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Society for Endocrinology BES 2023

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CONTENTS

Society for Endocrinology BES 2023

PLENARY LECTURES
Clinical Endocrinology Trust Visiting Professor Lecture PL1.1
Society for Endocrinology Starling Medal Lecture PL2.1
Society for Endocrinology Dale Medal Lecture PL3.1
Society for Endocrinology Jubilee Medal Lecture PL4.1
Society for Endocrinology International Medal Lecture PL5.1
Society for Endocrinology Transatlantic Medal Lecture PL6.1
British Thyroid Association Pitt-Rivers Lecture PL7.1
Society for Endocrinology European Medal Lecture PL8.1
Society for Endocrinology Medal Lecture PL9.1
Clinical Endocrinology Journal Foundation Lecture PL10.1

PRESIDENTIAL LECTURE
Antibodies and antibody mimics as pharmaceutical drugs PR1.1

DEBATE
Precision medicine is the future of diabetes care D1.1–D1.2

SOCIETY FOR ENDOCRINOLOGY JOURNAL AWARDS
Society for Endocrinology Journal Award – Journal of Molecular Endocrinology JA1
Society for Endocrinology Journal Award – Journal of Endocrinology JA2
Society for Endocrinology Journal Award – Endocrine Connections JA3
Society for Endocrinology Journal Award – Endocrine-Related Cancer JA4
Society for Endocrinology Journal Award – Clinical Endocrinology JA5

AWARDS AND PRIZES
Teaching Achievement Award TAA1.1
Outstanding Clinical Practitioner Award OCP1.1
Nikki Kieffer Medal NKM1

EARLY CAREERS AND PLENARY ORALS
Early Career Prize Lecture Basic Science EC1.1
Early Career Prize Lecture Clinical EC1.2
Clinical Endocrinology Trust Best Abstract Clinical EC1.3
Clinical Endocrinology Trust Best Abstract Basic EC1.4

SYMPOSIA
Bones from Bench to Bedside S1.1–S1.3
Metabolism under pressure – what has stress got to do with it? S2.1–S2.3
Emerging perspectives on reproductive hormones in breast and prostate cancer S3.1–S3.3
Hacking the reproductive clock S4.1–S4.3
Graves' disease – Understanding the cause and dealing with the consequences that matter S5.1–S5.3
Primary aldosteronism: old dog, new tricks? S6.1–S6.3

WHAT IS NEW? WIN1.1–WIN1.2

CLINICAL MANAGEMENT WORKSHOPS
Endocrine Emergencies CMW1.1–CMW1.4

HOW DO I…? SESSIONS
How do I…? 1 . . . . . HDI1.1–HDI1.6
How do I…? 2 . . . . . HDI2.1–HDI2.6

MEET THE EXPERT SESSIONS
Metabolism, Obesity and Diabetes MTE1.1
Neuroendocrinology MTE2.1
Nurse MTE3.1
Thyroid MTE4.1–MTE4.2
Endocrine Cancer and Late Effects MTE5.1
Adrenal and Cardiovascular MTE6.1
Reproductive and Neuroendocrinology MTE7.1
Bone and Calcium MTE8.1

EARLY CAREERS SESSION
Keep the Conversation Going: Communicating, Networking and Engaging in Science ECS1.1–ECS1.3

NURSE SESSIONS
Primary Hyperparathyroidism: diagnosis to treatment NS1.1–NS1.3
Thyroid Cancer NS2.1–NS2.3
What's innovative and new in Endocrine Nursing? NS3.1–NS3.3

ENDOCRINE NETWORK SESSIONS
Adrenal ENS1.1–ENS1.4
Bone and Calcium ENS2.1–ENS2.3
Endocrine consequences of living with and beyond cancer ENS3.1–ENS3.4
Reproductive Endocrinology ENS4.1–ENS4.3
Endocrine Cancer ENS5.1–ENS5.4
Metabolism, Obesity and Diabetes ENS6.1
Neuroendocrinology ENS7.1–ENS7.5
Thyroid ENS8.1–ENS8.6

RET@30 SYMPOSIUM SESSIONS RET1.1–RET2.3

BASIC SCIENCE WORKSHOP SESSIONS
Getting it right first time – experimental design BSW1.1–BSW1.3
How endocrine researchers can benefit from modern advances in structural biology BSW2.1–BSW2.3

DEVELOPMENTS IN UK ENDOCRINCE SERVICE DELIVERY ESD1.1–ESD1.3

LEGENDS OF ENDOCRINOLOGY LOE1.1–LOE1.3

ORAL COMMUNICATIONS
Bone and Calcium OC1.1–OC1.6
Endocrine Cancer and Late Effects OC2.1–OC2.6
Neuroendocrinology and Pituitary OC3.1–OC3.6
Reproductive Endocrinology OC4.1–OC4.6
Adrenal and Cardiovascular OC5.1–OC5.6
Metabolism, Obesity and Diabetes OC6.1–OC6.6
Thyroid OC7.1–OC7.6

ORAL POSTER PRESENTATIONS
Neuroendocrinology and Pituitary OP1.1–OP1.4
Metabolism, Obesity and Diabetes OP2.1–OP2.4
Reproductive Endocrinology OP3.1–OP3.4
Thyroid OP4.1–OP4.4
Adrenal and Cardiovascular OP5.1–OP5.4
Bone and Calcium OP6.1–OP6.4

RET and Endocrine Cancer OP7.1–OP7.4
Late Breaking Abstracts Respectively OP8.1–OP8.4

FEATURED CLINICAL CASE POSTERS CC1–CC10

POSTER PRESENTATIONS
Adrenal and Cardiovascular P1–P30, P156–P184, P303–P321
Bone and Calcium P31–P44, P185–P197, P322–P335
Endocrine Cancer and Late Effects P302, P46–P50, P198–P203, P336–P338
Innovation in Teaching P51, P339–P340
Metabolism, Obesity and Diabetes P52–P79, P204–P230, P341–P356
Neuroendocrinology and Pituitary P45, P80–P106, P231–P257, P357–P374, P399
Nursing Practice P150–P155
RET P125–P126, P276–P277, P381
Reproductive Endocrinology P107–P124, P258–P275, P375–P380
Thyroid P127–P149, P278–P301, P382–P398

AUTHOR INDEX

Plenary Lectures

Clinical Endocrinology Trust Visiting Professor Lecture

PL1.1

Are we restoring thyroid hormone signaling in patients with hypothyroidism?

Antonio Bianco
University of Chicago, Chicago, USA

The binding of T3 to its nuclear receptors (TR) triggers T3 signaling, modulating the expression of thousands of genes. These events are reversible and fluctuate according to the T3 levels. In developing tissues, T3 signaling also modifies chromatin folding, permanently affecting gene expression throughout life. Hypothyroidism occurs when, at any time, there is insufficient T3 signaling, frequently due to low plasma thyroid hormone levels. The treatment is with levothyroxine (LT4) at doses that normalize serum thyrotropin (TSH) levels. This is because we trust that the deiodinases activate T4 to T3, thus restoring T3 signaling and clinical euthyroidism. This has not been established through randomized clinical trials, but the vast majority of the well-controlled LT4-treated patients seem to remain asymptomatic. Nonetheless, there is evidence that treatment with LT4 does not restore thyroid hormone homeostasis. LT4-treated patients exhibit about 25% higher serum T4 and 5-6% lower serum T3 levels, which is likely to impair T3 signaling in tissues that depend on plasma T3 for their supply of thyroid hormone. We know little about T3 signaling in the brain of LT4-treated patients, only that defects in the deiodinases might further compromise T3 actions. This could explain why some LT4-treated patients (10-20%) exhibit residual symptoms (cognitive, mood, and metabolic deficits, impairment in psychological well-being and quality of life), despite having normal serum TSH levels. It is not clear what makes some patients susceptible to residual symptoms, but the relative deficiency of T3 has justified the addition of LT3 to therapy with LT4. A score of clinical trials concluded that both therapies are safe and equally effective (neither is superior), but patients prefer combination therapy. There is also increasing evidence that a specific subgroup of symptomatic LT4-treated patients benefit from combination therapy. They should be the focus of future clinical trials.

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Society for Endocrinology Starling Medal Lecture

PL2.1

Abstract Unavailable

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Society for Endocrinology Dale Medal Lecture

PL3.1

Abstract Unavailable

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Society for Endocrinology Jubilee Medal Lecture

PL4.1

Abstract Unavailable

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Society for Endocrinology International Medal Lecture

PL5.1

Abstract Unavailable

DOI: 10.1530/endoabs.94.PL5.1

Society for Endocrinology Transatlantic Medal Lecture

PL6.1

Hormones and nerves in sex-specific physiology

Holly Ingraham
UCSF, San Francisco, USA

Biological sex is one of nature's most robust variables. We are leveraging sex differences to discover how hormone-responsive nodes in the brain and peripheral tissues maintain metabolic, skeletal, and cognitive health using the mouse as our model system. Findings from our research program are highly relevant to women's health during estrogen-depleted states that include natural or drug-induced menopause commonly associated with anti-hormone breast cancer therapies. Currently, we are focused on estrogen-responsive neurons in the hypothalamus to understand how estrogen and melanocortin signaling via MC4R become integrated to drive spontaneous activity (Krause et al., 2021). We are also actively searching for a brain-derived osteoanabolic factor that can strengthen bone density and strength in older female mice. This is based on our findings that loss of estrogen signaling in hypothalamic neurons profoundly increases bone mass in female mice (Herber, Krause, et al., 2019). Defining the basic mechanisms that mediate this female-specific brain-bone communication may open up new therapeutic space for treating women suffering from osteoporosis.

DOI: 10.1530/endoabs.94.PL6.1

British Thyroid Association Pitt-Rivers Lecture

PL7.1

Understanding, manipulating and exploiting the sodium iodide symporter

Christopher McCabe
University of Birmingham, Birmingham, United Kingdom

Thyroid cancer is frequently treated by surgery, followed by administration of radioiodide, an ablative treatment utilising high energy beta-emitting ^{131}I. Given that the sodium iodide symporter (NIS) is the sole transporter of iodide into human cells, and is expressed predominantly in the thyroid, ^{131}I therapy selectively targets post-surgical thyroid remnants and metastases, markedly improving outcome and survival. Radioiodine therapy is thus a safe, specific, well tolerated and effective treatment. However, around a third of thyroid cancer patients with locoregional or distant metastases have disease that does not concentrate sufficient ^{131}I to achieve therapeutic benefit. The 10 year survival rate is ~56% for patients with sufficient ^{131}I uptake, but only ~10% for patients who are radioiodide resistant. Therefore in the central clinical area in which NIS is exploited, there is a pressing need for improved therapy. Over the past 10 years we have forged unique insights into the intracellular trafficking and processing of NIS, and have pioneered efforts to systemically enhance NIS function at the plasma membrane (PM) in vivo. We have now identified 2 different systemic drug approaches which significantly enhance the function of NIS in mice, by targeting (i) the rate of endocytosis of NIS within the thyroid, and (ii) the expression and proteasomal degradation of NIS. To offer future hope to patients with aggressive thyroid cancer, we now need to progress systemic strategies such as these to clinical trials so that NIS function can be enhanced at the time of radioiodine therapy, eliciting improved tumour and metastatic cell ablation.

DOI: 10.1530/endoabs.94.PL7.1

Society for Endocrinology European Medal Lecture

PL8.1

Abstract Unavailable

DOI: 10.1530/endoabs.94.PL8.1

Society for Endocrinology Medal Lecture

PL9.1

Precision medicine in diabetes: from discovery to implementation

Ewan Pearson
University of Dundee, Dundee, United Kingdom. BHF Data Science Centre, United Kingdom

People are all different, and this is no different when we consider people with diabetes, yet the current approaches to management of diabetes tend to treat everyone the same. The field of precision medicine aims to recognise these differences – whether at the level of their phenotype or at the molecular level. Faced with multiple, and increasing, treatment options for diabetes as well as increasing healthcare costs there is a clear need to target therapy to maximise benefit and reduce harm for every patient with diabetes. This talk will discuss advances in precision medicine and pharmacogenetics in diabetes. I will highlight recent work on how phenotypic variation matters, and how this maps to genetic variation, and will provide an overview of how genetic variants alter glycaemic response to commonly used diabetes drugs and how these inform on disease and drug mechanism. I will finish with an overview of iDiabetes – an intelligent diabetes platform that we will be using to implement precision diabetes care in Tayside in 2024.

DOI: 10.1530/endoabs.94.PL9.1

Clinical Endocrinology Journal Foundation Lecture

PL10.1

Hormonal changes initiating human lactation

Fadil Hannan
University of Oxford, Oxford, United Kingdom

Lactation is a hormonally controlled process that promotes infant growth and development and reduces the long-term maternal risk of diabetes, cardiovascular disease and breast cancer. Hormones, such as prolactin and progesterone, mediate mammary development during pregnancy and are critical for initiating copious milk secretion during postpartum days 1-4. However, the hormone concentrations and mechanisms mediating lactation onset during this period of secretory activation are ill-defined. The Larsson-Rosenquist Foundation Oxford Centre for the Endocrinology of Human Lactation (LRF OCEHL) has been established to characterize the molecular endocrine basis of lactation. We are conducting the Investigating hormones triggering the onset of sustained lactation (INSIGHT) study to establish reference intervals for the circulating hormone concentrations initiating postpartum milk secretion. This single centre study is recruiting pregnant women over a 3-year period. Blood samples are obtained at 36 weeks' gestation, and before and after a breastfeed during postpartum days 1-4. Colostrum and breastmilk are also obtained with RNA extracted for analysis of mammary cell hormone receptor expression. This presentation will describe our analysis of serum hormone concentrations and mammary hormone receptor expression during the secretory activation window in breastfeeding participants with healthy term pregnancies.

