given to 6-12 monthly calcium assessment, even in adulthood and consideration of treatment on a similar frequency with bisphosphonates.

10.1530/endoabs.77.LB8

LB9

Oncogenic osteomalacia: a rare cause of hypophosphataemia

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Background
Oncogenic osteomalacia is a paraneoplastic syndrome that occurs in the context of an FGF23 secreting tumour. We describe a case of a 42 year old gentleman who presented with this rare cause of hypophosphataemia.
Clinical Case
This gentleman presented with a history of multiple fragility fractures, and generalised bone and muscular pain. His biochemistry showed: serum phosphate 0.52 mmol/l (reference range 0.80-1.50 mmol/l), adjusted calcium 2.17 mmol/l (2.20-2.60 mmol/l), 25OH Vitamin D 79 nmol/l (>50 nmol/l), 1,25diOH Vitamin D 88 pmol/l (20-120 pmol/l) and an inappropriately elevated urinary fractional excretion of phosphate. Genetic testing for hypophosphatemic rickets showed no pathogenic variants detected in DMP1, ENPP1, FGF23, PHEX and SLC34A3. FGF23 levels were elevated at 111RU/ml (<100RU/ml). Technetium-99m-hydrazinonicotinamide-Tyr3-octreotide scintigraphy was performed and this showed somatostatin receptor-rich sclerotic areas within the right sacral ala and left femoral head. Whole body PET FDG CT showed several FDG-avid lesions corresponding to fractures within the right sacral ala, posterior iliac, ribs and the T1/T2 spinous processes. Magnetic resonance imaging showed a 9 mm lesion within the left femoral head which was indeterminate. As no definitive surgical target was identified, he was treated with oral phosphate replacement alongside alfacalcidol. His symptoms and biochemistry have improved: phosphate 0.76 mmol/l, adjusted calcium 2.26 mmol/l.
Discussion
Oncogenic osteomalacia is characterised by the presence of renal phosphate wasting due to elevated FGF23, which in turn results in hypophosphataemia and osteomalacia. Symptoms are non-specific and include bone pain, muscle aches, fractures and weakness. These lesions often express somatostatin receptors and may be detected by octreotide scintigraphy. If a causative lesion is identified, surgical removal can lead to biochemical cure. If surgical intervention is not possible as in this case, then patients can be managed medically with either phosphate supplementation and alfacalcidol, or with burosumab which specifically targets FGF23.

10.1530/endoabs.77.LB9

LB10

Interpreting hyponatraemia in the wider context and the use of desmopressin outside of endocrinology

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Hyponatraemia is the most commonly encountered electrolyte disturbance seen in 15-20% of inpatients. Regardless of severity, hyponatraemia is associated with increased length of stay, morbidity and mortality. We describe a case of a 60-year-old patient admitted with recurrent falls, head injury and hyponatraemia on a background of young-onset Parkinson's disease with predominant cognitive decline, bladder disturbances and autonomic failure. Following multiple treatments for nocturnal enuresis and her decline for urinary catheter, Desmopressin was introduced by uro-neurology to avert sleep disturbance and to mitigate risks associated with mobilisation at night. Previously she has had multiple admissions and frequent sodium checks in tertiary and primary care with reassuring sodium levels. As such the dose of sublingual desmopressin was increased from 60 mg to 120 mg a few months before admission. At presentation her serum sodium was 120 mmol/l. Desmopressin remained on regular prescription until review by endocrinology where it was stopped and fluid restriction commenced. Her thyroid function test and 9am cortisol were within normal range. Her serum sodium level slowly incremented to 134 mmol/l over 5 days. As a result, nocturnal polyuria and postural hypotension worsened with cessation of desmopressin and fluid restriction respectively. Due to the complexity of her neurological condition, her management received multi-disciplinary input from the autonomic failure and uro-neurology specialists. It was extremely challenging to achieve a delicate balance between normal serum sodium levels whilst simultaneously addressing frequent nocturia and postural disturbances with fluid restriction and desmopressin titration. This will be an ongoing challenge in the foreseeable future given her progressive neurological symptoms and autonomic failure. This case aims to raise awareness regarding the increased prevalence of desmopressin use outside of endocrinology, the challenges faced in the management of hyponatraemia and considerations needed when making medication changes taking into account the clinical context.

10.1530/endoabs.77.LB10

LB11

Mass spectrometry imaging for simultaneous analysis of lipid biomarkers, lysophosphatidic acid (LPAs) and lysophosphatidyl choline (LPCs), in fibrotic liver tissue

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Autotaxin (ATX) is a secreted enzyme that generates the lipid signalling molecule LPAs from LPCs. The ATX/lPA axis is strongly linked to fibrotic diseases and therapeutic inhibitors are in development. Assessing the balance of LPC/lPA in diseased target tissues is critical to inform pharmacokinetics/pharmacodynamics (PK-PD) and predict efficacy of ATX inhibitors *in vivo*. Mass spectrometry imaging (MSI) allows concomitant measurement of multiple molecules with histopathological correlation. We developed a universal MSI protocol to image LPA/lPC pairs simultaneously in fibrotic liver tissue as PK/PD markers. 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. Carbon tetrachloride treated (12 weeks; olive oil control) rat livers (n = 3/group) were cryosectioned (10μm) and imaged (150μm). LPA/lPC pairs (16:0, 18:0, 18:1), 17:0-LPA and 19:0-LPC were used for method optimisation and validation. LPCs ionised more readily as $[M+H]^+$ and $[M+Na]^+$ in equal abundance, whereas LPAs were observed as $[M+2Na\text{-}H]^+$, limit-of-detections (LODs) off-tissue (LPC: 0.1μg/mL; LPA: 1ug/mL). Following matrix screening, 2,5-dihydroxybenzoic acid (DHB) present in 50% MeOH. Addition of 20-40 mM sodium acetate facilitated sodiated ion formation for both LPAs and LPCs. Automated spray parameters were optimised; low flow 0.05mL/min helped to achieve a smooth layer of DHB + CH_3COONa on tissue surface. Using optimised parameters, LPAs and LPCs were successfully imaged in control and fibrotic rat livers recording different abundances (LPA: 18:0≥18:1>16:0>18:2≥20:4; LPC: 16:0>18:0>18:1≥20:4≥18:2). Lipid identification was confirmed following assessment of specific fragmentation patterns (LPC: loss of -59Da and -205Da from head group; LPA: loss of H_2O -18Da) on and off-tissue vs reference standards. More sensitive and specific detection was achieved using the FT instrument; mass accuracy 1ppm with 3mDa mass resolution. MALDI-FT-ICR-MS represents a useful approach for imaging

LPAs/lPCs simultaneously. Future work will investigate ATX inhibitors in preclinical efficacy models.

10.1530/endoabs.77.LB11

LB12

Hypoxia re-programmes adipocyte metabolism to drive cancer cell proliferation

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Obesity increases the risk of certain cancers, especially tumours that reside close to adipose tissue (e.g. breast cancers and ovarian metastasis to omentum). Adipose tissue in obesity and tumour micro-environmentsshare a common pathogenic feature, oxygen deprivation (hypoxia, Hx). Here we hypothesised that this hypoxic microenvironment causes changes in key metabolic pathways in adipocytes leading to increased cancer cell growth. To test this, human or mouse breast (BC) and ovarian cancer (OvCa) cell lines were co-cultured with human or mouse adipocytes respectively under hypoxia (0.5% O_2,24h) to resemble a tumour environment. Hypoxic cancer-conditioned media (CCM) increased lipolysis in both human and mouse adipocytes (i.e. non-esterified fatty acid release in Hx: human adipocytes with CCM *vs* adipocytes alone, 2.5-fold increase, $P < 0.001$). This led to increased transfer of lipids to cancer cells and consequent increased proliferation under hypoxia. These effects were dependent on the hypoxia inducible factor, HIF1α, expression in adipocytes, as adipocytes lacking HIF1α (Hif1αKO^{ad}) showed a blunted lipolytic responses under hypoxic conditions. Proliferation of cancer cells was also suppressed after co-culture with Hif1αKO^{ad} adipocytes (AUC proliferation assay for BC cells + control adipocytes *vs* BC cells + Hif1αKO^{ad} adipocytes; 116 *vs* 70, $P < 0.01$). To address whether metabolic changes driven by hypoxia in adipocytes can induce proliferation even in non-malignant cells, we performed LC/MS targeted metabolomics in the media of human Simpson-Golabi-Behmel Syndrome (SGBS) adipocytes after co-culture with MCF10A breast epithelial cells. Hx depleted glucose and increased lactate, pyruvate and ribose-5-phosphate levels in SGBS adipocytes. These re-programmed adipocytes increased proliferation of even the non-malignant cells (AUC proliferation assay for MCF10A in Hx; MCF10A alone *vs* MCF10A + SGBS, 188 *vs* 446, $P < 0.01$). Hypoxia re-programmes adipocyte metabolism, providing energy substrates for cancer cell proliferation and represents a key link between obesity and increased cancer risk.

10.1530/endoabs.77.LB12

LB13

Fatty acids prevent normal activation of key HIF-1α regulated genes during hypoxia in HEK293T cells

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Type 2 diabetes (T2D) affects 1 in 15 people in the U.K, ischaemic damage is predominant and caused by hypoxia. The physiological response to hypoxia is an increase in the transcription factor hypoxia inducible factor (HIF)-1α, which results in reduced oxygen consuming. Previously we have demonstrated that the diabetic heart fails to respond to hypoxia and the aim of this work was to determine if a similar effect was seen in the kidney. HEK293T cells were incubated for 8h in MEM media with or without 0.5 mM long-chain fatty acids (LCFA). After this initial incubation, media was replenished flasks were split between normoxiaand the hypoxic (2% O_2) for 16h ($n = 4$ for each condition). qRT-PCR was performed on HIF1α-mediated genes: VEGF-A, GLUT-1, CA9, NDRG1, and EGLN1. Gene expression was normalised to the geomean of housekeeping genes; b-actin, RPL13A and HRPT1. To assess cell viability, a separate 96 well plate was incubated and at 16h alamarBlue was added for another 4h, and absorbance read at 570 nm and 600 nm. In control HEK293T cells 16h of hypoxia significantly ($P < 0.05$) induced gene expression in all 5 of our target genes, compared to normoxia with between 30 and 70% increase in gene expression. Interestingly, cells incubated with LCFAs failed to increase gene expression in hypoxia, with no significant difference in any of the 5 genes when compared to normoxia. Incubation with LCFAs led to as 54% decrease in cell viability in hypoxia compared to hypoxic controls. Hypoxia significantly increases the expression of HIF1α-mediated genes: VEGF-A, GLUT-1, NDRG1, EGLN1, and CA9 in HEK293T cells. These data suggest that LCFAs blunt the normal HIF-1α response in hypoxia, preventing vital adaptation and cell survival. Thereby demonstrating that LCFAs, in T2D, could be responsible for increased damage during ischemia and increased mortality from renal complications.

10.1530/endoabs.77.LB13

LB14

Abnormalities of glucagon suppression and stimulation of insulin secretion in response to rising glucose concentrations interact in impaired fasting glucose and impaired glucose tolerance

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Impaired glucagon suppression is an overlooked contributor to the transition of prediabetes to type 2 diabetes. We used Graded Glucose Infusion (GGI) to examine the relationship of ISR and Glucagon Secretion Rate (GSR) with rising glucose. We studied 39 non-diabetic, weight-stable individuals (53 ± 2 yrs, 30 ± 1 Kg/M^2) categorized by fasting and glucose tolerance status following a 75g OGTT at the time of screening. After an overnight fast, at 07:00 a variable insulin infusion was used to maintain glucose at ~4.4 mmol/l (until 08:30) enabling the subsequent measurement of ISR and GSR in response to rising glucose concentrations. At 09:00 GGI commenced, starting at 1 mg/kg/min and doubling every 60 min until 13:00. GSR and ISR were calculated by nonparametric deconvolution from plasma concentrations of glucagon and c-peptide respectively. GSR exhibited an exponential relationship with glucose, that could be characterized by τ – the change in glucose necessary to suppress GSR by 50%. τ was increased in people with impaired fasting glucose (IFG) compared to those with normal fasting glucose (NFG) regardless of the presence or absence of impaired or normal glucose tolerance (IGT or NGT – 1.4 ± 0.2 vs. 1.5 ± 0.2 vs. 2.0 ± 0.2 vs. 2.5 ± 0.3 mmol/l, $P < 0.01$, NFG/NGT vs. NFG/IGT vs. IFG/NGT vs. IFG/IGT respectively). The glycemic threshold for stimulation of ISR was lower in subjects with IGT, regardless of the presence or absence of IFG (4.7 ± 0.1 vs. 4.4 ± 0.1 vs. 4.9 ± 0.1 vs. 4.4 ± 0.1 mmol/l, $P < 0.01$, NFG/NGT vs. NFG/IGT vs. IFG/NGT vs. IFG/IGT respectively). These data show that in non-diabetic humans, both α-cell and β-cell dysfunction contribute differentially to the subtypes of prediabetes. This may have implications for the design of targeted interventions for prediabetes.

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LB15

Development and testing of a novel 'GrowthMonitor' Smartphone App for growth monitoring and the detection of growth disorders

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Background
Childhood growth is an indicator of health/well-being. Growth monitoring identifies treatable conditions in apparently healthy children and prevents inappropriate referrals. Systematic growth monitoring is not currently a UK priority and growth disorders are frequently diagnosed late.
Objective
Develop and test the accuracy of GrowthMonitor, an app which enables families to measure a child's height at home as a cost-effective alternative to primary care growth monitoring.
Methods
'GrowthMonitor' calculates height data using augmented reality. Patients were measured by the app in parallel to stadiometer (gold standard) height measurements as part of routine care. The coefficient of variance assessed repeatability/precision of 3 consecutive app measurements for each patient. Linear regression evaluated the relationship between the app and stadiometer measurements to determine accuracy. The app uses novel algorithms that calculate height compared to UK population-based height references (HSDS), distance from target height (THSDSDEV) and HSDS change over time (ΔHSDS). Predefined cut-offs trigger green (normal), amber (monitor) or red (seek medical advice) alerts.

Results
A total of 79 (42M) patients participated with mean ± SD age 10.37 ± 4.1 yr (range 1.9-18.0). The average coefficient of variance for the app measurements was 1.5%, indicating excellent precision. Linear regression showed a clear linear relationship between the app and stadiometer measurements (R^2 0.99; $P < 0.0001$). A Bland-Altman plot gave a bias constant of 0.298, suggesting no consistent bias of either height measurement approach. Of the 12/79 (15%) individuals that triggered red alerts in the app (recommending referral), only 2 (2.5%) were incorrect. According to corresponding stadiometer measurements, these should have triggered amber alerts. One 'normal' app measurement was in the amber range according to the stadiometer measurement.
Conclusion
Our preliminary data suggest that the GrowthMonitor app produces accurate, reliable height measurements. This technology could transform the approach to growth monitoring and facilitate early referral/diagnosis of growth disorders.

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LB16

Management of hypoglycemia in hospitalized patients with diabetes

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Aim
To determine if inpatient hypoglycemia management in our trust is compliant with NICE guidelines and understand the conundrums in documentation and treatment of the hypoglycemic episodes.
Method
Retrospective audit on all patients admitted in Huddersfield Royal Infirmary who had hypoglycemic episode(s) in March 2021 which were picked up by wireless-enabled central capillary blood glucose monitoring system (cobas)[1].
Results
62 episodes of hypoglycemia were recorded during the period with 48 episodes in patients with diabetes and 14 episodes in patients without diagnosis of diabetes. So, the 48 episodes were studied in detail. 35 (73%) of these hypoglycemic episodes were documented in EPR (Electronic Patient Record) of patients and the remaining 13 (27%) were only picked up by cobas[1]. Of the 48 episodes, capillary blood glucose was checked on admission in 28 cases and in the remaining 20 cases, it wasn't checked until more than 24hrs of admission. Management of only 4 patients (11%) was compliant with NICE guidelines where all the essential 4 steps were followed. The first step in management by treating with 15-20gms of carbohydrate in conscious patients and IV glucose/glucagon in unconscious patients is most followed step in 29 patients (83%). Only 8 patients (23%) had their capillary blood glucose rechecked in 15 minutes and the rest did not have any documentation of re-checking. Of the 35 documented episodes, only 7 patients (20%) received additional carbohydrates on recovery and 28 patients (80%) didn't receive any additional carbohydrates according to the guidelines. 10 patients (29%) had continuing hypoglycaemia in 35-40 minutes and only 6 (60%) of them received intravenous treatment.
Conclusion
Results show that in only 4% of patients with hypoglycaemic episodes, all steps of hypoglycemia management were followed and this implies a significant scope in improvement in managing these patients. We are planning to arrange regular teaching for nursing staff on managing as well as documenting these episodes. Also, we are planning to include a "Hypoglycemia form" to fill in after each hypoglycemic episode in EPR which can further help in auditing future episodes (planned in 6 months) and aid in achieving better outcome.
1. Accu-Chek Inform II System (Roche) which connect with the COBAS POCT IT 1000 solution.

10.1530/endoabs.77.LB16

LB17

Challenges in the diagnosis and management of type 1 diabetes in older adults

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Aim
Diagnosis of type 1 diabetes in older adults can be challenging, and management can be complicated by co-morbid conditions. In this study we aimed to compare glycaemic control, microvascular complications and diabetic emergencies (severe hypoglycaemia and diabetic ketoacidosis) in the early years following diagnosis between younger adults (<50) and older adults (≥50).
Method
A retrospective cohort study was performed on people with newly diagnosed type 1 diabetes between 2012 & 2018. Data was gathered using SCI diabetes and Clinical Portal at: time of diagnosis; 1 year; 2 years and; most recent recorded value. Data included patient demographics, HbA1c, biochemical parameters including autoantibodies and complications.
Results:
122 patients were included following exclusion (253 patients). 77 were <50 at time of diagnosis (mean 33) and 45 were aged ≥50 (mean 58). 71% patients <50 were male while 64% patients ≥50 were female. 69% patients ≥50 had originally been diagnosed with type 2 diabetes, and 84% had GAD antibodies taken of which 76% positive. Of those aged <50, mean HbA1c was 95 at diagnosis; 60 at 1 year; 64 at 2 years; and most recent 68: while in 50 or over cohort, mean HbA1c at diagnosis was 108; 62 at 1 year; 66 at 2 years; and most recent 67. Both foot disease and CKD were more common (9% and 9%) in >50 group compared to <50 group (1% & 0%), but numbers not seen to progress during study period. More older adults had hypoglycaemia (7% in >50, 4% in <50), but younger adults had more DKA (11% in >50, 16% in <50).
Conclusion:
Complications were more common in newly diagnosed older adults with type 1diabetes despite having a similar glycaemic control during the study period. It emphasises the importance of individualisation of therapy in the care plan of older patients.

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LB18

Prevalence rate of undiagnosed diabetes in an asymptomatic population

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Background and Aim
Approximately 1500 people attend the Beacon Health Check Department annually involving a panel of blood tests being screened. Our aim was to compare what percentage of this asymptomatic population have diabetes or were pre-diabetic and what percentage of these were undiagnosed and therefore untreated conditions.
Methodology
This audit was a retrospective review of data collected from patients attending the Beacon Hospital Health Check Department during 2019. The data was applied for through the Beacon Hospital IT Department in excel format and screened by location. Void samples were excluded. In the case of HbA1c values, patients found to be in pre-diabetic or diabetic ranges as per WHO guidelines (43-47 and >48 mmol/mol) (Auto-analyser: Architect ci8200) had their Health check discharge letters retrieved to determine if the condition was a new or known diagnosis.
Results
- 1577 were examined, 14 had HbA1c values in the pre-diabetic range (0.89%).
- 13 patients had HbA1c values in the diabetic range (0.82%)
- 3 of 14 patients in the pre-diabetic range were known, 11 were newly diagnosed (0.70%).
- 7 of 13 patients found to be in the diabetic range were known, 6 were new diagnoses (0.38%)
- Our age range included patients from 19 to 86-years-old with a mean of 48 +/- SD. 10
- Age 45+ only results: 996 patients total with 3 newly diagnosed diabetics (0.30%).

Conclusion
- Data on undiagnosed prevalence of diabetes is scarce. According to our literature review, prevalence over the age of 45+ is 3.5%.
- Our overall results were substantially lower than this with 0.38% receiving new diabetic diagnoses.
- Excluding results outside of the age range documented in our literature review failed to correct for the variation in the data.
- With an observed frequency less than 1% being newly diagnosed with diabetes, these findings were lower than expected given the prevalence in the community.

10.1530/endoabs.77.LB18

LB19

Post noradrenaline infusion induced gangrene of the toes

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Noradrenaline (NE) is a peripheral vasoconstrictor reducing mortality by 11% and major adverse events by two-thirds compared to dopamine [1]. NE acts as an agonist at alpha1 and beta1 receptors, with little-to-no beta2 or alpha2 activity. This vasoconstriction effect can be potent and can result in completely occluded blood vessels more frequently in the peripheries due to lower blood pressure. Septic shock accounts for nearly 1 in 10 admissions to ICU, where it is the most common cause of death. One of the less reported undesirable effects of treating septic shock with NE is peripheral ischaemia. A 51 year-old woman called paramedics after a sudden onset of right-central pain, haemoptysis, confusion, and loss of urine control, and was promptly admitted to ITU due to suspicion of CAP. The patient then went into septic shock with a blood pressure of 80/40mmhg as such was given IV NE infusion. Immediately, the patient's toes became necrotic. Later, blood culture and sputum analysis found an Aspergillus interstitial lung infection, which most likely would have come from mould in the patient's bedroom. The patient had an extensive past medical history consisting of T2DM, COPD, alcohol dependency, depression, anxiety & heavy smoker. This female was admitted to the ITU & given an infusion of NE 0.33mL/min and further vasopressin support and mechanical ventilation were also needed. She developed necrosis of right foot toes 1-4 as well as blistering to the left foot toes, 2 hours after administration of noradrenaline. The necrosis presents more commonly bilaterally and symmetrically, known as Symmetrical Peripheral Gangrene (SPG), and this often requires amputation of the affected areas [2]. However, in the case described here, as necrosis was predominantly limited to the medial four toes of right foot, the patient was advised to wait for auto amputation.

10.1530/endoabs.77.LB19

LB20

Long-term clinical outcomes for pituitary cysts: experience of the multi-disciplinary team at the royal victoria infirmary

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Objective
Clinical management of pituitary cysts remains controversial, especially if asymptomatic. We retrospectively review clinical management and outcome of these patients undergoing long-term follow-up in our pituitary clinic.
Methods
All patients with MRI-based diagnosis of pituitary cyst were included. Clinical presentation, cyst size and endocrinopathies (secondary adrenal, thyroid or gonadal deficiency) were compared between surgical and observational cohort. Macrocyst were defined as lesion ≥ 1 cm in maximal diameter on imaging,
Results
Of 82 patients, 85% were observed with surveillance imaging and 15% underwent pituitary surgery at presentation. When compared to the observational cohort, the surgical cohort had a preponderance of females (100% v.s. 72%) older in age (57 v.s. 47 years), presenting with macrocyst (100% v.s. 21%). The surgical cohort had a higher incidence of visual dysfunction (50% v.s. 7%) and endocrinopathies (33% v.s. 14%), whilst 80% of pituitary cysts were incidentally found in the observational cohort (v.s. 41%). During a mean follow-up period of 63 months in the observational cohort, the pituitary cyst remained static in 61%, decreased in size in 22% and increased in size in 17% ($n = 10$). Of 4 patients who underwent surgical decompression, 3 had an increase in size during imaging surveillance. Overall, 20% of patients ($n = 16$) underwent surgery in our cohort. Improvement in vision was noted in 66% of those with prior visual abnormality. Recovery of previous endocrinopathy only occured in 1 patient. Incidence of new endocrinopathy post-surgery was 50%. Of 12 patients with longitudinal imaging follow-up, re-accumulation of cyst was noted in 5 (42%) and repeat surgical decompression was needed in 2 patients.
Conclusions
Majority of pituitary cysts can be managed conservatively, with a low risk of progression necessitating surgical intervention over a mean follow-up of 5 years. Risk of new endocrine dysfunction and cyst re-accumulation is high in those requiring surgical decompression.