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Presidential Lecture

Antibodies and antibody mimics as pharmaceutical drugs

PR1.1

Abstract Unavailable

DOI: 10.1530/endoabs.94.PR1.1

Debate

Precision medicine is the future of diabetes care

D1.1

Abstract Unavailable

DOI: 10.1530/endoabs.94.D1.1

D1.2

Abstract Unavailable

DOI: 10.1530/endoabs.94.D1.2

Society for Endocrinology Journal Awards

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

JA1

miR-514a-3p: a novel SHP-2 regulatory miRNA that modulates human cytotrophoblast proliferation

Rachel C Quilang, Sylvia Lui, Karen Forbes

Journal of Molecular Endocrinology, 2022, **68**(2), 99-110 (DOI: **https://doi.org/10.1530/JME-21-0175**)

DOI: 10.1530/endoabs.94.JA1

Society for Endocrinology Journal Award - *Journal of Endocrinology*

JA2

Liver is a Primary Source of Insulin-like Growth Factor-1 in Skin Wound Healing

Rita E Roberts, Jacqueline Cavalcante-Silva, Rhonda D Kineman, Timothy J Koh

Journal of Endocrinology, 2022, **252**(1), 59-70 (DOI: **https://doi.org/10.1530/JOE-21-0298**)

DOI: 10.1530/endoabs.94.JA2

Society for Endocrinology Journal Award - *Endocrine Connections*

JA3

Impact of add-back FSH on human and mouse prostate following gonadotropin ablation by GnRH antagonist treatment

Eleftherios E Deiktakis, Eleftheria Ieronymaki, Peter Zarén, Agnes Hagsund, Elin Wirestrand, Johan Malm, Christos Tsatsanis, Ilpo T Huhtaniemi, Aleksander Giwercman, Yvonne Lundberg Giwercman

Endocrine Connections, (2022), 11, (6), e210639 (DOI: **https://doi.org/10.1530/EC-21-0639**)

DOI: 10.1530/endoabs.94.JA3

Endocrinology Journal Award - *Endocrine Related Cancer*

JA4

The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms

Andreas Venizelos, Hege Elvebakken, Aurel Perren, Oleksii Nikolaienko, Wei Deng, Inger Marie B Lothe, Anne Couvelard, Geir Olav Hjortland, Anna Sundlöv, Johanna Svensson, Harrish Garresori, Christian Kersten, Eva Hofsli, Sönke Detlefsen, Merete Krogh, Halfdan Sorbye Stian Knappskog

Endocrine-Related Cancer, 2022, **29**(1), 1-14 (DOI: **https://doi.org/10.1530/ERC-21-0152**)

DOI: 10.1530/endoabs.94.JA4

Society for Endocrinology Journal Award - *Clinical Endocrinology*

JA5

TSH receptor specific monoclonal autoantibody K1-70TM targeting of the TSH receptor in subjects with Graves' disease and Graves' orbitopathy-Results from a phase I clinical trial

Jadwiga Furmaniak, Jane Sanders, Paul Sanders, Yang Li, Bernard Rees Smith

Clin Endocrinology (Oxf), 2022, 96, 878-887 (DOI: **https://doi.org/10.1111/cen.14681**)

DOI: 10.1530/endoabs.94.JA5

Awards and Prizes

Teaching Achievement Award

TAA1.1

Alex's osteoblast: revitalising teaching during covid

Alexander Comninos
Imperial College Healthcare NHS Trust, London, United Kingdom. Imperial College London, London, United Kingdom

In March 2020, the world went into covid lockdown. Students, trainees and consultants were all called to the front-line, working additional and highly stressful shifts. Amongst the numerous negative consequences of the pandemic, teaching fell by the wayside. All conferences and educational meetings were cancelled. Initially there seemed no time or mechanism to continue teaching. However, on the 27th April 2020, one month into the first lockdown, I presented the first 'Alex's Osteoblast' webinar on Zoom to several hundred endocrinologists and trainees around the world, mentally and physically exhausted from the hardest working experience of their lives, but eager to interact once again and learn. In this interactive teaching webinar, I discussed common queries related to Endocrine Bone disorders. There was exceptional engagement from the endocrine community and feedback was so positive that I decided to continue giving these webinars on different subtopics every few weeks. I drew up a comprehensive list of the most common clinical queries and systematically tackled each one in a practical, interactive and evidence-based webinar. So far there have been eleven free-to-view full episodes of 'Alex's Osteoblast' since the pandemic began. I have received positive feedback that these webinars have significantly improved the bone expertise of our international community and made bone endocrinology 'sexy' again. Here, I will discuss the concepts of this webinar series during covid, as well as other activities including setting up Endocrine Bone Teaching Clinics, Endocrine Careers Evenings and my wider roles as Head of Academic Tutoring improving study techniques for the next generation of doctors.

DOI: 10.1530/endoabs.94.TAA1.1

Outstanding Clinical Practitioner Award

OCP1.1

Management of pubertal delay in males & females: perspectives from an "adult" Endocrinologist

Richard Quinton
Translational & Clinical Research Institute, Newcastle University, Newcastle-on-Tyne, United Kingdom. Department of Endocrinology, Newcastle-on-Tyne, United Kingdom

Longstanding Paediatric guidance on the assessment and management of children with undifferentiated pubertal delay is not fit for purpose in relation to patients who are older and/or have obvious "red flag" clinical features to sign-post high risk for congenital hypogonadism. For these individuals, the well-intentioned stock phrases that "*constitutional (or self-limiting) delayed puberty is always the more likely diagnosis*", "*attainment of Tanner 2+ indicates that normal puberty has begun*" and "*hormone treatment should aim to recapitulate the normal tempo of puberty*" have been misleading clinicians and, consequently, letting down their patients for too long. "Red flags" can be classified as "reproductive", such as neonatal cryptorchidism or microphallus, or "non-reproductive", comprising the spectrum of congenital anomalies found in association with Kallmann, CHARGE, or Turner syndromes, for instance. Patients of both sexes, who should have been identified in childhood as having high risk of congenital hypogonadism and thus commenced on sex hormones at the median age of normal puberty onset, are instead only getting adequate diagnosis and treatment at a median age of 18-19 years. The possibility of diagnosing and treating absent neonatal male minipuberty with combined gonadotropin treatment continues to be missed in the vast majority of cases, leading to unnecessary surgical orchidopexy procedures and, potentially, worse fertility treatment outcomes in adult life. Hypogonadal men and women report high levels of anxiety, distress, depression and psychosexual dissues, including body shame and difficulty with intimate relationships. The outcomes of spermatogenesis-induction with gonadotropins remain disappointing, and women achieve uterine volumes that are only 60% of their eugonadal nulliparous peers as a result of historic protocols. Therefore, adult Endocrinologists with experience of managing patients with congenital hypogonadism over the course of their adult lives, should contribute more significantly to the next generation of guidelines relating to the investigation and management of delayed puberty.

DOI: 10.1530/endoabs.94.OCP1.1

Nikki Kieffer Medal

NKM1

Abstract Unavailable

DOI: 10.1530/endoabs.94.NKM1

Early Careers and Plenary Orals

Early Career Prize Lecture Basic Science

EC1.1

Abstract Unavailable

DOI: 10.1530/endoabs.94.EC1.1

Early Career Prize Lecture Clinical

EC1.2

Abstract Unavailable

DOI: 10.1530/endoabs.94.EC1.2

Clinical Endocrinology Trust Best Abstract Clinical

EC1.3

Biological heterogeneity in skeletal susceptibility to glucocorticoid induced bone loss: Short- and long-term BMD trajectories during unopposed GC treatment in adults

Benjamin Bakke Hansen[1], Katrine Rubin[2], Pernille Hermann[3], Morten Frost Munk Nielsen[3] & Bo Abrahamsen[2]
[1]Odense University Hospital, OUH OPEN Registry and Statistics, Odense, Denmark. [2]Research Unit OPEN, Department of Clinical Research, University of Southern Denmark, Odense, Denmark. [3]Odense University Hospital, OUH Department of Endocrinology, Odense, Denmark

Objective
Describe short- and long-term changes in BMD in adults exposed to varying intensities of systemic glucocorticoid (GC) treatment.
Methods
Setting
Danish Public Health Service Hospital, catchment area 500,000 individuals.
Data
BMD data from 2006-2021 and data on filled prescriptions.
Analysis
All adult patients with at least two DXA exams (left hip), with a minimum of 6 month intervals. Individuals with prescriptions for systemic GCs within 5y of their first DXA scan were excluded, with a 3 month grace period. Observations were censored after initiation of anti-osteoporosis agents. We included 7192 unexposed and 1834 GCs exposed individuals. GC exposure between each two successive scans were standardized into average daily prednisolone equivalent amount. Short-term bone loss (first time slice only) was annualized. Long-term bone loss was visualized with LOWESS scatterplot smoothing.
Results
Short-term bone loss (Table 1): Increasing GC exposure was accompanied by faster BMD loss but also by greater interpersonal variation (IQR Width). Though the majority of patients, both GC treated and untreated, experienced nominally negative trajectories, more than one in five in the upper tertile had a net positive change.

GC Exposure Intensity	% Median Annual Change (IQR Width)	% With Negative Annual Change	% With Positive Annual Change
Untreated	-0.72 (1.69)	71.9	28.1
Lower Tertile	-0.84 (1.33)	82.9	17.1
Middle Tertile	-1.02 (1.68)	80.2	19.8
Upper Tertile	-1.32 (2.84)	77.9	22.1

Long-term bone loss
LOWESS of six years of follow up and will be visualized; in brief the lower tertile GC group had lower loss early, but the tertiles approached identical total loss after four years.
Conclusions
These results underscore the heterogeneity of BMD response and highlights the scope for improved predictive models to identify individuals at risk of significantly accelerated bone loss, at the time of initiation of GC treatment.

DOI: 10.1530/endoabs.94.EC1.3

Clinical Endocrinology Trust Best Abstract Basic

EC1.4

Single-cell analysis for the human developing thyroid uncovers thyrocyte heterogeneity and active interactions during development

Hassan Massalha[1], Mi Trinh[1], Cecilia Icoresi-Mazzeo[1], Nadia Schoenmakers[2], Sam Behjati[1] & Roser Vento-Tormo[1]
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Normal functioning of the thyroid is of profound importance for lifetime health due to its role in hormone production. Dysfunction of the thyroid is associated with severe congenital pathologies, some of them appearing in childhood. For example, over half the babies born with congenital hypothyroidism appear completely normal and without symptoms. However, early diagnosis of thyroid defects is lacking mainly due to a poor understanding of the development of the tissue in utero. Here we have established a comprehensive spatiotemporal atlas of the developing human thyroid during the first and second trimester of pregnancy. Our dense profiling of more than 250k cells using single-cell sequencing has revealed the main cell types, their developmental relationships and transcription factors leading to the formation of the thyroid gland. We characterised the early development thyroid specific cell types including thyrocytes, parathyroid gland and parafollicular cells, known as C cells. Notably, we found that thyrocytes are heterogeneous epithelial populations and split thyroid-hormones production between different subsets. We further validated the spatial heterogeneity of thyrocyte subpopulations using multiple spatial transcriptomics methods. Lastly, we derived ligand-receptor interactions that drive the maturation of thyrocytes during development. Our results confirm the division of labour of the thyrocytes, and highlight active cell-cell communications during thyroid gland development. Altogether our analysis exemplifies the division of labour principle observed in other adult tissues also applies to the development of the thyroids, expanding our knowledge of thyroid-hormones synthesis and regulation. Future work includes how the function principles and potential interactions are altered in pathological conditions.

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Symposia

Bones from Bench to Bedside

S1.1

The new endocrinology of osteocytes

Lynda Bonewald
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Osteocytes make up over 90-95% of bone cells in the adult skeleton making their total cellular mass greater than the mass of the brain. These cells can exist for decades in the bone matrix, much longer than osteoblasts or osteoclasts. In addition to being mechanosensory cells, osteocytes are also secretory cells, releasing sclerostin that inhibits osteoblastic bone formation and producing Rankl, the major activator of osteoclasts. Mechanical loading reduces both sclerostin and Rankl expression, while simultaneously stimulating the release of positive regulators of bone formation such as prostaglandin E2, ATP, and nitric oxide. In addition to these autocrine factors, osteocytes produce paracrine factors such as fibroblast growth factor 23, which targets the kidney to regulate phosphate metabolism. Interestingly, neutralizing antibodies to sclerostin, Rankl, and FGF23, approved as therapeutics, are all osteocyte factors. Parathyroid hormone, PTH, or PTH related protein target osteocytes through the PTH type 1 receptor, highly expressed in osteocytes, to regulate calcium. The osteocyte then reduces the pH within its lacunae and generate enzymes that degrade matrix such as Cathepsin K, Trap, and MMPs to release calcium into the circulation. The major difference between male and female osteocytes is the elevated expression of these genes in females suggesting that osteocytes may be responsible for some of the sex differences in male compared to female bone. As these cells age, they lose their connectivity of their dendritic processes. In the aged skeleton, not only are senescent cells present, but also empty lacunae where previous cells existed. These changes in osteocytes may be the explanation for skeletal resistance to exercise with aging. New functions of osteocytes are being discovered such as conversion into inflammatory cells, in regulating adipogenesis, myogenesis and muscle function, potential crosstalk with the brain, and the role of osteocytes in various forms of cancer.

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S1.2

Abstract Unavailable

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S1.3

Abstract Unavailable

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Metabolism under pressure – what has stress got to do with it?