10.1530/endoabs.77.LB20

LB21

Long-term Clinical Outcomes for Cushing's Disease: experience of the multi-disciplinary team at the Royal Victoria Infirmary

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Objective
Standard Cushing's disease (CD) treatment is trans-sphenoidal surgery (TSS). However, reported postoperative remission and relapse rates are variable. We have retrospectively analysed clinical outcomes of patients with CD undergoing TSS at our centre.
Methods
Patients with CD currently under our long-term endocrine care were included. Diagnosis of CD was made following standard biochemical and radiological investigations. Post-operative remission criteria: suboptimal synacthen testing and ongoing steroid replacement or normal 24-hour urine free cortisol and/or overnight dexamethasone suppression test.
Results
48 patients were eligible. Mean age at presentation was 43 years (range 14–69), with a female preponderance of 73%. Mean clinical follow-up duration was 12 years (range 1–39). Available initial MRI for 38 patients identified 17 (46%) macroadenoma (>1 cm), 15 (40%) microadenoma, remaining 14% either normal, bulky or empty sella. 46 patients underwent TSS with a 58% remission rate. 16/27 (59%) subsequently suffered biochemical relapse. Remission rate after 2nd TSS was 45%. After 1st TSS 17 patients had persistent CD, 9 underwent further TSS with 33% remission rate post-surgery. After 1st TSS, remission rate in those with microadenoma was higher (66%) than in the macroadenoma cohort (52%). At latest follow-up, 19 (41%) patients remained in remission after ≥ 1 TSS. Further treatment modalities in those with persistent/relapsed CD included radiotherapy (12), bilateral adrenalectomies (3) or both (9). Incidence of pituitary hormonal losses were lower in patients with ongoing remission following 1st TSS than in those who suffered persistent/relapsed CD: hypoadrenalism (18% cf. 64%), hypothyroidism (27% cf. 57%) and hypogonadism (22% cf. 57%) ($P < 0.05$).
Conclusions
We observed a CD remission rate with ≥ 1 TSS of 41% over a mean follow-up period of 12 years. Further treatment of relapsed/persistent CD following 1st TSS is complicated with a high incidence of pituitary hormonal losses.

10.1530/endoabs.77.LB21

LB22

Effect of Enzalutamide on cortisol dynamics

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Background
Enzalutamide is a next-generation androgen receptor (AR) antagonist, used as a daily oral agent, in the treatment of castration-resistant prostate cancer. Its suppression of 11β-hydroxysteroid dehydrogenase-2 enzyme has been reported in the literature, leading to hypertension through a relative increase in cortisol concentration at the level of the mineralocorticoid receptors. Enzalutamide is also known to be a potent inducer of drug metabolising enzymes (cytochrome P450 isoenzyme 3A4). To our knowledge, its clinical effect on cortisol dynamics has not been previously reported. We report a case of altered glucocorticoid dynamics and false positive dexamethasone suppression test result in a patient on Enzalutamide.
Case
A 74-year-old male, with previous acromegaly secondary to a pituitary microadenoma, attended for routine clinical review. He remained in remission 11 years post pituitary surgery. He was recently diagnosed with metastatic prostate cancer and received radical radiotherapy. Soon after commencing Enzalutamide he developed hypertension and his diabetes control deteriorated. On examination he had increased abdominal adiposity but no other cushingoid features. After a low dose dexamethasone suppression test (LDDST) his cortisol remained unsuppressed at 181 nmol/l. His baseline ACTH was elevated at 148ng/l. A 24 hour urine cortisol (GC-MS) was normal at 112 nmol/day. His midnight and early morning salivary cortisol were within normal reference ranges. Untimed spot urine collection revealed relatively high cortisol metabolite concentrations on steroid profiling. These abnormal results were felt to be

strongly associated with induction of steroid metabolising enzymes by Enzalutamide. The drug was withheld for 3 weeks on advice from the oncology team and a repeat LDDST revealed normal suppression of cortisol to <20 nmol/l.
Conclusion
Enzalutamide, a potent CYP3A4 enzyme inducer, can alter glucocorticoid metabolism *in vivo*. Clinicians need to be aware of abnormal steroid dynamics and false positive dexamethasone suppression test results in patients on Enzalutamide.

10.1530/endoabs.77.LB22

LB23

Unexplained hypoglycaemia in a patient with craniopharyngioma and GAD positive encephalitis

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Case report
A 55 years old Caucasian gentleman presented with recurrent episodes of unexplained hypoglycaemia with slurred speech, lethargy, myoclonic jerks and seizures. He had background of craniopharyngioma at the age of 17 and underwent surgery but no radiotherapy. Subsequently he was started on hormonal replacement with desmopressin, levothyroxine, hydrocortisone, testosterone and genotrophin and remained stable on treatment for 38 years. Hypoglycaemia work up revealed blood glucose of 2.2 mmol/l with insulin inappropriately detectable at 16 pmol/l and C peptide 510 pmol/l (NR-190-990). On second occasion, blood glucose was 2.2 mmol/l with high insulin and C Peptide at 77 pmol/l and C-peptide 1184 pmol/l respectively. CT pancreas and gut hormones profile were normal. Extensive neurological work up showed positive GAD antibodies, encephalopathic pattern in EEG and reduced activity in the right basal ganglia on DAT scan. A diagnosis of GAD positive autoimmune encephalitis and Parkinson's plus syndrome was reached. He was given Prednisolone 60 mg for encephalitis in addition to physiological hydrocortisone dose resulting in termination of seizures and hypoglycaemia.
Discussion
Literature search showed impaired response of counter-regulatory hormones to hypoglycaemia in patients with craniopharyngioma who had undergone surgery extending to the hypothalamus. Anti-GAD antibodies are linked with destruction of Beta cells leading to type-1 diabetes. We wonder if in early phase of B cell destruction, excess insulin is released from preformed insulin containing granules causing hypoglycaemia. One case report demonstrates reactive hypoglycaemia in a non-diabetic patient with positive GAD antibodies. GAD antibodies are also linked with several neurological syndromes. In our patient, the clinical conundrum arises from the fact that he remained stable for 38 years post-operatively then developed GAD positive encephalitis and hypoglycaemia. Whether there is a unifying diagnosis linking his hypoglycaemia, GAD positivity, neurological sequelae and underlying craniopharyngioma remains to be answered.

10.1530/endoabs.77.LB23

LB24

Hypopituitarism caused by Langerhans Cell Histiocytosis

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Langerhans Cell Histiocytosis is an inflammatory myeloid neoplasia caused by mutations of several genes in the MAPKinase (MAPK) pathway which can present in single or multiple sites. Our patient presented to her GP with several months of amenorrhoea, thirst, tiredness and 3 stone weight loss. She was previously fit and well, working, and married with children. Blood tests revealed panhypopituitarism with low 9am cortisol 117 nmol/l (133-537). Oestrogen and gonadotrophins were low as were free T4 and TSH. Prolactin was raised 2767mU/l (102-496). MRI brain showed a 19 x 11 x 14 mm ill-defined heterogenously enhancing mass centred on the hypothalamus with compression of the pituitary stalk. She was started on replacement hydrocortisone and levothyroxine. She subsequently developed diabetes insipidus and was started on desmopressin. Lumbar puncture and CSF analysis were normal apart from raised lymphocytes. CT chest abdomen and pelvis was normal with no evidence of sarcoidosis. IgG4 subclass 4 level was normal (0.04G/l (0.04-0.86). She was referred to our local neurosurgical team who recommended 3 months surveillance whereupon FDG-PET CT scan showed a 20x15 mm focal mass with no lesions elsewhere. Given the rapid enlargement of the lesion and also a new clinical development of confusion, transphenoidal biopsy was arranged. Immunohistochemistry studies confirmed Langerhans Cell Histiocytosis. She was referred to haematology and discussed with the National Histiocytosis Advisory Panel. She was started on Clabridine and there was a reduction in size of the hypothalamic lesion indicating good response to treatment over 4 months. Unfortunately despite apparent improvement radiologically there was a deterioration in the patient's clinical state with increasing confusion and considerable weight gain with associated comorbidy such that she became unable to live independently.

10.1530/endoabs.77.LB24

LB25

Nelson syndrome - invasive macro-adenoma revealed by pituitary apoplexy

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Nelson syndrome (N S) is the set of symptoms related to a pituitary macroadenoma secreting ACTH developed following a bilateral adrenalectomy (BA). Its frequency is thought to account for up to 40% of adult cushing diseases (CD) who have undergone BA. We report the case of a patient with macroinvasive NS revealed by pituitary apoplexy. Mr M.L aged 35 years, followed for CD with negative imaging evolving for ten years, treated with BA. The evaluation at 03 months post-surgery noted a disappearance of signs of cushing but accentuation of melanoderma with an ACTH at 135pg/ml and a hemorrhagic adenoma of 08 mm on pituitary MRI. The patient was lost to follow-up for 05 years until he consulted again on a pituitary apoplexy chart with severe ophthalmoplegia revealing a pituitary macro-adenoma 33 mm high with multidirectional invasion and ACTH $>$ 2000pg/ml. He was rushed for transphenoidal surgery, followed a few months later by additional radiation therapy. Nelson's syndrome is a rare entity in practice, but relatively common following bilateral adrenalectomy for cushing's disease. Predictors of the onset of this syndrome exist but are controversial. Pituitary MRI monitoring should be routine in all CDs who have undergone BA. Treatment is mostly surgical, supplemented by radiotherapy in invasive cases. Drug treatments are being studied with promising results for dopaminergic agonists and somatostatin analogues.

10.1530/endoabs.77.LB25

LB26

A microfluidics approach of mimicking an obese maternal metabolic environment identifies modified pathways in the endometrial epithelium that may be important for implantation

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Women who are obese are more likely to suffer early pregnancy loss. Once factor that can contribute to this is endometrial dysfunction however, we are limited in our understanding of how stressors or treatments, may alter endometrial function. Mimicking the dynamic *in vivo* exposure of the endometrium to these stressors is difficult using *in vitro* static culture systems. The aim of this study was to use a microfluidic approach to mimic exposure of the endometrial epithelium to factors in maternal circulation representative of different metabolic states to identify pathways that may contribute to endometrial dysfunction. Ishikawa cells were seeded (1,000,000/mL) in microfluidic devices ($n = 3$) and exposed to one of the following treatments at a rate of 1 ul/mL for 24 hours: 1) Control, 2) Vehicle Control, 3) Leptin (L-non-obese; 11 ng/ml), 4) Leptin (LO-obese; 35 ng/ml), 5) Leptin obese + Metformin (LOM-500 ug/ml), or 6) Leptin (LOMA-obese 35ng/ml) + Metformin (500 ug/ml) + Adiponectin (2.5 ug/ml). Following RNA sequencing of extracted cells, differentially expressed genes (DEGs) compared to VC were identified and subjected to overrepresentation analysis using Webgestalt. In total 544 DEGs were identified in cells treated with normal physiological concentrations of leptin and are involved in pathways of protein folding and calcium pathway. In contrast, only 337 were different in LO and included pathways involved in peptide hormone metabolism, biosynthesis, and GABA receptor activation. Only 71 DEGs were in common between these two

comparisons. 375 DEGs were different in LOM treated cells. Overrepresented pathways included defective GALNT family members. In LOMA treated cells 381 DEGs were identified with an overrepresentation of transcripts associated with Mucins and O-linked glycosylation. Minimal overlap between all three comparisons (LO, LOM, LOMA) was observed demonstrating treatment-specific changes. Collectively these data have identified pathways to investigate for functional effects on implantation.

10.1530/endoabs.77.LB26

LB27

Efficacy of oestrogen implant in transwomen as hormone replacement therapy

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Background
Hormone therapy is an important part of transition for many gender nonconforming people and implant treatment is an alternative route of oestrogen administration. We assessed the efficacy of oestrogen implant in transwomen for hormone replacement therapy.
Methods
83 transgender women had 100 mg estradiol implant inserted subcutaneously in the anterior abdominal wall. All subjects graded their energy, drive and libido from a scale of 0 to 10 pre and post implant. Paired t-tests were done.
Findings
The energy level (4.8 $\pm$ 2.0 vs 7.5 $\pm$ 1.4, $P = 0.000$), drive (5.1 $\pm$ 2.7 vs 7.5 $\pm$ 1.5, $P = 0.004$) and libido (3.3 $\pm$ 2.4 vs 6.1 $\pm$ 2.2, $P = 0.001$) improved post first and second implant in comparison to pre implant status (1st pre E to 2nd post E: 4.57 $\pm$ 2.2 vs 8.0 $\pm$ 1.4, $P = 0.001$; 1st pre D to 2nd post D: 4.6 $\pm$ 2.7 vs 8.6 $\pm$ 1.4, $P = 0.006$; 1st pre L to 2nd post L: 1.9 $\pm$ 2.3 vs 6.2 $\pm$ 2.8, $P = 0.000$). Serum FSH level decreased from 21.5$\pm$ 23.5 IU/l to 7.1 $\pm$ 9.7 IU/l ($P = 0.011$) and LH level reduced from 16.3 $\pm$14.3 IU/l to 6.5 $\pm$ 5.1 IU/l ($P = 0.004$) between 1-2 and 1-4 implant (FSH: 23.4 $\pm$ 26.8 vs 4.4 $\pm$ 3.8, $P = 0.01$; LH: 14.9 $\pm$ 11.5 vs 5.5 $\pm$ 3.7, $P = 0.007$) respectively. The average interval in between 1-2 implant was more than 400 days (264 $\pm$ 177 vs 411 $\pm$ 240, $P = 0.000$) with similar figures for 1-3 and 1-4 implants (248 $\pm$ 161 vs 419 $\pm$ 199 days, $P = 0.000$). Energy, drive, and libido all significantly improved with oestrogen implant in comparison to other oestrogen delivery methods despite pre-implant oestrogen levels being in the adult female range. Gonadotrophins reduced suggesting that oestrogen levels were overall higher despite trough oestrogen being comparable with pre-implant oestrogen level.
Conclusion
Oestrogen implant is effective in improving general well-being and libido in transwomen compared to other oestrogen delivery methods with average interval ($>$400 days) between implants.