S2.1

Mechanisms of adipocyte health in cardiometabolic disease

Alexander Bartelt
Ludwig-Maximilians-Universität München, Munich, Germany

Adipocytes are important metabolic buffers and endocrine regulators of energy expenditure and satiety. Adipocyte dysfunction, either genetic or as observed in acquired obesity, is linked to hallmarks of the metabolic syndrome. I will discuss novel translational regulators of adipocyte function and focus on the role of the proteasome for cellular protein quality control, ER stress, and maintenance of healthy brown and white adipocytes in obesity, diabetes, and atherosclerosis in cells, transgenic mice, and humans.

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S2.2

How does a fat cell respond to overnutrition stress?

Kirsty Spalding
Karolinska Institutet, Stockholm, Sweden

Many metabolic diseases, including type 2 diabetes, strongly associate with obesity, making obesity one of the major health challenges facing the world today. Obesity is usually accompanied by an increase in fat cell size. As fat cells enlarge, they begin to secrete factors which promote adipose tissue inflammation and dysfunction. We recently describe a mechanism connecting an increase in fat cell size (hypertrophy) with the secretion of pro-inflammatory factors: We show that despite long being considered post-mitotic, mature human fat cells can activate a cell cycle program in association with obesity and hyperinsulinemia, with a concomitant increase in adipocyte cell size, nuclear size and DNA content. Chronic hyperinsulinemia in vitro or in humans, however, is associated with subsequent cell cycle exit, leading to a premature senescent transcriptomic and secretory profile. Premature senescence is rapidly becoming recognized as an important mediator of stress-induced tissue dysfunction, with much hope held for strategies that improve tissue function by selectively eliminating senescent cells. The identification and function of senescent adipocytes in human adipose tissue will be discussed.

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S2.3

Using genetics to untangle the complex relationships between metabolic and mental health

Jess Tyrrell
University of Exeter, Exeter, United Kingdom

The prevalence of both type 2 diabetes and depression are increasing globally and previous research has demonstrated evidence that diagnosis with both conditions leads to poorer diabetes control and an increased likelihood of developing treatment resistant depression. However, the relationship between type 2 diabetes and depression is complex with many unanswered questions. The aim of our research is to use longitudinal health records and genetic analyses in 10,000s of individuals to establish a more complete understanding of the relationships between type 2 diabetes and depression. We have used summary statistics from the largest available published Genome Wide Association Studies (GWAS) of depression and type 2 diabetes to perform Mendelian randomisation (MR) to explore causal pathways between type 2diabetes and depression. We have also used data from an unpublished type 2 diabetes GWAS in $>$2.5 million individuals where they identify 8 clusters of genetic variants that increase an individual's risk of type 2 diabetes via specific pathways (e.g. via adiposity based pathways). Our initial work indicates there was evidence that a higher genetic liability to depression predicted type 2 diabetes. A doubling of the depression risk was associated with a 1.04 (95%CI: 1.01, 1.08) higher odds of type 2 diabetes. There was also evidence of a bidirectional causal relationship between depression and type 2 diabetes but only when using the larger unpublished set of T2D variants and focusing on specific clusters of variants. This suggested that the association was driven by variants that predominantly acted via obesity and body fat pathways. Initial analyses in the UK Biobank study of 500,000 individuals suggests similar results. Initial work suggests bidirectional causal pathways between depression and type 2 diabetes and indicates the potential importance of adiposity/obesity pathways in this relationship.

DOI: 10.1530/endoabs.94.S2.3

Emerging perspectives on reproductive hormones in breast and prostate cancer

S3.1

Managing impacts of androgen deprivation therapy on bones

Janet Brown
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Prostate cancer is projected to be the commonest cancer by 2030, with 1 in 8 men receiving a diagnosis in their lifetime. Although there are more than 400,000 cases in Europe diagnosed each year, many new prostate cancer treatments have been introduced and patients now live with their disease for many years. Consideration of the long-term consequences of treatment is of therefore of increasing importance. More than one third of patients with prostate cancer receive androgen deprivation therapy (ADT), an endocrine-based treatment. Whilst highly successful in reducing testosterone levels and improving prostate cancer survival, ADT is associated with negative impacts on bone health, leading to bone loss and increased fracture risk. In addition, ADT causes sarcopaenia which increases the risk of falls, further compounding the risk of fractures. Many patients continue receiving ADT throughout their prostate cancer journey. However, these patients are often not routinely referred to bone specialists for optimisation of their bone health, despite the fact that bone loss and the resulting increased risks of osteoporotic fragility fractures (often requiring hospitalisation) represent substantial problems for patients and healthcare systems. The bone loss induced by ADT is linked to its effects in disturbing normal bone turnover, leading to increased bone resorption and reduction in bone density. The gold standard for measuring bone density is dual energy x-ray absorptiometry (DEXA) scan. However, our recent work using a sophisticated form of CT scanning (QCT) has revealed that ADT not only reduces bone density, but also impairs the mechanical properties of bone. Bone density loss can be prevented or repaired using bone targeted agents such as bisphosphonates or the fully humanised antibody, denosumab. In this presentation, recent detailed guidance for managing the skeletal health of patients receiving ADT will be discussed in the light of current treatment pathways for prostate cancer patients.

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S3.2

Androgen receptor interactions in endocrine resistant breast cancer - location, location, location

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Introduction
Aromatase Inhibitors (AI) are standard therapy for hormone receptor positive breast cancers in post-menopausal patients. Unfortunately, resistance is common and previous studies from our lab suggest that the altered steroid environment may be a driver. Using label-free mass spectrometry we set out to explore the unique androgen receptor (AR) interactome that supervenes in AI resistant breast cancer and associated hyper-androgenic environment.
Methods
AR expression was evaluated in a primary breast cancer tissue-microarray (n = 844) with nuclear and cytoplasmic localization quantified. LC-MS/MS analysis was utilized to identify proteins interacting with the AR in AI resistant cells in the presence of androgen excess. Validation was carried out by co-immunoprecipitation and imaging analysis. Live-cell imaging, Seahorse MitoStress Assays and flow cytometry were used to quantify changes in mitochondria and cell metabolism arising in AI resistant models post exposure to A4.
Results
Utilising digital pathology we evaluated the localisation of the androgen receptor (AR) protein in a large cohort of breast cancer specimens (n = 844) and show that abundant cytoplasmic AR protein associated with poor survival only in the post-menopausal cohort and most significantly in the therapy refractory Luminal B subtype ($p = 0.0085$). Exploration of the AR protein interactome via LC-MS/MS in AI resistant cell line models identified protein partners previously linked with castrate resistant prostate cancer (beta-catenin) and proteins associated with adaptive metabolic response and estrogen receptor repression (SLIRP, IGFBP5). Seahorse analysis confirmed A4 exposure causes a metabolic shift in AI resistant cells, increasing glycolysis.
Discussion
The findings of this study highlight novel non-genomic AR protein interactions that could aid our understanding of the role played by androgens in metabolic health and the development of endocrine-resistance in specific breast cancer subtypes.

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S3.3

Abstract Unavailable

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Hacking the reproductive clock

S4.1

Ageing and sperm health

Sarah Martins da Silva
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Ageing is an inevitable biological process that affects all aspects of human physiology including reproductive health. While much attention has been devoted to the age-related decline in female fertility, the impact of ageing on male reproduction is perhaps less well appreciated. This presentation aims to provide a concise overview of the relationship between ageing and sperm health, highlighting key findings and implications. Ageing has a significant impact on sperm health and male fertility. As men age, sperm quality and function decreases, including poorer sperm motility and an increase in DNA damage and abnormal sperm morphology. These changes are believed to be linked to a variety of factors, such as increased oxidative stress and reduced antioxidant defence, as well hormonal changes associated with ageing. Importantly, age-related changes in sperm can have profound consequences for male fertility. Advanced paternal age has been associated with longer time to conception and increased risk of infertility as well as higher likelihood of pregnancy complications. Moreover, older fathers may transmit genetic mutations and epigenetic changes to their offspring, contributing to a range of health issues in the offspring. In an era when couples are delaying parenthood, education and awareness of the implications of ageing on male fertility are of paramount importance. Understanding the impact of ageing on sperm health is crucial for healthcare providers, researchers, couples seeking to conceive, as well as for public health.

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S4.2

Fertility preservation in 2023

Marie Madeleine Dolmans
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The advances in cancer therapy over the past two decades have led to remarkable improvements in survival rates, but treatments such as chemotherapy, radiotherapy and/or surgery can induce premature ovarian insufficiency (POI) in some circumstances. Fertility preservation (FP) is therefore a key challenge for these women. At diagnosis, all women affected by cancer should benefit from an informed consultation on the threat of compromising their fertility with planned cancer treatment. In case of total body irradiation, pelvic irradiation, bone marrow transplantation and aggressive chemotherapy with high dose of alkylating agents, the risk is considered to be very high. However, only a small fraction of patients is actually referred to specialists to discuss FP prior to cancer treatments. The decision-making process is especially problematic since the long-term effects of cancer treatment have not been fully elucidated. The prevalence of subfertility is nevertheless known to be increased, even when ovarian function is maintained. The main issue is that health care workers are unfamiliar with the rapid advances taking place in FP research and their implementation in clinical practice. The question of FP in Turner syndrome (TS) was recently shared. While some experts still consider the technique experimental in Turner patients, we have always believed that they could be candidates for OTC, as long as there is a reasonable Journal Pre-proof 4 chance of finding primordial follicles in their ovarian tissue. In our opinion, OTC should be performed before puberty (at least before age 12) to avoid depletion of the ovarian reserve as best we can. We also agree with Dunlop et al. and Nadesapillai et al. that young patients should be psychologically prepared for OTC, as they need to make a decision they may not be emotionally or mentally ready for.
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S4.3

The genetics of the ageing ovary

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Menopause timing is highly variable, having a direct effect on reproductive lifespan, fertility and health outcomes in later life. Endocrine and imaging tests only record changes in ovarian function that have already taken place, thus disabling early prediction and identification of women with reduced reproductive lifespan. Human genetic studies have attempted to overcome this problem by identifying genetic markers associated with menopause timing and fertility. Using data from large scale population studies, such as UK Biobank, we assessed both common and rare genetic variation that influence menopause timing. Our work on common genetic variants led to the discovery of 300 genetic signals that influence age women begin menopause and the first evidence of our ability to, through gene manipulation in a mouse model, extend reproductive lifespan by 25% and improve fertility. To assess the impact of rare damaging variants on menopause timing, we queried whole-exome sequencing data for 106,973 post-menopausal women in UK Biobank and implicated novel genes with effect sizes up to 6 times larger than previously discovered. Finally, we found that genetic susceptibility to earlier ovarian ageing in women increases de novo mutation rate in their offspring. This provides direct evidence that female mutation rate is heritable and highlights a mechanism of the maternal genome influencing child health, which could have direct implications for the health of future generations given the link between de novo mutations and disease risk. The power of this information is that in the future we may be able to build the first genetic prediction test that will inform women about the timing of her menopause. In addition, knowledge of underlying mechanisms may also allow their manipulation, more specifically halting or temporising the process of the loss of ovarian follicles and provide a new direction for therapeutic approaches that might seek to treat infertility.

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Graves' disease – Understanding the cause and dealing with the consequences that matter

S5.1

Thyrotropin receptor autoantibodies, stimulating, blocking or neutral

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Graves' disease (GD) is caused by autoantibodies to the thyrotropin receptor (TSHR) which mimic the action of TSH. Thyroid stimulating antibodies (TSAB) predominantly signal via the cAMP/PKA cascade whilst blocking antibodies (TBAB) prevent TSH binding. Flow cytometry reveals TSHR antibodies which bind the receptor but do not activate cAMP or inhibit TSH binding. These 'neutral' antibodies were identified in people with euthyroid Graves' orbitopathy (GO, eye disease due to remodelling of orbital contents). Studies of murine monoclonal neutral TSHR antibodies revealed the ability to signal via alternative cascades (PKC) and may be relevant to GO pathogenesis. Recent studies using cryo-EM have provided valuable insight into TSHR activation by TSH and TSAB. The TSHR comprises extra-cellular (ECD) and 7 transmembrane domains (7TM) and naturally cleaves into A and B subunits joined by di-sulphide bridges. The ECD in an 'upright' position leads to activation, the unliganded receptor can transiently adopt this position, explaining its constitutive activity. TSH and TSAB stabilize an upright ECD because of steric clashes between ligand and membrane bilayer but TBAB maintain the ECD in a downward state. Residue E409 in the p10 peptide of the ECD interact with K660 in the 7TM to stabilize a fully activated receptor, i.e. bound to Gαs. The TSHR hinge region seems unnecessary for activation of Gαs, although many neutral antibodies bind this part. Further studies would be required to determine whether the hinge region is necessary for cascades signalling via Gβγ, Gαq or Gα13. Finally proteins for variant TSHR transcripts (lack the 7TM) have been identified in orbital tissues, demonstrated to bind both TSH and TSAB and thus are capable of modulating signalling via the TSHR.

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S5.2

Abstract Unavailable

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S5.3

Avoiding excess weight gain in Graves' treatment,

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Weight loss is a common symptom observed in the majority of patients presenting with autoimmune Graves' hyperthyroidism. The three main treatment modalities used for treatment of Graves' disease are associated with excess weight gain, reportedly over and above regain of lost weight. Hyperthyroidism is associated with alterations in satiety signals and there are conflicting data relating to whether lean or fat mass are increased following successful treatment. Risk factors for excessive weight gain include pre-existing obesity and more severe hyperthyroidism. Some studies indicate that weight gain is more pronounced with treatments that are associated with the induction of hypothyroidism namely the administration of radioactive iodine and surgery. Since the induction of hypothyroidism has been associated with reduced risks of mortality in patients with Graves' disease, this may a desirable outcome, although patients remain worried regarding the risk of gaining weight. Preliminary data indicate that dietary interventions may be useful in preventing excessive weight gain but no large randomised trials have been undertaken to indicate beneficial effects of lifestyle changes. This symposium will highlight the current evidence with regards to weight changes associated with Graves' disease and its treatment, explore the underlying mechanisms and provide an overview of potential therapeutic avenues that may be beneficial.

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Primary aldosteronism: old dog, new tricks?

S6.1

Abstract Unavailable

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S6.2

Abstract Unavailable

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S6.3

Abstract Unavailable

DOI: 10.1530/endoabs.94.S6.3

What is New?

WIN1.1

Abstract Unavailable

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WIN1.2

Abstract Unavailable

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Clinical Management Workshops

Endocrine Emergencies

CMW1.1

Abstract Unavailable

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CMW1.2

Severe hyponatraemia

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Hyponatraemia is the commonest electrolyte disturbance in hospitalised patients. Acute severe hyponatraemia is a medical emergency, leading to potential cerebral oedema and death if not actively managed. Prompt intervention with hypertonic saline is recommended to reverse neurological symptoms and prevent brain herniation, aiming for an initial sodium increase of 4 to 6 mmol. Overcorrection runs the risk of osmotic demyelination syndrome, hence further rapid sodium rise (to a limit of no more than 10 to 12 mmol within 24 hours) should be avoided. Lowering of sodium levels using intravenous 5% dextrose with or without desmopressin may be required under such circumstances. This presentation will review the principles of management of severe hyponatraemia, including recent evidence highlighting the importance of active management, and the benefits of bolus versus slow infusion of hypertonic saline.

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CMW1.3

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CMW1.4

Abstract Unavailable

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How Do I...? Sessions

How do I...? 1

HDI1.1

Long-term surveillance for endocrine sequelae after bone marrow transplantation

Yaasir Mamoojee
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Haematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, is a potentially curative therapy mainly indicated in malignant and non-malignant bone marrow disorders. It has resulted in improved survival for patients at the cost of long-term complications. Endocrine and metabolic disorders are the most prevalent sequelae following bone marrow transplantation, primarily caused by powerful conditioning chemotherapy associated with total body irradiation. Primary hypogonadism, as evidenced by secondary amenorrhoea, is treated with hormone replacement therapy in post-pubertal females, aiming to achieve physiological serum levels of oestradiol with due attention to appropriate endometrial protection. In males, onset of primary hypogonadism may be insidious post HSCT and delay in testosterone replacement may result in poorer quality of life (from hypogonadal symptoms), anaemia and osteoporosis at an early age. Long-term surveillance is therefore not only focused at identifying hypogonadal symptoms but also at biochemical and bone density assessment. HSCT recipients are at an increased risk of metabolic complications in the long term. Surveillance strategies post HSCT should therefore empower patients to adopt healthy lifestyle choices (dietary, exercise, smoking cessation and alcohol consumption) and focus on obesity prevention. Regular screening for dyslipidaemia, hypertension and diabetes allows for early detection and prompt treatment.

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HDI1.2

How do I follow up non-functioning pituitary adenomas in the long term?

Niki Karavitaki
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Non-functioning pituitary adenomas (NFPAs) are benign tumours not associated with clinical manifestations of hormonal hypersecretion. Based on population studies, their prevalence ranges between 7 and 41 per 100,000 people with the number of incidentally detected NFPAs increasing over the last decades. They cause clinical manifestations when they are large enough to exert pressure effects to surrounding structures. The initial management of non-apoplectic NFPAs depends mainly on their size and extensions. For microadenomas, imaging surveillance is advised; based on recent evidence, the first follow-up scan can be performed three years after the detection of the tumour due to the low probability of clinically relevant growth during this interval. Re-evaluation of the pituitary function is not required in the absence of microadenoma growth. Long-term studies clarifying safe duration of follow-up are not available. For macroadenomas managed conservatively, clinical, neuro-ophthalmological (if the tumour is in proximity with the optic pathways) and imaging monitoring are needed. Annual scanning is generally recommended for the first five years and this can be later extended if there is no evidence of enlargement. For operated NPFAs, clinical, neuro-ophthalmological (when relevant) and imaging monitoring are needed. The imaging protocol will mainly depend on extend of residual tumour, the administration of adjuvant radiotherapy and the presence of risk factors for aggressive tumour behaviour. In all cases, an earlier scan will be dictated by high index of suspicion of growth (e.g., visual field deficits) or clinical signs of apoplexy. Furthermore, monitoring of the hormonal replacement (when hypopituitarism is present) and regular assessment of the pituitary function (in patients offered radiotherapy) are required.

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HDI1.3

Abstract Unavailable

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HDI1.4

How do I screen for NAFLD and its progression in patients with diabetes?

Jeremy Tomlinson
University of Oxford, Oxford, United Kingdom

Non-alcoholic fatty liver disease (NAFLD), more recently renamed metabolic dysfunction associated steatotic liver disease (MASLD), is the most highly prevalent chronic liver condition and is associated with significant adverse outcomes, both through liver-specific morbidity and mortality, but perhaps more importantly, through adverse cardiovascular and metabolic outcomes. MASLD is a spectrum of disease, extending from simple steatosis, through to inflammation and fibrosis and risk of cirrhosis. It is tightly associated with obesity and type 2 diabetes both of which drive disease incidence and progression. Accurate diagnosis and staging are crucial as they provide prognostic information that impacts upon clinical management. Liver biopsy is still regarded as the gold-standard investigative tool; however, there are now an array of novel non-invasive biomarkers and imaging modalities that aim to accurately reflect the stage of underlying disease and their use will be discussed. This will include the most appropriate strategies to be incorporated into routine diabetes clinics in primary and secondary care and their association with clinical outcome. In addition, the best strategies for monitoring disease progression (including biochemical and imaging modalities) will be discussed.

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HDI1.5

Abstract Unavailable

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HDI1.6

Abstract Unavailable

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How do I...? 2

HDI2.1

Abstract Unavailable

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HDI2.2

Abstract Unavailable

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HDI2.3

Abstract Unavailable

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HDI2.4

How do I...use anabolic bone therapy in my management of osteoporosis?

Jennie Walsh
University of Sheffield, Sheffield, United Kingdom

Teriparatide (PTH 1-34) is licensed for treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures and treatment of corticosteroid-induced osteoporosis. It is administered as a daily subcutaneous injection for two years. It is used in patients with severe osteoporosis who have not responded to, or not been able to tolerate bisphosphonate treatment. It is contraindicated in hypercalcaemia, bone cancer, bone radiotherapy and Paget's disease. Non-response to bisphosphonates includes new fractures on treatment or decreasing BMD. Bone turnover markers are useful is assessing response, especially to oral bisphosphonates. Teriparatide increases BMD and decreases vertebral and non-vertebral fractures by more than 50%. Treatment needs to be continued with an anti-resorptive which can be challenging in patients with contraindications or intolerance of bisphosphonates. Romosozumab is a sclerostin antibody, which disinhibits bone formation. It is licensed for the treatment of severe osteoporosis in postmenopausal women at increased risk of fractures. It is administered as a monthly subcutaneous injection for 12 months. It reduces vertebral fractures by 70% compared with placebo and 40% compared with alendronate. It is contraindicated in patients who have had stroke and myocardial infarction due to excess events in the ARCH trial (vs alendronate). NICE have approved romosozumab for first-line treatment in women who have had a major osteoporotic fracture within the last two years and have low BMD. Cardiovascular risk factors should be considered and discussed with patients. Follow-on treatment with an antiresorptive is required to maintain the increase in BMD. Neer et al N Engl J Med 2001;344(19):1434-41 Cosman N Engl J Med 2016; 375(16):1532-1543 Saag N Engl J Med 2017; 377:1417-1427 NICE TA161, TA791

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HDI2.5

Abstract Unavailable

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HDI2.6

Abstract Unavailable

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Meet the Expert Sessions

Metabolism, Obesity and Diabetes

MTE1.1

The "other" islet cells - state of the art for endocrinologists

Patrik Rorsman
University of Oxford, Oxford, United Kingdom

The islets of Langerhans are the small endocrine micro-organs embedded in the exocrine pancreas. The beta-cells of the islets secrete insulin with its well-known blood glucose-lowering effects and that becomes deficient in diabetes. The islets also secrete glucagon (from alpha-cells), the body's principal blood glucose-increasing hormone. The release of glucagon also becomes impaired in diabetes, which contributes to the metabolic impact of the lack of insulin and complicates therapy. However, compared to the beta-cells, the alpha-cells have received very little attention. My talk will highlight the role of a third islet cell – the delta cell that secretes somatostatin. Although the delta-cells only comprise a few per cent of the islet number, they influence the function of most of the other islet cells via their long neurone-like extensions. Our studies have revealed a complex crosstalk between the different islet cells, which is required for normal physiological regulation of islet hormone release, how it becomes disrupted in diabetes and the potential therapeutic opportunities.

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Neuroendocrinology

MTE2.1

Abstract Unavailable

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Nurse

MTE3.1

Primary Aldosteronism: Is low K+ always the key?

August Palma
Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Primary aldosteronism (PA) or Conn's syndrome is a condition in which one or both adrenal glands produce aldosterone in excess, independent of the normal renin-angiotensin-aldosterone system (RAAS) such that renin is typically suppressed and aldosterone is non-suppressible by sodium loading. This excessive and autonomous production of aldosterone causes hypertension, sodium retention, cardiovascular damage, increased potassium excretion that, if prolonged and severe, may lead to hypokalaemia. Under the Endocrine Society Clinical Practice Guideline, the trilogy of confirming the diagnosis of PA includes a suppressed renin level, aldosterone of greater than 550 pmol/L, and hypokalaemia. PA is the most common cause of endocrine hypertension but only less than one percent is screened for it, let alone diagnosed, globally. PA patients have a three-fold risk of cardiovascular morbidity and mortality than age-and-gender matched patients with essential hypertension. PA is surgically curable if caused by a unilateral adrenal adenoma and more novel, less-invasive and adrenal-sparing approaches such as endoscopy-guided radiofrequency ablation procedures are currently being performed in clinical trials. Bilateral PA is managed medically with mineralocorticoid antagonist therapy. About five percent of PA patients develop prolonged hypoaldosteronism post-unilateral adrenalectomy.

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Thyroid

MTE4.1

Abstract Unavailable

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MTE4.2

Abstract Unavailable

DOI: 10.1530/endoabs.94.MTE4.2

Endocrine Cancer and Late Effects

MTE5.1

Abstract Unavailable

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Adrenal and Cardiovascular

MTE6.1

New Tools for the Clinical Management of Congenital Adrenal Hyperplasia

Adina Turcu
University of Michigan, Ann Arbor, USA

Congenital adrenal hyperplasia (CAH) is due to autosomal recessive genetic defects in enzymes required for cortisol synthesis. Defects in the gene encoding steroid 21-hydroxylase (CYP21A2) account for most CAH cases. In all cases of 21-OHD, obstructed cortisol synthesis prompts ACTH elevations, which, in turn, stimulate adrenal cortical growth and steroidogenic flux. The combination of ACTH elevation and 21-OHD favors the overproduction of adrenal androgens. The 2 main treatment goals in 21-OHD are: (1) to replace insufficient hormones (glucocorticoids and mineralocorticoids, when needed) and (2) to suppress excessive production of adrenal androgens.

This session will discuss:

1. the established and upcoming therapies for patients with classic and nonclassic CAH.
2. the utility of traditional and novel biomarkers for monitoring disease control and guiding therapy for patients with classic and nonclassic CAH.

DOI: 10.1530/endoabs.94.MTE6.1

Reproductive and Neuroendocrinology

MTE7.1

The GnRH pulse generator - shining a light into the black box

Allan Herbison
University of Cambridge, Cambridge, United Kingdom

Fertility is critically dependent upon episodic gonadotropin hormone secretion. Recent studies using genetic mouse models have identified that a population of kisspeptin neurons located in the arcuate nucleus (ARN) represent the gonadotropin-releasing hormone (GnRH) pulse generator in both males and females. These cells exhibit abrupt periods of synchronised activity for 1-2 min that, in turn, activate GnRH neuron processes to release GnRH over a similar time scale to drive pulsatile luteinizing hormone secretion. The remarkable similarities

between the activity patterns of mouse ARN kisspeptin neurons and early unidentified multi-unit recordings in the monkey infundibular nucleus by Knobil and colleagues, indicate that the kisspeptin pulse generator is highly conserved in mammals. Studies using in vivo CRISPR-Cas9 gene editing further demonstrate that the primary site of estrogen negative feedback in controlling GnRH secretion occurs through estrogen receptor alpha expressed by ARN kisspeptin neurons. These and other in vivo approaches are finally allowing the once enigmatic pulse generator to be characterized and explored.

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Bone and Calcium

MTE8.1

Abstract Unavailable

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Early Careers Session

Keep the Conversation Going: Communicating, Networking and Engaging in Science

ECS1.1

Listening and learning - how podcasting is more than a communication tool

Lorna Daniels[1] & Shilpa Nagarajan[2]
[1]Governement Office for Science, London, United Kingdom. [2]University of Oxford, Oxford, United Kingdom

Research Co-Culture is a podcast set up by industry-funded post docs from the University of Oxford who talk to researchers from various sectors (academic, pharma, start-ups, and more!) about the value of working together and how research can be better co-cultured.