10.1530/endoabs.77.LB27

LB28

A Heavy Heart

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Anabolic androgenic steroids (AAS) are class C drugs with adverse effects on health. Prevalence is increasing, often with a lack of awareness of the dangers. We present the case of a 33 year-old male with dilated cardiomyopathy and polycythaemia apparently due to AAS abuse over three years. The patient presented with five weeks of increasing breathlessness and chest tightness. Examination revealed evidence of congestive cardiac failure. Chest radiograph showed evidence of pulmonary oedema and cardiomegaly and electrocardiogram showed evidence of left ventricular hypertrophy. Biochemistry showed polycythaemia with haemoglobin of 196g/l (130-170) and haematocrit 0.61. Liver enzymes were raised - alanine transaminase 79IU/l (0-35) Cardiac MRI revealed a severely dilated left ventricle with concentric hypertrophy and significantly increased cardiac mass of 380g (mean average 145g). Left ventricular contractility was severely impaired with an ejection fraction of 10-15% and no regional wall motion abnormality. Myeloproliferative neoplasm panel was negative and erythropoietin was normal. Testosterone was 52 nmol/l (10-29) with completely suppressed gonadotrophins. Despite an initial denial of illicit drug use the patient conceded use of AAS supplied by a personal trainer. The patient was unaware of the health consequences AAS abuse and was distressed to learn of the implication on fertility. Although he was a weight lifter he reported that his motivation to take AAS had been low mood and the regimen was recommended by a personal trainer. Treatment consisted of intravenous diuresis and standard treatment for dilated cardiomyopathy. Regular venesection was required for 6 weeks. Ejection fraction improved to 30% over the following 6 months. He was able to return to the gym but expressed temptation to take androgens again despite now being aware of the dangers, and his desire to start a family. He was referred to psychological services. At 4 months testosterone was still low at 4.2 nmol/l.

10.1530/endoabs.77.LB28

LB29

Is Aloe vera always beneficial?

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A 45-year-old lady presented to her GP with sweating, poor memory, and decreased, concentration. Investigations revealed elevated oestradiol at 2204 pmol/l, LH at 28.1 IU/l, and FSH at 15.0 IU/l. This raised the possibility of a Gonadotrophinoma. A preclinic pituitary MRI showed a subtle rounded nodule of tissue within the right side of the anterior pituitary. In clinic, she revealed that she was consuming aloe vera juice for several years to improve her skin and general well-being. Her enthusiasm motivated her to become a business owner and distributor of aloe vera products. She was taking 60mls of concentrated juice every day containing 99.7% pure inner leaf aloe vera gel. She was advised to stop taking aloe vera supplements. Blood tests two weeks later had returned to normal level with Oestradiol 554 pmol/l, LH 1.6 IU/l, and FSH 2.8 IU/l. Her symptoms had resolved and were attributed to excessive doses of aloe vera. MRI was reviewed and thought to be an anatomical variation. Aloe vera is a phytoestrogen. These are plant-derived compounds with a similar structure to 17 beta oestradiol. In excessive quantities, they can lead to increased oestrogenic effects by binding to oestrogen receptors. The gel from the inner leaf contains the highest concentration of aloe vera. Health benefits suggest improvement in menopausal symptoms, decreased cardiovascular disease, and lower risk of obesity, type 2 diabetes and metabolic syndrome. Non-medical literature benefits include improvement in skin quality, bowel health, and wellbeing. The potential adverse effects due to the oestrogenic properties of phytoestrogens are infertility and increased risk of cancer in oestrogen sensitive organs. More studies are required to discover if highly concentrated preparations of aloe vera are associated with significant adverse effects which would outweigh the potential benefits. Should alternative therapies carry a health warning?

10.1530/endoabs.77.LB29

LB30

Pericarditis and sub-acute thyroiditis complicating Pfizer-BioNTech Covid-19 vaccination

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A 31 year old female with no prior history of thyroid disease presented to hospital four days after 2nd dose Pfizer vaccination with fever, myalgia, neck discomfort and chest pain; which was relieved by sitting forwards. A small goitre and tachycardia were noted on physical examination. CXR and echocardiogram were normal. ECG revealed sinus tachycardia. Troponin T was elevated (32 ng/l, normal $<$5). Free T4 was raised (26.6 pmol/l, reference 10-22) with an undetectable TSH concentration. The working diagnoses were acute pericarditis/myocarditis and subacute thyroiditis. Naproxen and Carbimazole were prescribed and the patient was discharged home from the Cardiology Unit. The patient was readmitted 10 days later with symptomatic hyperthyroidism, chest discomfort, anterior neck pain and odynophagia. Clinical examination identified hyperthyroidism and a large firm tender macronodular goitre. Inflammatory markers were elevated (CRP 92, ESR 55), Thyroid function tests had deteriorated (free T4 71.8 pmol/l, free T3 19.1 pmol/l, TSH undetectable) and auto-antibodies were negative (TRAb, anti-TPO). Propranolol and Prednisolone were introduced with good symptomatic relief. Sub-acute thyroiditis classically presents with neck pain, goitre and features consistent with hyperthyroidism. It is most commonly triggered by viral infection but is a well-recognised complication associated with other mRNA vaccines. Safety data for the Pfizer vaccine has been reassuring to date, although more serious 2nd dose side-effects such as myocarditis and pericarditis have been reported. A small number of thyroiditis cases have been

reported following the 2nd dose of the Pfizer-BioNTech vaccine and it has been postulated that the spike protein of the vaccine may demonstrate thyroid peroxidase molecular mimicry that could potentiate thyroiditis via this mechanism. Clinicians should be mindful of possible immune-mediated complications of vaccination as it is taken up by the wider population - as these conditions can present with non-specific symptoms, as demonstrated in this case.

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LB31

Mapping of aldosterone and glucocorticoids in mouse kidney using mass spectrometry imaging

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Aldosterone and glucocorticoids stimulate sodium transport by the renal tubule, which is important for blood pressure homeostasis. Corticosteroid excess and/or abnormal steroid hormone activity within the kidney can cause hypertension. Circulatory and urinary steroid concentrations can be measured routinely but steroid concentrations at a tissue and cellular level are largely unknown, and the kidney remains a "black box". Mass spectrometry imaging (MSI) permits localisation of steroids in histological zones based on regional markers. This approach has been previously applied to localise steroids in brain and testes. Our aim was to use MSI to map and quantify glucocorticoids and aldosterone in different histological zones (cortex, medulla) of mouse kidney. Cryosections kidney from male C57BL6 mouse (age 12 weeks, $n = 6$) were subject to MSI analysis following Girard T reagent derivatisation and α-cyano-4-hydroxycinnamic acid matrix application. Matrix assisted laser desorption/ionisation (MALDI) was used as a sampling method, coupled to Fourier Transform Ion cyclotron mass spectrometry. Ions with m/z 458.3010 (Δppm $= 0.65$), 460.3166 (Δ ppm $= 0.65$), and 474.2957 (Δppm $= 1.05$) were detected, using MALDI,in renal sections for derivatives of 11-dehydrocorticosterone, corticosterone and aldosterone respectively. Untargeted evaluation of ions was conducted to find regional markers that would allow definition of kidney histological zones. Heat maps indicated that corticosterone intensity was higher in the inner cortex than the rest of the kidney. In contrast 11-dehydrocorticosterone was detected in medulla and aldosterone signal was equally strong in medulla and outer cortex. Steroid co-localisation with zonal markers by MSI permitted mapping in functional renal zones. This approach provides fundamental new insights into the physiological control of sodium transport by steroids and opens doors to understanding changes in disorders of blood pressure.

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LB32

Dolutegravir increases Peritoenal fat of adult HIV patients but not serum lipids. A preliminary finding of a Pilot study

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Background
In people with HIV on ARV treatment receiving Dolutegravir (DTG)-based regimen, weight and lipodystrophy have been reported.
Aim
The aim of this is to evaluate the effect of DTG on the lipid profile and fat distribution on patients who have been switched from a non to a Dolutegravir (DTG)-based regimen on the lipid profile and fat distribution.
Methods
One hundred patients above 18yrs of age were recruited into two arms of the study (50 patients each). The Non-DTG group were initiated with a protease inhibitor (PI) and the DTG group on ABC/3TC/DTG regimen. The serum lipid profile, blood glucose concentration, body mass index (BMI), were measured. Peritoneal fat was measured by ultrasound scan and skinfold thickness was measured by a skin calliper. All measurements were done at 3 and 6 months. Statistical comparisons were assessed and determined using the chi-square test.
Result
The mean of the study participants was 41.3yrs in the DTG group and 43.6yrs in the non-DTG group. There was no statistically significant difference in fasting glucose ($P = 0.176$) and total cholesterol ($P = 0.045$). The mean total cholesterol concentration was 185, 172, 179 and 168 mg/dL at baseline, 3 and 6 months, for the DTG and non-DTG based regimen respectively ($P = 0.026$). Similarly, mean low-density lipoprotein concentration demonstrated no significant change, with values of 109, 90, 92 and 96 mg/dL at baseline, 3, 6 and 12 months ($P = 0.025$). Triglycerides and LDL levels were also similar. However, there was an increase in the peritoneal fat of the participants on the DTG based regimen ($P = .021$).
Conclusion
The use of DTG may be associated with lipodystrophy and this could have clinical implications. There is the need for further research, with a multicenter study using a larger sample size.

10.1530/endoabs.77.LB32

LB33

Complex management of unilateral post-Covid-19 adrenal haemorrhage during pregnancy

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Background
Management of large indeterminate adrenal masses detected during pregnancy is challenging due to the risk of malignancy and the obstetric risks of surgical intervention. The spectrum of endocrine-related complications of Covid-19 is expanding. We present a case that highlights the challenging management of a large adrenal mass during pregnancy and draws attention to a rare complication of Covid-19.
Case description
26 yr-old lady presented with Covid-19 pneumonia. CTPA showed an incidental 12.6 cm heterogeneous left adrenal mass. Unenhanced CT showed Hounsfield Units 21. Upon referral in November 2020, she was 7-weeks pregnant without clinical features of glucocorticoid or androgen excess. Adrenal androgens, 24hr urinary free cortisol, and plasma metanephrines were normal. The likelihood of malignancy and the obstetric risks of surgery were discussed with the patient. MRI scan performed 3 months after the initial scan showed no loss of signal on chemical shift but size reduction to 7.9 cm, arguing against malignancy. The 24hr urine steroid metabolome pattern also did not suggest adrenocortical carcinoma. Doppler ultrasound showed a non-vascular, well-defined round 7 cm lesion consistent with adrenal haematoma. The patient had spontaneous miscarriage at 12 weeks. Our Adrenal MDT continued radiological surveillance and MRI scan 3 months later showed further size reduction to 5.5 cm. In June 2021, she was again pregnant. Repeated Doppler ultrasound at 5-weeks' gestation showed stable adrenal mass, suspicious for the presence of an underlying adrenal tumour. Given the patient's young age, the Adrenal MDT decided to continue radiological monitoring after delivery.
Conclusion
Unilateral adrenal haemorrhage has very rarely been reported following Covid-19. With history of recent Covid-19, adrenal haematoma should be considered in the differential diagnosis of large heterogeneous adrenal masses. Herein, management was further complicated by pregnancy. Inappropriate adrenal surgery was avoided, hence an experienced multidisciplinary approach is important in complex cases for best clinical outcome.

10.1530/endoabs.77.LB33

LB34

Adrenal lymphoma 'The Great Imitator'

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Introduction
Adrenal lymphoma and its association with intravascular lymphoma is rare but needs consideration in cases presenting with bilateral adrenal masses and

unexplained neurological symptoms. We present two recent cases presenting with multiple cerebral infarcts associated with primary adrenal lymphoma.
Case 1
A 67-year-old male was admitted to the stroke unit with symptoms of middle cerebral artery (MCA) stroke. MRI demonstrated multiple infarcts. Repeat imaging after the patient's rapid neurological decline showed multiple new cortical infarcts. Carotid doppler, echocardiogram, and vasculitic screen were all normal. LDH was raised-2554u/l (reference range: 225-425); CTCAP demonstrated bilateral adrenal masses suggesting an infiltrative process. PET showed highly avid adrenal glands. EUS-guided biopsy confirmed the presence of high-grade diffuse large B cell lymphoma. R-CHOP chemotherapy was commenced with no further cerebral infarcts.
Case 2
A 74-year-old female was re-admitted under the stroke team with worsening neurological deficit (after recent admission for MCA stroke). Repeat CT and MRI scans revealed multiple cerebral infarcts. CT angiogram, doppler, echocardiogram, and vasculitic screen were negative.LDH was 363u/l (reference range: 90-225); CTCAP showed marked enlargement of both adrenals, with PET-CT demonstrating bilaterally enlarged and hyper-metabolic adrenal glands. US-guided biopsy revealed a high-grade lymphoma.
Discussion
1. There is a well-documented association between adrenal lymphoma and CNS disease. 2. Cerebral intravascular lymphoma is a 'great imitator' and can present with various neurological presentations without the classical characteristics of lymphoma. 3. The radiological features of adrenal lymphoma include enlargement of the adrenals whilst retaining the normal adrenal contours and significant avidity on PET. 4. Intravascular lymphoma poses a significant diagnostic challenge due to the lack of expected features of lymphoma (lack of symptoms without significant rises in LDH, CRP, or ESR in all cases). The association with adrenal hyperplasia and PET-avidity should alert clinicians to the diagnosis.

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LB35

Two cases of peri-operative adrenal crises: lessons in patient safety

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Case 1
A 73-year-old woman underwent two separate major abdominal surgeries, one month apart, for the management of ovarian endometrioid adenocarcinoma. She had hypotensive crises about 30 minutes into each of the procedures, requiring metaraminol and noradrenaline infusions. Cortisol levels post-surgeries were 99 nmol/l and 23 nmol/l, respectively. Further questioning revealed exogenous steroid use, including high dose inhaled steroids (Fostair-800mcg/daily) and IM steroid injections, the last one within 12 months of surgery. Once adrenal insufficiency diagnosed, she was managed with parenteral, then oral, hydrocortisone, in the usual way. She will have further testing when appropriate – she is currently undergoing chemotherapy.
Case 2
A 53-year-old woman became hypotensive during a bilateral hip replacement. She was given dexamethasone intraoperatively, then became hypotensive again and was admitted to ICU, requiring support with metaraminol for three days. Early morning cortisol was measured at 38 nmol/l, 48 hours after surgery, and 83 nmol/l, seven days later. Further questioning revealed exogenous steroid use, including multiple steroid injections to the hip (methyl prednisolone 40-120 mg) and oral prednisolone, within a year of surgery. Once adrenal insufficiency diagnosed, she was managed with parenteral, then oral hydrocortisone, in the usual way. Two months later, she underwent Synacthen testing: 0min cortisol 354 nmol/l; 30min 401 nmol/l; basal ACTH 47ng/l. She is no longer taking oral hydrocortisone.
Conclusion
Patients with hypothalamo-pituitary adrenal suppression due to exogenous steroids, across all routes, are at risk of adrenal crisis during surgery as they are unable to mount a cortisol response in response to physiological stress. IM steroids seem to be a particular issue as they result in prolonged HPA axis suppression. Risk of HPA axis suppression can be considered depending on dose of steroids given. Patients should be covered with hydrocortisone, as per standard surgical perioperative guidance. Further confirmatory testing can be done at an appropriate time, after surgery.

10.1530/endoabs.77.LB35

LB36

Small cell lung cancer presenting as hyperglycaemia and paraneoplastic syndrome

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- A 54-year old Lithuanian man presented with symptomatic hyperglycaemia and weight loss.
- A diagnosis of new onset diabetes type 2 was confirmed for which he received treatment. In addition, his serum potassium remained low despite of intervention.
- CXR was done and showed a bulky right sided hilar mass.
- The combination of refractory hypokalaemia, hyperglycaemia, and lung cancer suspicion led to endocrinology review. Suggestion was made that these findings could be secondary to hypercortisolism.
- A corticotrophin-releasing hormone (CRH) test was performed as a differential diagnosis of adrenocorticotropic hormone (ACTH) dependent Cushing's syndrome.
- Supraclavicular node biopsy showed an undifferentiated small cell cancer of lung origin. L1 vertebral body fracture and extensive metastatic disease was also seen on the MRI scan.
- Oncology review concluded poor prognosis and suggested palliative chemotherapy.
- The patient eventually expired in the hospital.
- This highlights the vitality in recognising the evolving clinical manifestations of paraneoplastic disease and seek specialist advice appropriately and urgently.
- He presented with two weeks history of polydipsia, polyuria, lethargy and weight loss. Otherwise, fit and well and independently mobile.
- He worked in a supermarket factory and lived at home with his partner.
- As both of them did not speak English, a collateral history was taken from his cousin.
- On admission capillary blood glucose (CBG) was 34.1 mmol/l (normal ref: 4-8 mmol/l).
- Further blood tests showed hypokalaemia K+ 2.6 mmol/l (ref: 3.5-5.3 mmol/l), and mildly elevated white cells 12.39 10*9/l (ref: 4.0-11.0) and neutrophils 9.87 10*9/l (ref: 2- 7.5).
- Physical examination and the rest of blood tests were unremarkable.

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LB37

Thyroid dysfunction with Zoledronic acid infusion for osteoporosis

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Introduction
It has been seen that Zoledronic acid (ZA) infusion induces an acute inflammatory response associated with rise in inflammatory markers and changes in thyroid function tests resembling non thyroidal illness syndrome. It is also postulated that amino group of ZA has a role in causation of these thyroid function abnormality. (1)
Material and methods
An observational study at tertiary care hospital of India where thyroid functions tests were studied at day 0,1,2,3,7 and day 42 post ZA infusion. Anti TPO Antibodies were also done at baseline. Subjects with pre-existing thyroid disorders, on therapies which can alter thyroid functions, critically ill patients, secondary osteoporosis patients, who received ZA in past and patients with BMI > 30 Kg/m^2 were excluded from study.
Results
Total of 168 patients participated in the study. 159 (94.6%) were post-menopausal females and 9 (5.35%) patients were males. In our study it was observed that there was transient fall in free T3 at day 1 and day 2 and it normalized by day 7 (P value <0.05). Changes in FT4 post ZA infusion were not statistically significant. TSH rose after ZA infusion in our study and this rise continued till final follow up till day 42 post ZA infusion. Rise in TSH post ZA infusion was higher in patient having positive anti TPO antibodies. (P value <0.05).
Conclusion
Study found that Free T3 hormone falls significantly after 5 mg ZA infusion at day 1 and day 2. The present study also found that TSH hormone rises significantly after ZA infusion when followed till day 42. Rise in TSH was significantly higher in subjects having evidence of thyroid autoimmunity.
Reference
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LB38

An interesting case of Hypophosphataemia: Oncogenic Osteomalacia

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Introduction
Causes of hypophosphataemia include reduced intestinal absorption, inadequate intake, transcellular shifts (refeeding syndrome, glucose/insulin infusion), renal loss which is either FGF23 mediated (inherited forms or tumour induced osteomalacia) or non-FGF23 mediated (hyperparathyroidism, drugs)
Case report
We present a case of 51 years old female referred to us with multiple fractures during her half marathon. She suffered from bilateral metatarsal fractures & had distal fibula fracture in 2017. Her routine blood results revealed low phosphate. She had low phosphate levels since 2019 ranging from 0.41 to 0.63 mmol/l. Her Urine calcium excretion was slightly low and phosphate excretion was within normal range. Her ALP and FGF23 levels were high as below: This pointed towards FGF23 mediated hypophosphataemia likely tumour induced. A whole body SPECT CT scan showed multiple non-specific uptakes at left Clavicle, ribs, both pubic rami and Left foot third metatarsal likely Oncogenic Osteomalacia. Subsequently, an Octreotide/Tektrotyd scan was performed which picked up faint activity at right Pubic symphysis medial to the pectineus muscle about size of 2 cm. MRI scan also spotted a small focus in Right pectineus muscle 17×11mm. After discussion at Soft Tissue/Bone MDT, she underwent resection and biopsy was consistent with phosphaturic mesenchymal tumour. Her phosphate levels have normalized now.
Discussion
Tumour Induced Osteomalacia (TIO) is a rare paraneoplastic syndrome causing muscle weakness, fractures and bone pains. FGF23 is secreted by the mesenchymal tumours & impairs phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D at renal tubules. Most common tumours are in the skin, muscles, and bones of extremities or paranasal sinuses. First line treatment is surgery, if not feasible then phosphate & Vitamin D supplementation is helpful.

Table 1

Blood test	Result	Normal Range
Phosphate	0.41 mmol/l	0.74-1.14 mmol/l
Alkaline Phosphatase	320 U/l	30-120 U/l
FGF23	341 RU/ml	<100 RU/ml

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LB39

Metabolomic analysis of succinate dehydrogenase subunit knockout in phaeochromocytoma and neuroblastoma cell lines

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Loss of function of succinate dehydrogenase (SDH), caused by mutations in each of the 4 subunits – *SDHA/B/C* and *D* – is associated with development of phaeochromocytomas and paragangliomas (PPGLs). The mutations lead to loss of enzymatic activity and subsequent accumulation of the oncometabolite succinate, a driver of tumourigenesis. It is well established but poorly understood why mutations in *SDHB* are associated with more aggressive metastatic disease than the other SDH subunits. Moreover, it is not known why these SDH-deficient tumours arise predominantly from chromaffin cells as opposed to other cell types. Using CRISPR/Cas9, we have generated knockouts of subunits A and B in both the rat phaeochromocytoma-derived PC-12 chromaffin cell line and the human SH-SY5Y neuroblastoma neural crest cell line. We have subsequently used a mass spectrometry-based metabolomics approach to compare the metabolite profiles of the knockouts in both the phaeochromocytoma and neuroblastoma cell lines. This analysis has identified metabolite profiles that are unique to the chromaffin knockout cell models, potentially identifying metabolic vulnerabilities that are specific to PPGLs and could be targeted in the treatment of these tumours.

10.1530/endoabs.77.LB39

LB40

Novel ultrasound approaches permit the visualisation of the microvascular effects of glucagon-like peptide-2 in the gut with unprecedented resolution

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The screening and monitoring of intestinal diseases still provides challenges within *in vivo* and clinical research. For example, patients with Crohn's disease will typically have a biannual endoscopic examination – this invasive procedure is distressing for patients and hence its frequency is limited at the expense of sufficient monitoring of pathological progression. Modalities such as CT and MRI can image the GI tract, however, they are ionising, which normally precludes them for screening purposes, and limits their frequency for monitoring. Recent advances in post-processing techniques with Contrast Enhanced UltraSound (CEUS) allows functional imaging of the GI tract with resolutions of approximately 60um. Ultrasound is relatively cheap, non-invasive, and non-ionising, thus, supporting its use for regular screening and monitoring. Anaesthetised rats received, via IV, a vehicle control infusion followed by either vehicle control or Teduglutide (a GLP-2 agonist) infusion. During each infusion a bolus of microbubbles (MB) – commonly used as ultrasonic contrast agents – were injected and high frame-rate, high frequency CEUS sampled the 15 minute bolus response. For the first time, intestinal villi were visualised non-invasively. Furthermore, novel metrics such as blood velocity and perfusion within the villi were quantified and a significant difference was found between control animals and animals receiving Teduglutide. Specifically, Teduglutide was found to increase: the peak intensity response and the area under a time intensity curve, indicating greater perfusion; the blood velocity in duodenal villi; and the diameter of mesenteric arteries. The unprecedented functional resolution achieved with our novel methods are translational to a multitude of applications, for example: rapid quantification of dose response within drug discovery programs; the localised microcirculatory response to food could be quantified during digestion; and longitudinal structural change to the villi or bowel wall thickness could be tracked. Moreover, the non-invasive nature of this method could dramatically reduce animal numbers.