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ECS1.2

Abstract Unavailable

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ECS1.3

Abstract Unavailable

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Nurse Sessions

Primary Hyperparathyroidism: diagnosis to treatment

NS1.1

Primary Hyperparathyroidism: Can innovative technologies improve current diagnostic and therapeutic pathways?

Tom Kurzawinski
UCLH, London, United Kingdom

Primary Hyperparathyroidism (PHPT) is, after diabetes and thyroid diseases, the third commonest endocrine disorder and its incidence and prevalence is rising globally. In the United Kingdom, the incidence of PHPT has been estimated to be 25/100,000, and prevalence has risen from 1.8 to 6.7 per 1000 between 1997-2006, implying that in the UK alone, about half a million people suffer from this condition and 12.000 develop it each year. Recognition of increased PHPT related morbidity and mortality, through links with hypertension, diabetes, cancer, cerebrovascular and cardiovascular events, have widen criteria for surgery in patients previously classified as asymptomatic. As a result, number of parathyroidectomies performed in the UK has doubled with similar trend observed in other countries. Current surgical paradigm for patients with PHPT is based on performing either Bilateral Neck Exploration through large incisions with little or no pre-operative imaging or Minimally Invasive approach with heavy reliance on pre-operative scans. The downside of the former is poor cosmesis, slower recovery, longer operating time and hospital stay, of the latter, overreliance on multiple pre-operative imaging aimed to maximise cure rate. Rising demand for parathyroid surgery, the only treatment able to provide long term cure and prevent or reverse morbidity of PHPT, calls for rationalisation and simplification of existing surgical pathways. In my talk I will explore innovative technologies which can challenge current status quo and increase number of minimally invasive procedures but at the same time decrease number of preoperative scans and improve cure rates but allow for faster completion of surgery. I will also discuss surgical outcomes of parathyroidectomy in adults and children (yes, children can get Primary Hyperparathyroidism too), impact of genetic testing on decision making (interesting and important) and finally, comment (frankly) on new fads in parathyroid surgery posing as progress.

DOI: 10.1530/endoabs.94.NS1.1

NS1.2

Abstract Unavailable

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NS1.3

Parathyroid UK and the Patient Perspective

Caroline Fryer
Parathyroid UK, East Grinstead, United Kingdom

Parathyroid UK is a national patient organisation committed to improving the quality of life for everyone with parathyroid disorders. We provide information and support to empower our 5,000 members affected by a parathyroid condition to become active in the management of their condition. In Primary Hyperparathyroidism too much parathyroid hormone is produced by one or more enlarged or overactive parathyroid glands, causing hypercalcaemia. This impairs quality of life and increases the risk of osteoporosis, heart attacks, stroke and cancer. Surgery is the only effective treatment which can prevent complications and restore good health. The condition is the third commonest endocrine disorder in the UK, mostly diagnosed in women, particularly postmenopausal women, but can affect both men and women and all ages, including, less commonly, children. We work closely with our dedicated clinical advisors to help raise awareness to all health professionals about management challenges and the unmet needs that patients experience and we contribute to research and guidelines to ensure that the patient voice is heard. Communications Officer, Caroline Fryer, will detail the support offered by Parathyroid UK and explore the patient experience of primary hyperparathyroidism, both from her own perspective and drawing on the experiences of other support group members. She will cover common symptoms, the difficulties of getting appropriate testing and diagnosis, the pathway to surgery and post-surgery aftercare, all from a patient perspective. Caroline will also explain how Parathyroid UK works closely with its medical advisory team to raise awareness about this distressing illness, improve access to treatment and ensure the patient voice is heard. Importantly, she will explore how healthcare professionals can support patients on their long and onerous journey towards a cure and will give time for any questions that arise from the audience.

DOI: 10.1530/endoabs.94.NS1.3

Thyroid Cancer

NS2.1

Nurse led - Holistic care in Thyroid cancer

Nicola Armstrong
Newcastle Upon Tyne NHS Trust, Newcastle Upon Tyne, United Kingdom

The management of patient care is to ensure that individuals are provided with appropriate support and representation during their cancer journey, from the point of diagnosis, throughout treatment and into survivorship. The Clinical Nurse Specialist (CNS) role has become pivotal in many specialities, providing aspects of care such as meeting information needs, holistic nurse led follow up, managing care and providing psychological and social interventions, including referral to others, often through the role of keyworker. The use of Holistic needs assessment (HNA) assists the CNS to achieve good survivorship care. It is a process of gathering and discussing information with the patient and /or carer / supporter in order to develop an understanding of what the person living with and beyond cancer knows, understands and needs. Holistic assessment is focused on the whole person; their entire well-being is discussed – physical, emotional, spiritual, mental, social, and environmental" . By identifying these needs, improvements in care can be made in a responsive manner. HNA's have been used by the Newcastle Thyroid CNS nurse for well over 10 years now which has enabled clear communication between the CNS and patient group. It has allowed development of services including HNA Nurse led telephone clinic, Moving on groups and Survivorship Days.

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NS2.2

Abstract Unavailable

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NS2.3

Informing, supporting, empowering: the role of the patient support group

Julia Priestley
British Thyroid Foundation, Harrogate, United Kingdom

Having access to reliable information is an essential element of the quality treatment and management of a health condition. However, all too often patients tell us they were given very little information, both at diagnosis and throughout their recovery and ongoing management. In a recent survey of 453 patients who had had thyroid surgery (54% for thyroid cancer), 31% told us they did not have enough opportunity to discuss the risks and benefits of the treatment options, 38% said they were not given contact details of who to contact with questions between appointments and only 23% told us they were signposted to patient organisations for further information and support. Having a cancer diagnosis is very frightening and is likely to lead to distress, anxiety and isolation. Much of the information available online is confusing and misleading and often risks increasing these feelings. The BTF works closely with patients and medical professionals to provide evidence-based information that is patient focussed and accessible to people of all ages. Volunteers and staff offer support through a telephone helpline and online forums provide safe spaces for patients to share their concerns and ask tips from others who have been through similar experiences. This talk will discuss the services and support the BTF can provide for your patients but will consider the unmet needs of people living with thyroid cancer and what might be done to manage them.

DOI: 10.1530/endoabs.94.NS2.3

What's innovative and new in Endocrine Nursing?

NS3.1

Abstract Unavailable

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NS3.2

PeopleWith supporting nurses to better understand patient treatment journeys

Mark Bradley
PeopleWith, Omagh, United Kingdom

As information scales in non clinical environments, people are faced with challenges as to what information is relevant to healthcare teams. PeopleWith is a digital health company developing solutions to help people engage with their health. Patients who engage with their health get better treatment outcomes. How do we support patients on this journey to become fully activated in their health and become a participant in conversations to optimise outcomes.

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NS3.3

Abstract Unavailable

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Endocrine Network Sessions

Adrenal

ENS1.1

CaHASE1: what did we learn?

Aled Rees
Cardiff University, Cardiff, United Kingdom

Congenital adrenal hyperplasia (CAH) is a genetic endocrine disorder associated with long-term health risks. Supported by the Society for Endocrinology, the original CaHASE study consisted of an initial questionnaire to UK centres providing specialist care to adults with CAH, followed by a nationwide audit. Three hundred and seventy-three patients from 17 centres were contacted between 2004 and 2007, 203 of whom agreed to participate (138 women, 65 men, median age 34 (range 18-69) years). Patients were evaluated for metabolic, anthropometric and subjective health status, comparing values with Health Survey for England data or appropriate reference cohorts. Only a minority of patients were under specialist care, glucocorticoid replacement was largely non-physiological and androgen concentrations were poorly controlled. This was accompanied by a high prevalence of adverse metabolic risk markers, subfertility and impaired quality of life. This presentation will review these data and will highlight the areas of clinical practice where improvements in management are required.

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ENS1.2

CaHASE2: Current clinical practice and future research

Nils Krone
University of Sheffield, Sheffield, United Kingdom

Congenital adrenal hyperplasia (CAH) is one of the commonest forms of primary adrenal insufficiency with an incidence of about 1 in 15,000. Over 10 years ago, several studies highlighted the suboptimal health status and care provision in adults with CAH that were associated with significant co-morbidities in relatively young adults. The Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) supported by the Society for Endocrinology was formed in 2003 to study the health status of adults with CAH. CaHASE has become the landmark global study informing on the health status in adults with CAH and identified poor health outcomes and variability in care provision However, considering that recruitment into CaHASE took place from 2003 and 2007, the data from this study reflects the situation in the UK from 15 to 20 years ago. CAH clinical guidelines publicised in the early 2000s suggested changes in the use and dosage of corticosteroid replacement in CAH in all age groups. Thus, there is now a generation of young adults with CAH, who should have been treated differently during childhood and adolescence than the cohorts investigated in the early to mid 2000s. In addition, the health status of older adults remains elusive. This year, the Society for Endocrinology performed an online survey of its members suggesting significant variation in CAH care provision in the UK and Ireland. This included the clinical setting, frequency of clinical reviews, treatment regimens and CAH monitoring.

We have therefore developed a programme of work:

- To reassess the clinical management and health status of adults living with CAH in the UK and Ireland, twenty years after the first CaHASE study.
- To implement a strategy for prospective continuous recruitment with longitudinal data collection in I-CAH.
- To identify specific unmet needs, through standardised, deep clinical phenotyping across all participating centres.

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ENS1.3

I-CAH – a platform for data collection and network activities

S. Faisal Ahmed
University of Glasgow, Glasgow, United Kingdom

Following the roll-out of the I-DSD Registry in the 2000s, there was a consensus view that there was a need for a registry for congenital adrenal hyperplasia (CAH) and this was launched in 2014 as a dedicated module within the original registry. There are approximately 150 centres from 50 countries that are currently using the I-DSD/I-CAH/I-TS family of registries and between them there are almost 3,000 cases of CAH that have now been entered. In addition to supporting and promoting research, the I-CAH Registry can act as a tool for care quality improvement and surveillance of novel therapies. Its robust governance ensures adherence to international standards for data protection while promoting research in rare conditions. For further information visit https://sdmregistries.org/.

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ENS1.4

Abstract Unavailable

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Bone and Calcium

ENS2.1

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Abstract Unavailable

DOI: 10.1530/endoabs.94.ENS2.3

Endocrine consequences of living with and beyond cancer

ENS3.1

Abstract Unavailable

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ENS3.2

Abstract Unavailable

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Abstract Unavailable

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Reproductive Endocrinology

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Endocrine Cancer

ENS5.1

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ENS5.2

Abstract Unavailable

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ENS5.3

People With': A new patient focused digital platform

Mark Bradley
N/A, Omagh, United Kingdom

Information is becoming increasingly available in non clinical environments with the scale in functionality in smart mobile devices, wearables and home health devices. This creates a challenge for patients and Clinicians as to what information to capture and how to present and share it. PeopleWith has been developed by a healthcare veteran with 30 years experience working in Nursing and the Pharmaceutical industry. This information is known as Patient generated health data and is becoming increasingly influential in health practice and patient management.

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ENS5.4

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Metabolism, Obesity and Diabetes

ENS6.1

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Neuroendocrinology

ENS7.1

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ENS7.3

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ENS7.4

The Pituitary Society International Consensus on the Treatment of Prolactinoma

John Wass
Oxford University, Oxford, United Kingdom

This review was published in Nature Reviews Endocrinology. It covers recent advances in treatment of pituitary tumours secreting prolactin including long-term adverse effects of dopamine agonist therapy, outcomes following dopamine agonists withdrawal, advances in surgical tumour resection. In addition, there are sections on management during pregnancy, effects of hyperprolactinemia on bone and fracture risk, the management of cystic and aggressive prolactinomas. Prolactinomas in children and transgender patients are also covered. With regard to valvulopathy and cabergoline, screening of patients under a dose of 2mg is likely unnecessary. With patients on more than 2mg cardiac echo is recommended every 2-3 years. Dopamine agonist withdrawal is important and looking for factors which predict successful remission on withdrawal include low maintenance dose of cabergoline treatment, duration of $>$ 2 years and substantial adenoma size reduction. Surgery in an experienced neurosurgical hand, can achieve initial normoprolactinemia in up to 93% individuals with microprolactinoma and 75% of those with selected macroprolactinomas. There's an argument in some patients for suggesting surgical treatment. Particularly in those with intolerance of dopamine agonists and resistance to dopamine agonists. The presence of a cystic component is not uncommon in all pituitary adenomas. Dopamine agonist therapy can demonstrate a high efficacy in cyst reduction. Giant prolactinomas are rare and observed mainly in men. They usually respond well to dopamine agonist therapy. Surgical treatment is restricted to those with apoplexy or CSF leakage. Male sex of a young age and invasiveness are associated with an increased risk of dopamine agonist resistance. During pregnancy cabergoline is now preferred by the majority of centres. Dopamine agonist withdrawal should be considered postmenopausally. In patients with psychiatric disorders, management requires careful collaboration between psychiatry and endocrinology. Assimilation of these guidelines is important. They cover all important aspects of the modern management of prolactin secreting tumours.

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ENS7.5

Abstract Unavailable

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Thyroid

ENS8.1

Abstract Unavailable

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ENS8.2

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ENS8.3

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ENS8.6

Abstract Unavailable

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Ret@30 Symposium Sessions

RET1.1

Discovery of RET as an endocrine cancer gene

Bruce Ponder
CRUK Cambridge Institute, Cambridge, United Kingdom

My group identified RET 30 years ago as the gene for Multiple Endocrine Neoplasia type 2. My involvement was pure chance: as a medical oncologist 'borrowed' from Urology for a day to help in the Thyroid Clinic, the first case notes I opened were of an MEN2 family. With the help of many colleagues, we established Consortia across disciplines (and countries) to assemble families for genetic linkage mapping, and in parallel helped to build the human gene map for chromosome 10, where early results showed MEN2 must lie. The final steps to the gene were proving difficult, until I realised from a hotel staircase conversation that we were following the wrong genetic model. A phone call home, and three days later we had the gene.

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RET1.2

Current understanding of RET genotype-phenotype correlation

Louise Izatt
Department of Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom. Department of Medical and Molecular Genetics, King's College London, London, United Kingdom

The ret proto-oncogene (RET) encodes a transmembrane tyrosine kinase receptor of growth factors belonging to the glial-derived neurotrophic family, essential for the normal development of the kidneys, ureters, peripheral and enteric nervous system. Pathogenic variants in the RET gene result in multiple different phenotypes, which can range from isolated pathologies to multi-system disease, as a result of both loss and gain of RET function. Missense gain of function pathogenic variants in the RET proto-oncogene cause Multiple Endocrine Neoplasia type 2 (MEN2), an autosomal dominant cancer syndrome, where the hallmark of disease is development of medullary thyroid cancer (MTC). There are distinct subtypes of MEN2:- MEN2A, which includes families formerly described as familial MTC (FMTC), MEN2A with cutaneous lichen amyloidosis, MEN2A and Hirschsprung disease (HD) and MEN2B. The aggressiveness of MTC is correlated with specific RET pathogenic variants and stratified into three risk levels (highest, high, and moderate risk) based on the penetrance and aggressiveness of the MTC. Families with MEN2A may develop phaeochromocytomas (PCC) and primary hyperparathyroidism. In MEN2B, MTC develops early, often predating striking physical features that develop (Marfanoid habitus, mucosal neuromas, coarse facies and ganglioneuromatosis) and PCC. Activating somatic RET mutations are linked to development of sporadic MTC. Gain of function RET gene rearrangements also cause a subset of papillary thyroid cancer, lung cancer and chronic myelomonocytic leukaemia cases. In contrast, loss of function pathogenic variants throughout the RET gene are identified in 50% of patients with hereditary HD and 15-20% of patients with sporadic HD. Furthermore, inactivating pathogenic RET variants are identified in 5-30% patients with Congenital anomalies of the kidneys or urinary tract and kidney agenesis. This talk will highlight how knowledge gained over the last 30 years can be used to personalise care in respect to inherited oncogenic driver pathogenic variants in MEN2.

DOI: 10.1530/endoabs.94.RET1.2

RET1.3

Abstract Unavailable

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RET1.4

Life With a RET Gene Change

Joanna Grey
AMEND, Tonbridge, United Kingdom

These days, many children with a RET gene change are diagnosed through genetic screening programmes when there is a parent with the gene change. I wasn't one of those children and was not diagnosed with MEN2 until I was 31 years old. My son was diagnosed through screening at 2 years old. I will share our family's story of how we adjusted to the 'new normal', and how we live with this condition day-to-day more than 20 years down the line. I will also share some thoughts of the wider community in my role as CEO of the Association for Multiple Endocrine Neoplasia Disorders (AMEND).

DOI: 10.1530/endoabs.94.RET1.4

RET2.1

Cellular mechanisms of RET dysfunction in cancer cells

Lois Mulligan[1], Tim Walker[1], Brandy Hyndman[1], Eduardo Reyes-Alvarez[1], Larissa Oliveira[1], Douglas Richardson[2] & Costin Antonescu[3]
[1]Queen's University, Kingston, Canada. [2]Harvard University, Cambridge, USA. [3]Toronto Metropolitan University, Toronto, Canada

The RET receptor tyrosine kinase is an established oncogenic driver in multiple cancers. Activating RET point mutations give rise to the cancer syndrome Multiple Endocrine Neoplasia type 2 (MEN2), characterized by medullary thyroid carcinoma and pheochromocytoma. Correlations of specific RET mutations with MEN2 disease phenotypes and severity have been well documented, however the molecular mechanisms that distinguish the functions, locations, and protein interactions of specific MEN2 mutants as compared to wildtype RET receptors remain poorly understood. In cell models for MEN2A and MEN2B RET mutants, our studies suggest differences in MEN2-RET signaling may be determined in part by the localization of RET mutants in distinct cellular compartments and the duration of their stay at the cell membrane or intracellular regions. We have further validated the importance of RET cellular location in cells depleted for the pheochromocytoma susceptibility gene TMEM127 where we showed wildtype RET protein accumulation on the cell surface, altered membrane dynamics and decreased protein internalization and subcellular trafficking. As a result, we demonstrated that increased RET receptor density in cell membrane domains facilitated constitutive ligand-independent activity and downstream signaling, driving cell proliferation. Our data suggest that oncogenicity of MEN2 mutants is determined in part by aberrant subcellular trafficking of these receptors, which alters receptor localisation and signal duration. Further, these effects can be recapitulated by altered location and trafficking of wildtype receptors, as seen in TMEM127 deficient cells. Together, our data suggest novel mechanisms for RET-mediated transformation which may provide alternative therapeutic opportunities that have not been previously explored.

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RET2.2

Abstract Unavailable

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RET2.3

Surgical Precision for RET-related tumour syndromes in the era of Precision Medicine

Tom Kurzawinski
UCLH, London, United Kingdom

Genetic testing for RET gene was available in the United Kingdom within few years of its discovery, undoubtedly another bonus of universal, nationwide health care system. It was the beginning of Precision Medicine era, which became a watchword for preventative and personalized treatments based on phenotypic, biomarker and genetic characteristics. Surgical Precision on the other hand is an idiom for doing something very well and with meticulous attention to detail. In my presentation I will explore how "precise" surgeons should or can be when treating patients with thyroid, parathyroid and adrenal tumours caused by RET

mutations. Although I will discuss the importance of somatic mutations in sporadic tumours and their impact on surgical strategies, main focus of my talk will be on centrality of germline mutations in planning treatments for patients with familial tumour syndromes. I will discuss genotype-phenotype correlations in common and rare mutations and outline how this allows us to tailor timing and extent of surgery in individual patients, with examples from my practice how this works well in most but not all cases. National UK Audit of Prophylactic Thyroidectomies in Children with MEN2 is an important source of information about 'real world evidence" highlighting quality of treatment these children received. I will present data from years 1995-2013 (with some updates), especially in relation to timing of genetic test and surgery and their impact on histology, postoperative complications and long term follow up with calcitonin. Last part of my presentation will attempt to give insight into how surgical services deliver treatments for these patients now and how they can be improved.

DOI: 10.1530/endoabs.94.RET2.3

Basic Science Workshop Sessions

Getting it right first time – experimental design

BSW1.1

Selecting the right model for your research

Paul Fowler
University of Aberdeen, Aberdeen, United Kingdom

While axiomatic, it is worth reflecting carefully when planning research. The first step requires careful review of the sequence of processes linking the current state of the art of the evidence, to the hypothesis, then to the question/s testing the hypothesis and on to the nature of evidence required to answer those questions., This is of course required well before any consideration of the "how" those questions can be answered. One of the confounders in this careful review process is, of course the issue of practicality: what expertise, facilities, funding, resources, does the lab have access to? Inevitably each lab will have its own range of "favourite" techniques and approaches, based on historical and local particulars as well as what methods are established and validated in the lab. The more towards the early career researcher end of the spectrum an individual is, then the more circumscribed they are likely to be by these factors and by their principal investigator and their funding. Given the need to establish biological plausibility as well as, in many cases, human relevance, selection of appropriate model/s for a specific research project may not be simple. Furthermore, the need for biological plausibility and confirmatory work will frequently impose a requirement for the use of different model systems and approaches. The talk will be aimed at considerations and thoughts around matching model/s to be used with the hypothesis answering requirements in general and acknowledge that the issue around practicalities cannot be ignored.

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BSW1.2

Basic Science Workshop 1 – Getting it right first time – experimental design: Accounting for circadian rhythms

Ann Louise Hunter
University of Manchester, Manchester, United Kingdom

Most endocrinologists are aware of biological rhythms. As undergraduates, we might learn about the menstrual cycle in humans, seasonal changes in reproductive physiology in many animal species, and the circadian and ultradian patterns of cortisol secretion. In recent decades, research has started to uncover the full scope of the circadian clock's influence on physiology (and pathophysiology). It is increasingly clear that we need to account for this in experimental design. In this workshop, I will discuss examples of how time of day can influence the results of sampling or interventions, in both human and animal studies. I will also talk about strategies to standardise practice, and how doing so can yield more meaningful data.

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BSW1.3

Accounting for sex differences in experimental design

Aileen King, Lydia Daniels Gatward & Matilda Kennard
King's College London, London, United Kingdom

Despite well-established sex differences in blood glucose homeostasis, female mice are highly underrepresented in preclinical diabetes research. Reasons for this may be the milder diabetic phenotype often seen in female mice and/or the assumption that the estrus cycle causes excessive variability in blood glucose concentrations. During this workshop talk we will discuss these points and the importance of accounting for sex differences. Using continuous glucose monitoring technology, we have quantified variation in normal non-fasted blood glucose concentrations in male mice and in female mice in either proestrus/estrus or metestrus/diestrus. We have shown that variation in blood glucose concentrations in male mice consistently exceeded that of female mice, irrespective of stage of estrus. Male mice show a more robust response to the glucose tolerance test than female mice. It has been argued that this heightened response to glucose is required to detect effects of drugs. We investigated the effect of metformin in improving glucose tolerance in both sexes and used the data to carry out sample size calculations. Although the drug effect was smaller in female mice, due to lower variability, the number of mice needed to detect significant differences in females did not differ from males. Not only is it relevant to understand how sex differences may affect data, in some circumstances this may become an important factor in understanding disease processes. To this end, we have studied a model of diabetes with clear sex differences (the KINGS mouse) and consider what this can inform us about diabetes development. Overall, we will consider sex differences in the context of preclinical diabetes research. We will discuss what differences exist, when these differences should be embraced rather than ignored and methods to ensure both sexes are represented in pre-clinical studies.

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How endocrine researchers can benefit from modern advances in structural biology

BSW2.1

Abstract Unavailable

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BSW2.2

Abstract Unavailable

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BSW2.3

How to make the most of protein structural data to interpret consequences of genetic variants?

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Investigating the protein structural context of human genetic variants offers a powerful framework for understanding their effects. Recent years have witnessed an exponential growth in our ability to access structural information about the human proteome, driven by advancements in cryo-electron microscopy and computational protein structure prediction, exemplified by AlphaFold. In this talk, I will first briefly cover approaches obtaining a 3D structural model of your protein of interest, including through computational structure prediction of individual proteins and protein complexes. Next, I will review computational tools for prediction of variant effects, focusing on tools that can be used to score variants in terms of their likely pathogenicity, and the increasing importance of protein structural information in this. Finally, I will discuss how protein structural models can be used provide insight into the likely molecular mechanisms underlying disease mutations, and how these mechanisms can have implications for genetic diagnosis and treatment.

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Developments in UK Endocrince Service Delivery

ESD1.1

Peer review

Antonia Brooke
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The need for Peer Review of UK endocrine units was agreed by the Clinical Committee of the Society for Endocrinology in 2001. The service is relevant to the agendas of clinical governance in endocrinology, and ensuring good quality universal care across the UK for patients. Peer Review presents an opportunity to improve patient care, support and facilitate service provision and innovation. Since Covid-19 (2020) there has been significant changes to the way we work and peer review has changed to reflect this. In addition to a reformed in depth peer review across one service, there is now the opportunity to do a networked review across several centres. This will encompass more explicitly secondary and tertiary care centres, and also focus on networking and multidisciplinary services. It is a qualitative assessment that will help find solutions and uses the information from GIRFT but has more focus internally on the endocrine service. It will give all centres an opportunity to discuss common themes and find mutually helpful solutions via networking centres to share strengths and areas to improve. The first networked review of 3 centres has just happened and this is an opportunity to hear all about it and how it can help your centre to feel reinvigorated and energised to make realistic changes.

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ESD1.2

Advice and guidance

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There have always been conversations between clinicians about management and potential referral of patients, predominately from primary care to specialists. This has been called variously 'advice and guidance (A&G)', 'specialist advice' or 'advice and refer' by NHS England (NHSE). In the last few years, A&G has become increasingly relevant with escalating clinic pressures and is now part of the NHSE/GIRFT 'elective care recovery and transformation programme', but uptake by hospitals has been variable. All Trusts in England are now required to develop an effective advice and guidance system. Similar pressures and responses exist in the other UK nations. There are potential advantages listed across NHSE websites for patients, referrers, specialists, and provider organisations, some more compelling than others. It's clear that providers and commissioners are finding different ways of approaching A&G, depending on local arrangements and individual clinician enthusiasm. However, there are concerns in secondary care about how it will be integrated into endocrine clinical workload and specifically into job plans. There are worries from primary care about work being shifted back into their very busy practices without additional resources, and from both sides, about how clinical responsibility is allocated. By November's BES, I will have been trialling the NHSE electronic advice and guidance platform in a secondary care endocrine clinic for four months. I'm using this time to review my workload, experiment with different ways of using A&G, note its impact on local referrals and discuss with operational managers and local GPs. I am polling endocrine colleagues across the UK and in my integrated care role, examining how it is supported by managers in different hospitals. From this I can present some observations and suggestions relevant to endocrine services in general and possibly yours in particular.