10.1530/endoabs.77.LB40

LB41

Intestinal Organoids as Vehicles for Therapeutic Peptide Delivery

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Background
Therapeutic peptides are medicines with high potency, low toxicity, and, broad disease targets. However, the widespread use of peptides is limited by their easy degradation in human body. The intestinal organoid technology can be utilized to design a novel cell-based peptide delivery system. Intestinal organoids feature intestinal epithelial tissue-like structure, harboring all the expected *in vivo* epithelial cell types, including enteroendocrine cells (EECs). EECs are collectively recognized as the largest endocrine system.
Objective
This study aims to use EECs as target cells for the manufacture and *in vivo* delivery of therapeutic peptides. Insulin was used as a representative peptide to generate proof-of-concept data to validate the use of intestinal organoids as a system for delivery of therapeutic peptides.
Methods
Human proinsulin coding sequence was integrated into the genome of murine duodenal organoids. This genetic modification was conducted by electroporation using *piggyBac* transposon. The human proinsulin gene was driven by NeuroD1 or CMV promoter. The proinsulin gene co-expressed with tdTomato, red fluorescence indicated the expression of insulin. mRNA expression levels of different clones were assessed by qPCR. Clones with the highest transcription were selected to assess insulin secretion using ELISA. Wholemount immuno-fluorescence staining of insulin was performed to locate insulin-secreting cells.
Results
Transgenic clones with CMV promoter gave rise to a scattered pattern of red fluorescence and significant insulin mRNA expression. Clones with NeuroD1 promoter showed no red fluorescence and low levels of insulin mRNA. Insulin secretion of CMV clones was significantly higher than that of NeuroD1 clones. Immunostaining showed few insulin-positive cells.
Conclusion
Genetically modified insulin-expressing intestinal organoids delivered using the *piggyBac* transposon system functioned properly at the transcriptional level but

not at the peptide level. This model faces challenges such as low levels of insulin secretion, possible misfolding of insulin protein structure. Solving these issues may provide a usable system.

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LB42

Identifying biomarkers of psoriasis-driven metabolic disease

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Background
Inflammatory skin diseases such as psoriasis induce changes in the skin-secretome, which potentially lead to dysfunction of key metabolic tissues and increased risk of psoriasis co-morbidities, such as type 2 diabetes (T2D). However, the proteins and peptides that make up the skin-secretome remain poorly characterised. Proteomic analysis has identified vimentin, parathymosin, prothymosin-alpha, dermcidin, and desmin as potential skin-secretome factors, which may induce metabolic and inflammatory effects in psoriasis (Evans, 2020). This project investigated the impact of these candidate proteins on mouse pancreatic islet and subcutaneous adipose tissue (sAT) function.
Methods
Pancreatic islets were isolated from 8-week-old CD1 male mice. sAT was collected from male 26-week-old C57BL/6 mice fed either standard or 60% high-fat-high-fructose diet (HFHFD). Islets were treated with recombinant proteins at a range of (patho)physiological concentrations, while sAT was treated with a cocktail treatment (vimentin;500 ng/ml, dermcidin;1000 ng/ml, prothymosin-alpha;1000 ng/ml, parathymosin;1000 ng/ml, desmin;500 ng/ml). Pancreatic islet health was determined by glucose-stimulated insulin secretion (GSIS; radio-immunoassay) and cell apoptosis (caspase-glo 3/7 assay). sAT function was determined by qRT-PCR measurements of gene markers of sAT function and inflammation.
Results
Vimentin;500 ng/ml and prothymosin-alpha;1000 ng/ml islet treatments decreased GSIS, whereas parathymosin;1000 ng/ml, dermcidin;1000 ng/ml, and desmin;500 ng/ml increased GSIS, with parathymosin;1000 ng/ml and dermcidin;1000 ng/ml also inducing significantly elevated levels of cytokine-mediated cell apoptosis ($P < 0.01$). Cocktail treatment of mouse sAT induced a significant increase in expression of IL-1β, IL6, and LCN2 ($P < 0.01$), along with a significant reduction in the expression of functional markers GLUT4 and PPAR-γ ($P < 0.05$) both in the standard and 60% HFHFD samples.
Conclusion
Distinct factors present in the skin-secretome could orchestrate the impaired metabolic function observed in psoriasis, possibly through inducing changes in the functional and secretory profile of sAT and islets that could exert systemic effects on key metabolic organs, increasing the risk of T2D.

10.1530/endoabs.77.LB42

LB43

GLP-1 receptor agonists offer protection against fatty acid induced insulin resistance in 3D kidney spheroids

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Increased fatty acid (FA) concentration is implicated in the development of insulin resistance (IR) in tissues such as the kidney. Research indicates the protective role of glucagon-like peptide (GLP)-1 receptor agonists; GLP-1 (7-36) amide and incretin mimetic; liraglutide, against IR. We aimed to induce IR in HEK293T cells, using the three most abundantly consumed FAs; palmitate, oleate, and stearate, or in a combination termed POS. This model was used to assess the extent of protection upon co-treatment with 1μM GLP-1 amide and liraglutide, in HEK293T cells, following IR and hypoxia (2% O_2). To increase physiological relevance, studies were performed under traditional 2D methodologies and 3D spheroid cultures. Palmitate (50-750μM) induced the highest toxicity (up to 60%) compared to all other FAs at all concentrations using the alamarBlue assay. Stearate offered the lowest toxicity (33%), whilst POS appeared to be an average of all three. Hypoxia increased toxicity of palmitate treated cells in comparison to normoxia. Co-administration of GLP-1 agonist with POS, significantly reduced cellular toxicity in both normoxic and hypoxic conditions, when compared to POS-only ($P \leq 0.05$). 3D viability studies showed a reduction in toxicity of all FAs when compared to 2D. Interestingly, GLP-1 agonists offered higher protection at high concentrations of FA (500 and 650μM) compared to 2D. To determine the mechanism of action for GLP1 agonists, several key proteins in the GLP-1R cascade were targeted. Inhibition of CPT1 (Etomoxir) or PPARα (GW6471), in the presence of fatty acids, decreased toxicity, similar to the effects of GLP1. In conclusion, the presence of FAs in HEK293Ts decreases cell viability and induced IR, which can be partially reversed using GLP-1 agonists. GLP-1 and liraglutide may offer therapeutic management of FA-induced toxicity, although the mechanism of protection needs further investigation, it appears to involve PPARα and handling of mitochondrial FA uptake.

10.1530/endoabs.77.LB43

LB44

Depression and islet function during pregnancy: Generation of a depressive phenotype using UCMS

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Gestational diabetes (GDM) occurs when beta-cell insulin secretory capacity is insufficient to meet the increased demands required to maintain normoglycemia during pregnancy. Considerable clinical evidence supports a link between depression and GDM, although underlying mechanisms are unclear. We used the unpredictable chronic mild stress (UCMS) rodent model of depression to examine the metabolic effects of depression in pregnant mice. C57BL/6J females were divided at 4-weeks-old into control or UCMS-treated groups. UCMS-treated mice were singly-housed and subjected daily to multiple stressors for 6-weeks, whilst controls were pair-housed under normal conditions. Sucralose preference testing showed UCMS mice had reduced sucralose preference, indicative of increased anhedonia ($72.6 \pm 0.7\%$ *vs* Control $83.4 \pm 0.65\%$ $P < 0.0001$). UCMS mice exhibited depressive-like behaviours in both Porsolt Swim and Splash tests, with decreased latency to immobility (81 ± 6s *vs* Control 129 ± 19s $P = 0.02$) and increased latency to grooming (121 ± 15s *vs* Control 75 ± 11s $P = 0.02$), respectively. Whilst baseline plasma corticosterone levels were indistiguishable between groups ($P = 0.98$), the increase in costicosterone in response to the Porsolt test was significantly reduced in UCMS mice (78.2 ± 7.6ng/ml *vs* Control 107.5 ± 6.2ng/ml $P = 0.0005$). Mice underwent intraperitoneal glucose tolerance (IPGTT) and insulin tolerance (IPITT) tests, both before pregnancy and at gestational days 16-18 of pregnancy. Non-pregnant UCMS females showed a trend for improved glucose tolerance (1452 ± 46 AUC *vs* Control 1590 ± 56 $P = 0.07$), whilst pregnant UCMS females had significantly improved glucose tolerance (1616 ± 97 AUC *vs* Control 2051 ± 188 $P = 0.05$). There were no changes in insulin sensitivity (non-pregnant $P = 0.96$, pregnant $P = 0.15$) or plasma insulin levels (non-pregnant $P = 0.26$, pregnant $P = 0.52$) between groups. In conclusion, UCMS provides a good depression model in C57BL/6J females, with increased anhedonia, behavioural despair and a blunted HPA-axis stress-response. However, rather than correlating with impaired glucose tolerance, our study suggested depression produced a protective metabolic phenotype, improving glucose homeostasis, independently of insulin sensitivity.

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LB45

Challenges and solutions for the management of inpatient diabetes care during and post COVID 19 pandemic

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Background
During the first wave of the COVID pandemic a large proportion of diabetic clinics and services were reduced or postponed, combined with a move to telephone consultations for GPs. Diabetic nurse specialists were also re-deployed from regular inpatient services. Additionally, patients were reluctant to seek out healthcare services either due to the risk of contracting COVID or not wanting to place unnecessary stress on the healthcare services.
Audit & results
A local audit carried out in March to May 2020 showed an increase in newly diagnosed diabetics presenting with more severe complications such as

hyperglycaemic hyperosmolar syndrome or diabetic ketoacidosis. The audit also noted a large increase in patients admitted with delayed presentations of acute diabetic foot problems following the end of the first lockdown, and a similar pattern of reduction in admission with the second lockdown. Young patients were less likely to engage with virtual services as compared to face to face consultations. The use of dexamethasone for the management of COVID further complicated the inpatient management of diabetes.
Actions
Given that a third of all deaths in the first wave of COVID were diabetic, good diabetic control is key. The implementation of a new management of hyperglycaemia protocol has resulted in better control of blood glucose for inpatients, especially those prescribed dexamethasone and 0 datixes on hypoglycaemic events since the implementation of the protocol. Outpatient and inpatient services must be continued to ensure adequate ongoing diabetic care.
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LB46

Improvement in the delivery of Diabetes foot care after implementing a restructured referral form: An experience from a District General Hospital
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Background
There are nearly 5 million people with diabetes mellitus in the UK with an estimated 10% of diabetes patients developing a foot ulcer at some point in their lives. Nearly 9500 diabetes-related amputations are reported in the UK per year and approximately 80% of the NHS budget on diabetes care is spent on treating complications. Limb/life-threatening diabetic foot problems are referred to acute services immediately and all other active diabetic foot diseases are referred to Multi-Disciplinary Foot care service according to local protocols and pathways for triage.
Method
A generic referral proforma with patient demographics, the reason for referral and relevant clinical information was sufficient to complete the referral. We restructured the existing pro forma and added more care centric questions to assess clinical status and urgency. Specific information regarding recent wound swabs, imaging, lab investigations, current arterial status and offloading, were incorporated. Electronic records and referral Data were gathered prior and 8 months later after implementation of the new proforma.
Results
Improvement in the quality of patient care, as well as compliance with standards, was noted. Average waiting time for appointments was reduced by 15% and 17% for urgent and non-urgent referrals respectively. Nearly a quarter of the urgent referrals were identified as requiring assessment within 24 hrs. Patients, who had their wound swabs taken and lab investigations sent, increased from 30% & 27% to 68% and 72% respectively. In addition, more patients had off-loading and imaging done along with referrals.
Conclusion
A restructured referral form with specific care focused questions had the potential to improve the quality of patient care and to enhance compliance with standards.
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LB47

Evening Chronotype and type 2 diabetes: what link in menopause?
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Chronotype is defined as a trait determining the subject circadian preference in behavioral and biological rhythms relative to external light-dark cycle.The morning chronotype (MC) prefers activities earlier in the day, while the evening chronotype (EC) perform its main activity late in the day. Intermediate chronotype (IC) is in an intermediate position between MC and EC. EC as well as menopause have been associated to an increased risk of cardiometabolic diseases (CMD) in obesity. However, the prevalence of chronotype categories in menopause and their role in determining menopause-related CMD, mostly in obesity, have not been investigated. Thus, we aimed to investigate the prevalence of chronotype categories in post-menopausal women (PMW) with obesity and their role in menopause-related cardiometabolic risk. In this cross-sectional study we enrolled 49 pre-menopausal (PW) and 74 PMW with obesity. Anthropometric parameters, lifestyle habits, adherence to the Mediterranean Diet (MD), sleep quality, chronotype and the presence of CMD were studied. No significance differences were detected in terms of lifestyle, antropometric parameters and adherence to the MD between PMW and PW. Chronotype was classified as MC in 66 (53.6%), EC in 20 (16.3%) and IC in 37 (30.1%) women. In addition, PW with obesity showed a significantly higher chance to have IC ($P = 0.004$) whereas PMW with obesity showed a trend to have a MC ($P = 0.051$) although it did not reach statistical significance. However, EC had a significant higher risk to have T2DM compared to MC ($P = 0.005$) and to the intermediate chronotype ($P = 0.013$) in PMW with obesity. In conclusion, IC was significantly more prevalent in PW with obesity compared to PMW. EC was associated to T2DM in PMW. These results support the importance of including the assessment of chronotype in the management of PMW.
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LB48

Post-HUS diabetes mellitus in 3 years old child: the challenging management of glucose control and the advantages of SAP therapy initiation
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Introduction
Hemolytic-uremic syndrome (HUS) is a clinical condition characterized by nonimmune hemolytic anemia, thrombocytopenia and progressive kidney failure mediated by E.Coli Shiga-like toxin. In rare cases the inflammatory process may lead to beta-cell necrosis and, hence, overt diabetes mellitus. Post-HUS DM is characterized by severe insulin depletion and very high insulin sensitivity, making its therapeutic management particularly challenging.
Case report
We report the case of a 3 years old female admitted to her town emergency department for fever (39°C) associated with diarrhea, generalized oedema, oliguria and drowsiness. Blood test revealed metabolic acidosis, leucocytosis, increased inflammatory markers, anemia, thrombocytopenia and acute kidney failure. Based on the diagnosis of Haemolytic-uremic syndrome the patient was referred to a third level children hospital. Assisted ventilation, haemodialysis and parenteral nutrition was instituted. Blood glucose levels increased above 200 mg/dl with peaks at 500 mg/dl. GAD-Ab and ICA were negative and C-peptide below normal values. Therefore, multiple daily injections (MDI) insulin therapy was instituted with the following regimen: detemir 2U daily, aspart 0.5U for BG > 200 mg/dl. Despite very low amount of insulin, the patient experienced frequent and severe hypoglycaemia in the following 24h. MDI was replaced with Sensor-Augmented Pump (SAP) therapy set at 0.025U/h basal rate and 0,05U/g Insulin:Carbohydrates ratio for meal boli. Optimal glucose control was achieved without hypoglycaemia. Moreover, excellent glucose control was maintained after enteral and oral nutrition introduction.
Discussion
This case illustrates the potential role for SAP therapy in the management of a severe insulin deficient post-HUS diabetes in a 3 years old child. Although glucose control is challenging due to the high insulin sensitivity, low insulin requirement and consequent high risk of hypoglycaemia, SAP therapy optimization offers an effective and versatile treatment option. Furthermore, early SAP therapy initiation might be beneficial in terms of infection resolution and timely recovery.
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LB49

Diabetes and Deafness: Think outside the box
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A 47-year-old Caucasian gentleman was diagnosed with diabetes mellitus in September 2019. He presented with blood glucose 29.5 mmol/l and negative ketones in December 2020 and was treated with variable rate insulin infusion. He had short stature with height of 161 cm and weight 53.5 kg (BMI 20). There was mild weakness of quadriceps (4/5). Laboratory tests revealed high lactate (5.38

mmol/l) and HBA1c (70 mmol/mol), reduced eGFR (47 ml/min) and negative antibody. He had gradual decline in hearing required hearing aids from May 2019 and two episodes acute heart failure from 2018. Echocardiogram and cardiac MRI revealed extensive myocardial fibrosis with severely impaired left ventricular (LV) systolic function and LV thrombus requiring warfarin. He had undergone implantation of a CRT-D device in 2020 for progression of hypertrophic cardiomyopathy. He had chronic renal impairment preceding the diagnosis of diabetes with high urine PCR (235 mg/mmol) His mother had diabetes, hearing loss short stature and died of myocardial infarction. His grandmother had deafness and heart failure. His maternal two uncles had deafness and neuropathy. His sister had gestational diabetes and her child was under investigation for deafness. Genetic testing confirmed maternally inherited diabetes and deafness (MIDD) with presence of heteroplasmic m.3243A > G pathogenic mutation of MT-T11 at a level of 24%.

Discussion

Early diagnosis of MIDD is challenging when other clinical manifestations precede the diagnosis of diabetes. This case is a reminder of the importance of considering a genetic condition when diabetes is associated with additional key clinical features and a significant family history.

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LB50

A plasma and serum 5-HIAA assay with comparable diagnostic performance in patients with neuroendocrine tumours

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Introduction

Neuroendocrine tumours (NET) are a diverse group of neoplasms originating from cells within the diffuse endocrine system. Urine 5-HIAA is commonly used in the diagnosis and monitoring of patients with NET in particular small intestinal neuroendocrine tumour with carcinoid syndrome. Urine 5-HIAA collection over a 24 hour period and the potential exposure to acid preservative in the sample container, limit the use of urine 5-HIAA.

Methods

Samples were obtained from 80 patients with NET and 30 healthy volunteers. We developed and validated a liquid chromatography tandem mass spectrometry (LC-MS/MS) assay for plasma and serum 5-HIAA. Sensitivities and specificities of the plasma and serum 5-HIAA assays were assessed using a ROC curve. Comparison was made between urine 5-HIAA and 5-HIAA in plasma and serum.

Results

The assay showed acceptable analytical performance. Area under the curve (AUC) from ROC analysis for plasma 5-HAA was 0.899 and 0.902 for serum 5-HIAA. Sensitivity of 91.2% with a specificity of 61.9% were obtained at a cut off of 135 nmol/l for both plasma and serum 5-HIAA. A statistically significant correlation was observed between the plasma and serum 5-HIAA assay. Bland-Altman analysis showed a good agreement between both assays. A statistically significant agreement was shown when plasma and serum 5-HIAA was compared with urine 5-HIAA in patients with NET, $\kappa = 0.675$ (95% CI 0.49 to 0.86), $P < 0.001$. Similar finding was observed in healthy volunteers when plasma and serum 5-HIAA was compared with urine 5-HIAA, 0.967 (95% CI 0.828 to 0.999), $P = < 0.001$.

Conclusion

We developed an LC-MS/MS assay for plasma and serum 5-HIAA and have demonstrated that they compare well with the urine 5-HIAA assay. The plasma and serum 5-HIAA assays were shown to be comparable; hence either sample type may be used as an alternative to the urine 5-HIAA assay.

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LB51

An unusual recurrence of a non-functioning pituitary adenoma as mantle cell lymphoma

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We present a case of a 73 year old female with recurrent non-functioning adenoma and co-existent mantle cell lymphoma within the pituitary fossa. Mantle cell lymphoma (MCL) is rare comprising around 6% of non-Hodgkin lymphoma diagnoses. It infrequently involves the central nervous system, with only one published case of involvement of the pituitary gland. Our patient initially presented in April 2003 with marked visual loss due to a large non-functioning cystic pituitary macroadenoma. She underwent successful transsphenoidal decompression in 2003 and continued to have regular surveillance scans. Over a period of 11 years there was evidence of slow regrowth of the residual adenoma, requiring further debulking surgery in 2007 and 2014. Later in 2017 the patient received a new diagnosis of MCL. This responded well to chemotherapy treatment going into complete remission. In early 2020 MCL recurrence was identified in the soft palate on positron emission tomography. Further repeat pituitary magnetic resonance imaging (MRI) in 2020, organised for routine surveillance, showed a substantial increase in size of the pituitary lesion impinging on the optic chiasm. The MRI reported rapid growth of the residual pituitary macroadenoma with the mass measuring 17 mm in the midline compared with 11 mm previously in 2018. There was significant reduction in the cerebrospinal fluid plane between the chiasm and the tumour. As a result of these findings the patient underwent further re-do transsphenoidal surgery in December 2020. She has since received radiotherapy and has been considered for Ibrutinib treatment. Notably, the latest pituitary histology results showed both non-functioning adenoma with evidence of MCL combined. This case highlights the importance of recognising alternate pathology with a rapidly growing pituitary adenoma, which previously was observed to slowly recur over several years. Review of other published literature suggests that this is an exceptionally rare case presentation.

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LB52

Central serous retinopathy as a manifestation of cushing's disease – two case reports

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Introduction

The hypercortisolaemic state of Cushing's syndrome can lead to ophthalmic complications. We present two case reports of rare association of central serous retinopathy (CSR) and Cushing's syndrome.

Case 1

A 46-year-old man presented with gradual deteriorating vision. He was diagnosed with CSR and was referred to the Endocrine department for screening for Cushing's given suspicious clinical features. Past history included hypertension and type 2 diabetes mellitus. On examination, he had increased nuchal fat pad, centripetal obesity and truncal striae. Cushing's syndrome was confirmed biochemically with elevated 24-hour urine free cortisols: 278, 335 and 436 nmol/l (Normal < 165); unsuppressed 9 am cortisol in dexamethasone suppression test (128 nmol/l: Normal < 50) and elevated midnight salivary cortisol (2.9 nmol/l; normal < 1.7). CRH testing, MRI (pituitary micro-adenoma) and petrosal sinus sampling was consistent with ACTH dependent Cushing's disease. Biochemical and clinical remission was achieved following transphenoidal hypophysectomy in December 2020.

Case 2

43-year-old man presented with vision loss and was diagnosed with central serous retinopathy. In addition he had clinical features of plethoric facies, easy bruising, thinning of the skin, hypertension and central obesity. He had raised urinary free cortisol (1292), elevated dexamethasone post low dose dexamethasone suppression test. He underwent a transphenoidal hypophsectomy and had full biochemical and clinical remission post operatively. His CSR is currently in remission.

Discussion

In CSR the choroid layer in the retina is thickened and congested with increased blood vessels, resulting in increased pressure which can cause capillary damage to the retina. Excess steroids is the greatest risk factor for CSR. Treatment for Cushing's along with specific ophthalmic treatment for CSR can potentially reverse the disease and protect sight.

Learning points

1. Cushing's syndrome is a diagnosis to consider in patients with CSR and no history of steroid use. 2. Treatment of Cushing's syndrome can potentially be sight preserving.

10.1530/endoabs.77.LB52

LB53

Central diabetes insipidus as initial presentation of Acute myeloid Leukaemia monosomy 7

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Introduction
The association of central diabetes insipidus (CDI) and acute myeloid leukaemia is rare. The onset of CDI is variable during the disease course and can be a presenting feature of AML
Case:
A 75 years old Caucasian male patient presented with acute right sided abdominal pain. His initial CT abdomen was normal. He had normocytic anaemia, thrombocytosis and monocytosis. A repeat CT scan 3 days later showed bilateral swollen adrenal glands and an inflammatory process affecting the retro-peritoneum. Prior to this, he reported headaches for 2 months associated with symptoms of polyuria and polydipsia. Diabetes Mellitus had been excluded in primary care. Endocrine investigation showed a low morning cortisol of 59 nmol/l with ACTH of 20.1 ng/l and free T4 pmol/l of 6.6 with TSH of 1.27mU/l in keeping with mixed primary and secondary adrenal insufficiency and secondary hypothyroidism respectively. MRI pituitary showed focal thickening of the pituitary infundibulum. Subsequent water deprivation testing was equivocal but arginine vasopressin test was normal with initial Co-peptin levels of 3.8 pmol/l rising to 3.9 pmol/l after Arginine infusion. Steroid and levothyroxine replacement was commenced. Due to ongoing symptoms desmopressin was given with good response. Initial suspicion was IgG-4 disease with pituitary and retroperitoneal involvement. PET CT scan showed resolving adrenal oedema and completely resolved retroperitoneal inflammatory changes. However, there was diffuse homogeneous marrow activity and mild splenic activity. A blood film showed circulating blasts and a bone marrow biopsy confirmed AML with AML FISH panel showing monosomy 7. He was commenced on Azacitidine and Venetoclax chemotherapy with good response to treatment so far and resolution of some of the endocrinopathies.
Conclusion
The association of AML with monosomy 7 and CDI has been reported in the literature. Our patient also presented with anterior pituitary and adrenal involvement (hypophysitis and adrenalitis) which responded well to AML treatment with partial resolution of hormone deficiencies.