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ESD1.3

Abstract Unavailable

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Legends of Endocrinology

LOE1.1

Abstract Unavailable

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LOE1.2

On the shoulders of giants: the gnrh sagas from discovery to new therapies

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The discovery of GnRH involved extraordinary insight, determination and creativity as well as conflict and competition where the players inadvertently advanced each other's endeavours. However, many of us experienced great collegiality, collaboration and sharing reagents in these halcyon years. Many colourful and ambitious characters were involved in the recognition that a portal system transferred a factor from the brain to the pituitary supported by elegant experiments by Harris against vitriolic counter argument from the powerful Zuckerman. The purification of GnRH and TRH involved a tour de force and furious competition between Schally in New Orleans and Guillemin at the Salk Institute. The task involved purification from millions of brains, an effort never again matched as technical advances and the genomic era eased the task. Synthesis of GnRH and structure/activity studies yielded the production of agonists and antagonists and heralded an impressive acceleration of basic and clinical sciences and unprecedented novel treatments for diverse diseases. Basic GnRH research advanced hand in hand with clinical research. The discovery that pulsatile GnRH was stimulatory of gonadotropin but continuous was inhibitory gave rise to treatment for hormone-dependent diseases such as prostate cancer and other conditions. We are now in the era of GnRH antagonists which have immediate inhibition and can be dosed via non-peptide orally active antagonists. A new era emerged with my lab's discovery that there were many variants of GnRH and importantly that one of these, GnRHII was conserved in all vertebrates and was involved in reproductive behaviours. We also succeeded in the cloning the GnRH receptor which accelerated the development of new analogues. The wide distribution of GnRH and cognate receptor in the brain suggested that it had diverse functions, including sexual behaviour and appetite and this year saw the discovery that pulsatile GnRH improves cognition in Down syndrome.

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LOE1.3

Cell and gene therapy for diabetes

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An increased understanding of the DNA sequences and transcription factors (TFs) involved in regulating expression of the insulin gene, and the role that these TFs play in the developing pancreas has opened up new prospects for cell and gene therapy for diabetes. Gene therapy involves injection of an insulin gene construct into muscle, chosen as the most accessible tissue. The major challenges are efficiency of uptake and expression of the exogenous gene, processing of proinsulin to insulin, and regulated release in response to changes in circulating glucose levels. Efforts are also underway to generate islets that can be used to overcome the paucity of donor material for transplantation. Such cell therapy approaches include deriving functional islets from embryonic stem (ES) cells, and reprogramming of exocrine pancreatic tissue. Protocols are now widely available for deriving islet-like structures from ES cells and clinical trials are currently underway. ES-derived islets can also provide insights and models for human islet development and a major academic facility is available within the UK. Islets can also be generated from the exocrine tissue that is left over from the islet isolation procedure. This is based on the now accepted ability of (TFs) to reprogramme a variety of adult cell types for therapeutic purposes.

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Oral Communications

Bone and Calcium

OC1.1

Vitamin D metabolites are associated with overuse musculoskeletal and bone stress injury in young adults

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We investigated the association between vitamin D metabolites and incidence of lower body (pelvis and lower limb) overuse musculoskeletal and bone stress injury in 1637 men and 530 women (22.6 $\pm$ 7.5 years), undergoing 12 weeks initial military training. We measured serum 25-hydroxyvitamin D (25(OH)D) and 24,25-dihydroxyvitamin D ($24,25(OH)_2D$) by high-performance liquid chromatography tandem mass spectrometry, and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by immunoassay during training week 1. Using logistic regression, we examined whether vitamin D metabolites were associated with overuse injury, including whether the relationship between 25(OH)D and $1,25(OH)_2$-D:$24,25(OH)_2D$ ratio was associated with overuse injury. During training, 21.0% sustained ≥ 1 overuse musculoskeletal injury, and 5.6% sustained ≥ 1 bone stress injury. After controlling for sex, BMI, 2.4 km run time, smoking, bone injury history, and Army training course, overuse musculoskeletal injury incidence was higher for participants within the second lowest *vs* highest quartile of $24,25(OH)_2D$ (OR:1.62 [95%CI 1.13-2.32; $P=0.009$]; 3.2-5.1 *vs* 7.7-29.6 $nmol \cdot L^{-1}$) and lowest *vs* highest cluster of 25(OH)D and $1,25(OH)_2$-D:$24,25(OH)_2D$ (OR:6.30 [95%CI 1.89-21.2; $P=0.003$]; 6.9-38.5 $nmol \cdot L^{-1}$ and 125-307 *vs* 107.2-222.5 $nmol \cdot L^{-1}$ and 6-32). Bone stress injury incidence was higher for participants within the lowest *vs* highest quartile of $24,25(OH)_2D$ (OR:4.02 [95%CI 1.82-8.87; $P<0.001$]; 0.4-3.1 *vs* 7.7-29.6 $nmol \cdot L^{-1}$) and lowest *vs* highest cluster of 25(OH)D and $1,25(OH)_2D$:$24,25(OH)_2D$ (OR:22.08 [95%CI 3.26-149.4; $P=0.001$]), after controlling for the same covariates. Greater conversion of 25(OH)D to $24,25(OH)_2D$, relative to $1,25(OH)_2D$ (*i.e.*, low $1,25(OH)_2D$:$24,25(OH)_2D$), and higher serum $24,25(OH)_2D$ were associated with a lower incidence of overuse injury. Serum $24,25(OH)_2D$ may have a role in preventing overuse injury during arduous physical training.

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OC1.2

A large in-frame deletion of the calcium-sensing receptor extracellular domain causes familial hypocalciuric hypercalcaemia type 1 (FHH1) and is partially responsive to cinacalcet

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Familial hypocalciuric hypercalcaemia type 1 (FHH1) is mainly caused by loss-of-function missense mutations of the extracellular calcium-sensing receptor (CaSR), which is a parathyroid- and kidney-expressed G-protein coupled receptor that plays a pivotal role in mineral metabolism. Here, we report the unusual occurrence of a novel heterozygous in-frame *CASR* exon 4 deletion, c.(492+1_493-1)_(1377+1_1378-1)del, in a family with FHH1. This mutation is predicted to delete 295 amino acids from the Ca^{2+}-binding region of the CaSR extracellular domain (ECD), resulting in loss of >25% of the CaSR protein. We hypothesised that this large in-frame deletion would affect CaSR signalling, expression, and responsiveness to cinacalcet, which is a CaSR-positive allosteric modulator. *In vitro* expression studies involving transient transfection of wild-type (WT) and mutant N-terminal-FLAG tagged CaSR constructs into HEK293 cells, followed by immunofluorescence analysis showed that the mutant CaSR protein localised to the cell surface. However, Western blot analysis demonstrated that the mutant CaSR protein was 3.7-fold less abundant ($P<0.01$) and truncated (~30% smaller), compared to WT CaSR. Moreover, dose-dependent fluo-4 intracellular calcium mobilisation assays showed that, compared to WT CaSR, the mutant protein abolished $Ca^{2+}{}_i$-dependent receptor signalling, while HEK293 cells co-transfected with WT and mutant CaSR constructs to mimic the heterozygous state showed a significant rightward shift in the $Ca^{2+}{}_i$-dependent receptor response curve ($P<0.0001$). HEK293 cells expressing only the mutant CaSR were unresponsive to treatment with 100nM cinacalcet. However, cinacalcet treatment normalised $Ca^{2+}{}_i$-dependent receptor responses in HEK293 cells expressing a 1:1 ratio of WT to mutant CaSR. These findings indicate that cinacalcet has therapeutic potential for symptomatic FHH1 patients harbouring the heterozygous form of this mutation. In summary, this study has identified, functionally characterised, and evaluated targeted therapy for the first known naturally occurring deletion of the CaSR Ca^{2+}-binding region in a family with FHH1.

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OC1.3

The role of glucocorticoid metabolism in the skeletal pathophysiology of chronic kidney disease

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Background
Osteoporosis is a common feature of chronic kidney disease (CKD), associated with premature mortality. Glucocorticoids (GCs) are steroid hormones, that in excess, can drive the suppression of bone formation. We have shown that the glucocorticoid (GC) activating enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is dysregulated in CKD, where it may contribute to the suppression of bone formation. We utilised a murine model of CKD with transgenic deletion of 11β-HSD1 to examine its contribution to bone metabolism.
Methods
8-week-old male mice with wild-type (WT) or 11β-HSD1 knockout (11BKO) genetic background received either normal chow diet or chow treated with 0.15% adenine for 7-weeks to induce renal impairment. Renal function was determined by histology and serum urea and creatinine (IDEXX). Within tibia, trabecular bone parameters were assessed by micro-CT and measures of anabolic and catabolic bone metabolism assessed by quantitative RT-PCR.
Results
In both WT and 11BKO animals, adenine induced comparable renal impairment with increased urea and creatinine levels in both WT (fold increase 3.16 and 2.79, $P<0.0001$) and 11BKO mice (fold increase 4.69 and 4.10, $P<0.0001$ respectively) with increased atrophy of glomeruli. In both groups, renal impairment coincided with a marked reduction in bone volume/total tissue volume (BV/TV), trabecular number (TrbN) and thickness (TrbTh). Bone loss was more marked in 11β-HSD1 animals relative to WT controls (BV/TV; WT 48% vs 11BKO 73%; $P<0.001$) with greater loss in TrbN and TrbTh. However, no changes in markers of formation or resorption were apparent between groups at this timepoint.
Conclusion
This study reveals that the adenine model of CKD results in marked systemic bone loss that matches that seen with human disease. Blockade of steroid metabolism in 11BKO animals exacerbated this phenotype *in vivo*. The mechanism underpinning observation has yet to be determined.

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OC1.4

Mendelian randomisation and colocalization analyses reveal novel drug targets for the prevention of kidney stone disease by modulating serum calcium and phosphate concentrations

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Kidney stone disease (KSD) is a recurrent condition with limited prophylactic therapies. This study aimed to use Mendelian randomisation (MR) and colocalization analyses to identify novel drug targets for KSD. Utilising UK Biobank genome-wide association study data for MR, we identified forty-nine 1Mbp regions where genetic loci increase risk of KSD via effects on albumin-adjusted serum calcium or phosphate concentrations. Multi-trait statistical colocalization analyses identified full colocalization of KSD, serum calcium and phosphate concentrations in three regions (posterior probability > 0.99) harbouring likely causal variants associated with *DGKD* (rs838717-G), *SLC34A1* (rs10051765-C), and *CYP24A1* (rs6127099-A). *DGKD* encodes diacylglycerol kinase delta, implicated in the calcium-sensing receptor (CaSR) signalling pathway; rs838717 (G) associates with higher serum calcium and lower phosphate concentrations, consistent with impaired CaSR-signal transduction. *SLC34A1* encodes the renal sodium-phosphate transport protein 2A (NPT2a). Biallelic loss-of-function mutations in NPT2a cause idiopathic infantile hypercalcaemia (IIH) type 2 via increased renal phosphate excretion. IIH type 2 can be successfully treated with oral phosphate supplementation; rs10051765 (C) is associated with higher serum calcium and lower phosphate concentrations, consistent with renal phosphate leak. *CYP24A1* encodes 24-hydroxylase which inactivates 1,25 hydroxyvitamin-D. Biallelic loss-of-function mutations in 24-hydroxylase cause IIH type 1; rs6127099 (A) is associated with higher serum calcium and phosphate concentrations, consistent with increased vitamin-D activation. Using drug target MR we demonstrated the potential utility of reducing serum calcium concentrations via genes implicated in CaSR-signalling (*CASR* OR = 0.67, 95%CI = 0.48-0.93, $P = 0.02$) or vitamin-D activation (*CYP24A1* OR = 0.04, 95%CI = 0.02-0.10, $P = 1.49 \times 10^{-14}$) to prevent KSD. There were insufficient genetic instruments to confirm whether elevation of serum phosphate concentrations via *SLC34A1* may reduce risk of KSD. These findings indicate that positive allosteric modulators of the CaSR or alteration of vitamin-D metabolism may represent novel therapeutic approaches to prevent KSD.

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OC1.5

CTNNB1 pathogenic variants can cause an autosomal dominant osteoporosis-pseudoglioma-like syndrome: a new form of osteogenesis imperfecta?

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A 27-year-old woman with familial exudative vitreoretinopathy (FEVR) experienced multiple childhood fractures, including wrist (aged 7y), hip (aged 10y) and numerous vertebrae. She had low bone mineral density (BMD) (Z scores < -2.5 at multiple sites aged 9; persistently low BMD as an adult) and was short (height below 1st centile). Other features included an unusual facies and mild intellectual impairment. Her mother also had FEVR, dental hypoplasia, mild intellectual impairment, and height below 1st centile. At age 36 her mother fractured her humerus, scapula and clavicle after a fall from standing height; and she had profoundly low BMD (lumbar spine: T-score -5.2, Z-score -4.3, neck of femur: T-score -4.0, Z-score -3.0). These features strongly suggested osteoporosis pseudoglioma syndrome (OPPG); however, LRP5 screening was negative. Exome sequencing showed both women carried a missense CTNNB1 likely pathogenic variant (c.1723G > A; pGly575Arg, not present in gnomAD, affecting a highly conserved base, predicted deleterious by multiple in silico tools). CTNNB1 variants can cause autosomal dominant FEVR, with variable expressivity and penetrance; and have been associated with autism, developmental delay, and intellectual disability. Association of CTNNB1 pathological variants and bone disease in humans has not been described previously, although common variants in this locus are associated with BMD. CTNNB1 codes for ß-catenin which, along with LRP5, forms part of the canonical Wnt signalling pathway critical for normal skeletal development. ß-catenin stabilisation and knockout causes osteopetrotic and osteopaenic phenotypes respectively. LRP5 mutations are an established cause of OPPG, usually considered a recessive condition. However, heterozygous parents of children with OPPG have low BMD. Conversely, LRP5 variants can cause isolated FEVR. This the first report of a bone phenotype in patients with FEVR due to a CTNNB1 mutation, representing a novel autosomal dominant cause of OPPG. Whether pathogenic variants can cause an isolated osteogenesis imperfecta syndrome remains unknown.