10.1530/endoabs.77.LB53

LB54

An unusual neuroglycopenic presentation in a case of Insulinoma

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Insulinoma is an insulin-secreting tumour of beta cells resulting in hypoglycemia. This rare tumour presents with hypoglycemic symptoms and can be easily confused with transient ischemic attack or epilepsy or delirium. The diagnosis of an insulinoma is usually made biochemically and confirmed by localizing the tumour with imaging. We present this case of a 56 years old woman who repeatedly presented to emergency for her symptoms of diplopia and word finding difficulty. She also could not express herself properly. Each episode lasted for about 20 minutes. Her physical examination and investigations in emergency department were unremarkable, except the ECG that showed bradycardia which was believed due to her sports activity. Since she developed headache after this event, Stroke Consultant was inclined to believe that she had an episode of a migraine with aura. In some episodes she experienced diplopia, blackouts, confusion and in some she was found to have slurred speech, balance issues and was argumentative. She was reviewed during her regular neurology follow up and neurologist came across that once an ambulance was phoned and her glucose was apparently bit low. She started doing capillary blood glucose and often in the morning found glucose level of 2.1 mmol/l and 1.9 mmol/l. And once it was noticed that her symptoms might be correlated with an episode of hypoglycemia, she was referred for urgent endocrine review. During her 72 hour fast she had hypoglycaemia within few hours of the tests and results showed glucose-1.8 mmol/l, c-peptide 906 pmol/l, insulin-185 pmol/l and C-peptide-906 pmol/l. She had gallium-dotatate scan which showed intense activity neuroendocrine tumour. The tumour was less than 1 cm in diameter and was fully removed surgically. Post-operative, the patient reported complete resolution of symptoms.

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LB55

Optimising diagnostic and management clarity in two opposing sodium centenarians

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Introduction
Hyponatraemia is one of the most common electrolyte abnormalities seen in clinical practice [1] and can be caused by a myriad of aetiologies.
Aim
To report two cases of severe hyponatraemia caused by different aetiologies.
Case report
A 56-year-old male patient was admitted with 2 episodes of tonic-clonic seizures at his care home. The patient had a background of small cell lung cancer and brain metastases in late 2020. Laboratory investigations revealed a sodium level of 101 mmol/l, serum osmolality of 250 mosm/kg, urine osmolality of 457 mosm/kg and urine sodium of 158.6 mmol/l. His CT head showed a left occipital lobe cystic lesion with some surrounding vasogenic oedema. The cause was multifactorial with relative glucorticoid deficiency and a degree of cerebral salt wasting. Sodium was increased by initially slow IV saline (and some fluid restriction), increased dose of dexamethasone (4 mg from 2 mg) and demeclocycline 300 mg. Similarly, a 73-year-old female patient presented to hospital with dizziness and a fall. The patient has a background of hypertension, type 2 diabetes mellitus and mild axonal neuropathy for which she took bendroflumethiazide 2.5 mg OD, omeprazole 20 mg, candesartan 10mg OD, felodipine 2.5 mg OD, gliclazide 40 mg and simvastatin 20 mg ON. Blood tests revealed sodium of 100 mmol/l with a serum osmolality of 214 mosm/kg, urine osmolality of 272 mosm/kg and urine sodium of 41.2 mmol/l. The cause was determined as drug-induced, the most likely culprits being a thiazide and omeprazole, and appropriately stopped along with fluid restriction of 1.5L/day.
Conclusion
Both cases presented with varied clinical presentations and causes but both with profound hyponatraemia of 100 mmol/l. There are profound risks associated with this yet with precision in diagnostics and selective treatment plans, both patients had excellent outcomes with restoration of sodium levels.

10.1530/endoabs.77.LB55

LB56

Placental levels of miR-1-3p and miR-133a-3p are decreased in pregnancies complicated gestational diabetes with large-for-gestational-age birth outcomes and may be influencing vascular smooth muscle differentiation

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Introduction
Gestational diabetes (GDM) affects 1 in 6 pregnancies globally, increasing babies' risk of being born large-for-gestational-age (LGA). This can cause birth injuries and predisposes offspring to developing cardio-metabolic disease in adulthood. The cause of LGA in GDM is unclear, however GDM placentas have been shown to display abnormal morphology indicative of vascular network immaturity. MicroRNAs (miRNAs) are known regulators of vascular development, including skeletal muscle specific 'myomiRs', which control vascular smooth muscle (VSM) differentiation in other systems. We aimed to determine whether myomiRs may be involved in the development of LGA in GDM pregnancies and to investigate their roles in placental VSM differentiation.
Methods
Placentas were collected at delivery and birth outcomes recorded. Levels of vascular myomiRs were quantified via RTQPCR. Primary placental mesenchymal stromal cells (PMSCs) from uncomplicated pregnancies were isolated by collagenase and dispase digestion. PMSCs were characterised via flow cytometry and immunocytochemistry. Differential potential of PMSC was assessed through their ability to differentiate down adipogenic and osteogenic lineages. Differentiation down the VSM lineage was induced through supplementation of growth media with TGF-β1 on a collagen matrix, myomiRs and MYH11 were measured by RTQPCR.
Results
Two of the four myomiRs tested, miR-1-3p and miR-133a-3p, were significantly decreased in GDM-LGA ($n = 15$) placentas compared to GDM pregnancies with appropriately-grown-for-gestational-age offspring ($n = 12$; $P < 0.05$). Characterisation of MSC markers and differential potential confirmed that the cells isolated were PMSCs ($n = 3$). When induced to differentiate down the VSM lineage, PMSCs on average showed a 6-fold upregulation of VSM marker

MYH11, as well as 15- and 12-fold increases in miR-1-3p and miR-133a-3p, respectively ($n = 3$; $P > 0.05$).
Conclusions
Decreased levels of placental miR-1-3p and miR-133a-3p in GDM-LGA may be contributing to placental vascular immaturity since these myomiRs appear to be involved with VSM differentiation, however further experiments with a larger cohort are required to confirm this.

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LB57

A Novel LC-MS/MS Method for the Simultaneous Detection of Multiple Steroids in Plasma and Tissue Lysates, used to verify Cell Autonomous Sex Identity in birds

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Cell autonomous sex identity (CASI) of birds is the concept that sex-steroids have little or no effect on the development of secondary sexual characteristics in birds, and that sexual dimorphisms are determined by the sex-chromosome content of cells in individual tissues. In avian species males have a ZZ sex chromosome, while females are ZW. Sexual dimorphisms in chickens, such as muscle mass, comb and wattle size and hackles and spur development are believed to be determined by the sex chromosome content of cells in individual tissues. We wanted to compare steroid profiles in male birds, female birds and female birds with sex-reversed gonads following treatment with Fadrozole an aromatase inhibitor which prevents the conversion of androgens to estrogens, and commonly leads to ovary-to-testis sex reversal or ovotestis formation in birds. To do this we developed and validated a sensitive, automated LC-MS/MS method to profile estrogens, androgens, progesterones and glucocorticoids - in total 18 steroids including estradiol, estrone, androstenedione, testosterone, dihydrotestosterone, progesterone - in plasma (200 μL) and tissue from chickens to investigate CASI. Here we assessed the effects of blocking estrogen synthesis on steroidogenesis in the chicken in embryo gonads and birds at 10 weeks and sexual maturity (26 weeks). We successfully measured steroid levels in the embryonic gonads of male and female chickens. We also profiled circulating steroids in chickens and found that those produced by the sex-reversed female (ZW) gonad is indistinguishable from that produced by a typical male (ZZ) gonad, and clearly demonstrated that, unlike mammals, gonadal steroids have minimal (if any) effect on the development of secondary sexual characteristics. We showed that both male and female embryonic gonads are steroidogenically active during the earliest stages of gonadal medulla differentiation. This study highlights an evolutionary divide in the role of steroid between birds and mammals.

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LB58

Silver Russell syndrome – Rare case of sibling

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Silver-Russell syndrome (SRS) is a rare syndrome. It was first reported by Silver, Russel and al, who described children with low birth weight, postnatal statural delay, peculiar facies and asymmetry of the body. We report the case of two sibling children born to non-consanguineous parents, admitted to our level for the exploration of severe staturo-weight retardation in relation to marked intrauterine growth retardation. The first child is a 04-year-old girl, born at term. It currently has a statural delay at -5DS/Tm,-4DS/Target size, underweight with BMI 10kg/m2, and relative macro-cephaly. The second, his brother, aged 2 and a half, born prematurely at 34 WA. It has severe stunted growth dysharmonious with current size at –7DS, – 6DS /Target size and underweight: BMI at 14kg/m2; An asymmetry of the lower limbs is noted (difference of 0.5 cm), as well as a fontanelle still palpable. Examination of the external genitalia finds a poorly developed scrotum, a penis at 5.5 cm and bilateral cryptorchidism of latero-penile seat confirmed on ultrasound. Both children have a language delay, eating difficulties such as anorexia and a dysmorphic syndrome made of triangular facies, a prominent forehead, micrognatism, fragile, irregular teeth and a mouth facing downwards. The biological and hormonal investigations are without abnormalities. Standard X-rays do not reveal bone malformations. The genetic study is ongoing. SRS is a rare genetic disease. The diagnosis is often clinical based on the Netchine–Harbison score, and on the presence of additional signs described in this syndrome but the genetic test can confirm this diagnosis in 60% of cases. The etiology remains, however, unknown in a good number of patients. Cases of inter-sibling recurrence are very little described and seem to be most often associated with mutations in the center of the parental imprint. Genetic counseling in this case is of interest.

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LB59

Study of the efficacy of sublingual route administration of levothyroxine Na nablets vs oral route in cases with refractory primary hypothyroidism

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Background
Hypothyroidism is a common disorder, with a prevalence of approximately 5% and incidence of approximately 250/100,000 per year in the adult population, but both prevalence and incidence keep raising. Refractory hypothyroidism is defined by persistent TSH increase despite the administration of supra physiological weight-based dose of levothyroxine, which is usually >1.9ug/kg/d in patients with primary hypothyroidism.
Aim of the Work
To compare the efficacy of the sublingual levothyroxine Na tablets administration with respect to oral levothyroxine tablet in hypothyroid patients refractory to treatment.
Patients and Methods
This was a cross over clinical trial of 6 weeks duration that was conducted at 6th October and Ain Shams university hospitals on 40 subjects who were diagnosed 1ry hypothyroidism and who are documented to be refractory to treatment Thyroxine level was assessed using (Thyroxine absorption test) during standard oral Levothyroxine administration and 1 week after shifting to sublingual route Patients were shifted to the sublingual route on the same dose used with oral route administration Antiparietal cell antibodies, anti-TGA were measured. TSH and free T4 value were assessed finally after 6 weeks of sublingual route administration.
Results
Our study revealed highly statistically significant decrease in TSH level with Sublingual levothyroxine Na tablets (Eltroxin) compared to Oral levothyroxine tablets (Eltroxin) and also statistically significant increase in FT4 with Sublingual levothyroxine Na tablets after 1week compared to Oral levothyroxine tablets, while after 6 WEEKS sublingual levothyroxine Na tablets insignificant compared oral levothyroxine.
Conclusion
Our study revealed that sublingual levothyroxine Na tablet may be more effective than oral levothyroxine tablets in controlling TSH levels in refractory hypothyroidism and sublingual levothyroxine Na tablets may overcome some absorption problems of oral levothyroxine tablets. Autoimmune gastritis should be taken into consideration as an additional factor influencing the daily requirement of levothyroxine Na.

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Iodinated Contrast-induced Thyrotoxicosis

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Introduction
The common causes of thyrotoxicosis are Graves' disease, toxic multinodular goitre and toxic adenoma which account for >90% of cases of this condition. Iodine-induced thyrotoxicosis (Jod-Basedow syndrome) is infrequently considered as a cause of thyrotoxicosis. This case describes a lesser known cause of iodinated contrast-induced thyrotoxicosis.
Case Report
A 47 year old man with known alcoholic liver disease and recurrent pancreatitis had two hospital admissions within a space of a few weeks under 2 different teams-surgery and medicine with four contrast CT scans performed during this time. He was diagnosed and treated for alcoholic hepatitis. He developed new

onset tremor after few weeks of his admission. His thyroid function test (TFT) showed thyrotoxicosis with TSH < 0.01 mU/l, T4 33.7 nmol/l, T3 4.5 nmol/l. There was 12 day delay in his parent team referring him to Endocrinology due to various factors. His only symptom was of tremor. He had been abstinent from alcohol for > 4weeks since his admission. He did not have any previous or family history of thyroid disease. He was on amiodarone which was stopped 3 months prior due to prolonged QTc. He did not have a palpable goitre and had mild tremor of the outstretched hands on examination. Upon repeat, his thyroid function test showed improvement with suppressed TSH, T4 25.6 nmol/l and T3 4.2 nmol/l. He was diagnosed to have iodinated contrast induced thyrotoxicosis and a monitoring approach was instituted. His TFTs normalised within 10 weeks and remained so for 3 months later. His TRAb was mildly positive.

Conclusion

Iodine-based contrast agents are widely used in angiographic and other radiological procedures providing patients with supraphysiological load of organic iodide. There needs to be increased awareness of the risk of thyrotoxicosis in susceptible patients undergoing radiological investigations by non-endocrinologists and awareness by endocrinologists of this cause of thyrotoxicosis.

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