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OC1.6

Management of Vitamin D deficiency in primary hyperparathyroidism: a systematic literature review and meta-analysis

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Objective
Vitamin D deficiency is frequently encountered in patients with primary hyperparathyroidism (PHPT), a condition characterised by excessive parathyroid hormone (PTH) secretion and hypercalcemia. This systematic literature review and meta-analysis aimed to assess the management of vitamin D deficiency in PHPT by evaluating vitamin D supplementation regimens and their impact on vitamin D and PTH levels and calcium levels.
Methods
A comprehensive search of electronic databases, including Embase and Pubmed, was conducted to identify relevant studies. Inclusion criteria were predefined in select studies focusing on native vitamin D supplementation in patients with PHPT and reporting data on vitamin D, PTH, and calcium levels. A qualitative and quantitative data synthesis was performed using Review Manager 5.43 software, and a random effect model was employed to analyse pooled data.
Results
A total of 11 studies involving 434 patients met the inclusion criteria. The meta-analysis demonstrated a significant increase in vitamin D levels following vitamin D supplementation ($Z = 5.0$, $P < 0.00001$), indicating the efficacy of various regimens in addressing vitamin D deficiency in PHPT patients. Moreover, a significant reduction in PTH levels was observed after vitamin D supplementation ($Z = 2.88$, $P = 0.004$), suggesting its potential to modulate PTH secretion and improve calcium homeostasis. Our analysis also revealed a significant reduction in calcium levels with vitamin D supplementation ($Z = 2.86$, P 0.004), indicating its favourable effect on hypercalcemia associated with PHPT.
Conclusion
This systematic literature review and meta-analysis provide evidence supporting the positive impact of vitamin D supplementation on vitamin D and PTH levels in patients with PHPT. Additionally, our findings highlight its favourable effect on calcium levels, an aspect not extensively explored in previous meta-analyses. However, heterogeneity across studies and limitations in data availability necessitate cautious interpretation of the findings.

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Endocrine Cancer and Late Effects

OC2.1

Manipulating NIS endocytosis as a druggable target to enhance radioiodide uptake and prognostic indictor of thyroid cancer recurrence

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Background
Diminished sodium iodide symporter (NIS) activity at the plasma membrane (PM) is frequently associated with suboptimal radioiodide (RAI) uptake and poor prognosis in differentiated thyroid cancer (DTC). Endocytosis is a key determinant of symporter activity, with our recent study demonstrating specific interaction of NIS with Adaptor Protein 2 (AP2) – a central player in endocytosis. Here, our objective was to determine whether NIS endocytosis can be exploited as a druggable target to enhance RAI uptake, as well as identify predictive markers of recurrence.
Methods
Chloroquine (CQ) was used as a candidate endocytosis inhibitor. NIS localisation was quantified via NanoBRET and cell surface biotinylation assays (CSBA). NIS function was monitored by RAI (^{125}I) uptake assays in vitro and technetium-99m pertechnetate (^{99m}Tc) uptake in wild-type BALB/c mice.
Results
CQ rapidly increased ^{125}I uptake in TPC1-NIS (2.54-fold; $P < 0.0001$) and 8505C-NIS (1.93-fold; $P < 0.05$) cells peaking after 8 hr. CSBA confirmed elevated levels of cell-surface NIS in CQ-treated cells, which was supported in live CQ-treated cells via KRAS-NanoBRET assays. To challenge this, we ablated the endocytic factor PICALM, known to recruit AP2/clathrin to the PM, which prevented CQ induction of RAI uptake. *in vivo*, CQ treatment of BALB/c mice

enhanced thyroidal ^{99m}Tc-uptake in combination with HDACi SAHA (52.7%; $P=0.0003$), as well as increasing NIS (2.2-fold; $P<0.0001$), TSHR (1.9-fold; $P=0.001$) and PAX8 mRNA expression (1.6-fold; $P=0.003$). Appraisal of TCGA identified 102 significantly dysregulated endocytic genes in RAI-treated DTC. Importantly, recurrent DTC had greater endocytic gene dysregulation, and higher AP2 expression. A predictive risk model using 30 AP2-related genes showed a markedly worse prognosis in high-risk RAI-treated DTC (Hazard Ratio = 57.27,95%CI 16.49-198.87; $P<0.001$; $n=137$).

Conclusions

Our findings suggest that extensive dysregulation of endocytic genes results in NIS mislocalisation away from the PM, thereby reducing RAI uptake. We identify CQ as an FDA-approved pharmaceutical agent targeting NIS endocytosis, with translatable potential to improve RAI therapy.

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OC2.2

^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) in Metastatic/inoperable phaeochromocytomas and paragangliomas and focus on the impact of genetic variations in SDHx mutation on treatment outcomes – A single centre retrospective analysis of experience at an ENETS Centre of Excellence

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Introduction

Metastatic phaeochromocytomas (PCC) and paragangliomas (PGL), collectively known as metastatic PPGL (mPPGL), represent uncommon neuroendocrine tumours for which no standardized treatment guidelines exist. The emerging therapeutic modality employing ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) has exhibited favourable tolerability in the management of these patients.

Methods

In this retrospective analysis, we investigated the efficacy and safety of PRRT in mPPGL and explored the influence of germline pathogenic variations in Succinate Dehydrogenase (SDHx) subunit-encoding genes on treatment outcomes. Nineteen patients with mPPGL who received 2 or more cycles of ^{177}Lu-DOTATATE therapy were included. Clinical, radiological and biochemical responses were assessed 8-12 weeks after the final PRRT cycle, and comparative analysis was conducted to evaluate the effects of PRRT therapy on various parameters between the SDHx-positive and SDHx-negative groups. Progression-free survival was estimated using Kaplan-Meier survival analysis.

Results

The median follow-up duration from cycle 1 of PRRT was 29 months (range: 5-114 months). Post-treatment radiological evaluation confirmed stable disease in 10 patients (53%), partial response in 1 patient (5%), and progressive disease in 8 patients (42%). The overall median PFS for the entire cohort, PGL patients, SDHx-positive cohort, SDHx-negative cohort from the initiation of PRRT was 15 (95% CI, 6.16-23.84), 15 (0.00 – 40.88), 13 (0.00 – 27.32), and 18 (95% CI, 0.00 – 53.28) months respectively. Overall survival for the total study cohort and median PFS for PCC could not be assessed. No CTCAE grade 3-4 cytopenia or nephrotoxicity were observed.

Conclusion

This study provides evidence supporting effectiveness of PRRT in patients with mPPGL as it demonstrates promising outcomes in terms of PFS and minimal occurrence of severe adverse effects. However, further prospective, randomised and controlled studies are necessary to validate these findings.

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OC2.3

Cellular landscape of adrenocortical carcinomas at single-nuclei resolution

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Background

Adrenocortical carcinoma (ACC) is a rare but devastating tumour of the adrenal gland and the molecular mechanisms of pathogenesis remain incompletely understood. To gain novel insights into the cellular landscape of ACC, we compared single nuclei RNA sequencing (snRNA-seq) datasets from ACC and normal adrenal glands (NAGs).

Methods

We isolated single nuclei from 12 ACC snap-frozen samples, including 6 primary tumours, 3 local recurrent adrenal tumours and 3 metastatic lesions from 8 different patients. snRNA-Seq was performed using inDropTM technology. Data analysis, integration and exploration was performed using the Seurat R package. Initial cell types were predicted using NAG as a reference, combined with unsupervised clustering followed by differential gene expression and hallmark gene set analysis.

Results

We found the ACC tumour microenvironment to be relatively devoid of immune cells compared to NAG tissues, consistent with known high tumour purity values for ACC as an immunologically cold tumour. Our analysis revealed 7 subpopulations of ACC-specific adrenocortical cell types, including two populations of mitotically active cells strongly overexpressing MKI67 and DIAPH3 as their top marker genes. DIAPH3 has recently been shown to localize to the centromere during cell division, and we confirmed that expression of this gene is strongly associated with patient outcome in the TCGA. We postulate that mitotic populations play a role in generating the remaining ACC-specific cell types, including two major cell types expressing genes associated with the early stages of cholesterol synthesis (HMGCS1, HMGCR) and calcium signalling (CALN1, CADPS), respectively. These cell types are distributed in a mutually exclusive pattern across patients that reflect patterns of gene expression at the imprinted DLK1/MEG3 locus.

Conclusion

Our study provides insights into the cellular heterogeneity of ACC, revealing a hierarchical process of differentiation that could represent the basis for adrenocortical pathogenesis.

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OC2.4

Communication between peri-prostatic adipocytes and epithelial cells drives prostate cancer aggressivity in obese men

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Prostate Cancer (PC) affects 1-in-6 men in the UK, and obesity 1-in-3, with rates of both increasing. High-fat diet is linked with increased risk of PC death, and volume of peri-prostatic adipose tissue (PPAT) is associated with increased risk of lethal PC/reduced therapy response. **Despite this, molecular mechanisms underpinning obesity-driven PC remain poorly-understood**. This is important since weight-gain and central obesity are major side-effects of PC treatment using androgen-deprivation therapy. Adipose tissue (AT) shows altered secretory profiles in obese *vs* lean patients. This includes cytokines and extracellular-vesicles (EVs), which represent potential pro-tumourigenesis communication tools through delivery of proteins and non-coding RNAs such as microRNAs. Indeed, PPAT EVs promote ovarian and breast cancer progression and contain abundant small RNAs, but near-absence of mRNA/DNA. **This project investigates EV-mediated mechanisms of communication between PPAT and PC epithelial cells, and their clinical implications.** We optimised primary PPAT explant culture and *in vitro* adipocyte differentiation, and comprehensively characterised PPAT EVs. PPAT EVs from obese patients significantly increased proliferation and migration of PC cells but reduced angiogenesis compared to EVs from lean patients, consistent with elevated hypoxia observed in AT in obesity. We also observed reduced levels of angiogenesis-promoting cytokines in conditioned medium of obese *vs* lean PPAT. Small RNA-seq analysis identified 48 significantly-altered microRNAs in PPAT EVs from obese *vs* lean patients, with targets over-represented in MAPK signalling and actin cytoskeleton. Further, PPAT-derived EVs significantly altered the PC cell transcriptome: obese *vs* lean PPAT EV differentially-modulated pathways include Rac/Rho, Wnt and EGFR signalling and actin cytoskeleton. Top PPAT EV-dysregulated genes are increased in PC *vs* normal tissue and are associated with reduced survival. Anti-tumourigenic cytokines are decreased in conditioned medium of obese *vs* lean PC patient PPAT. **Integrative analysis of these data will elucidate novel, actionable drivers of PC progression for personalised medicine.**

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OC2.5

Androgen mediated metabolic perturbation in endocrine resistant breast cancer

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Introduction
Although breast cancer (BC) is considered a treatable disease, $>30\%$ of patients with hormone receptor positive tumours will suffer recurrence post endocrine therapy. One of the fundamental features of cancer cells is their ability to modulate cell metabolism to facilitate survival, stress response, and proliferation. Increasing evidence suggests that these mechanisms play key roles in the development of treatment resistance. Recent publications from our group have shown that an androgenic steroid environment is associated with poor response to aromatase inhibitor (AI) therapy. Of significance, we have previously shown that androgens mediate increased expression of serum-and-glucocorticoid kinase-3 (SGK3), a known substitute for AKT, that is associated with second-line resistance in BC. Here we investigate the role of androgens in modulating cellular metabolism in BC cell lines via SGK3 regulated mechanisms.
Methodology
Using in-house isogenic models of endocrine resistance (MCF7 and LetR) and a novel SGK3-PROTAC1 degrader, we explore the impact of androgenic steroids and SGK3 inhibition on intracellular lipid accumulation and cell metabolism using a combination of Seahorse Mito Stress assays, flow cytometry, protein analysis and imaging studies.
Results
SGK3 inhibition associates with the stabilisation of 17βHSD4, a D-bifunctional enzyme that plays a key role in peroxisomal lipid β-oxidation and androgenic steroid inactivation. Exposure of BC cells to androgens influenced mitochondrial morphology, coincidental with increased mitochondrial membrane potential, mitochondrial mass and glycolytic capacity. Additionally, androgen exposure altered intracellular lipid accumulation and distribution.
Conclusions
Regulation of 17βHSD4 highlights the potential role of androgen driven SGK3 in modifying the steroidogenic tumour environment. This altered steroid micro-environment mediates significant changes in cell metabolism, which mirrors disorders of androgen excess in women, such as PCOS, which are linked to lipid toxicity and deranged metabolism. Further studies will explore androgen mediated SGK3 in regulating steroid homeostasis and associated metabolic reprogramming as drivers of endocrine resistance.

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OC2.6

A critical role for the proto-oncogene PBF in regulating cellular adhesion and motility in thyroid cancer

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The progression of thyroid cancer is dependent on cell motility, a highly complex process that involves the co-ordination of multiple signalling pathways, cell adhesion, and actin dynamics. The proto-oncogene pituitary tumor-transforming gene (PTTG)-binding factor (PBF/PTTG1IP) potently stimulates thyroid cancer cell migration and invasion via PBF phosphorylation by Src kinase at residue Y174. Recent phosphoproteomic and RNA-Seq analyses revealed that upregulation of PBF in Nthy-ori thyroid cells resulted in altered expression and phosphorylation of adhesion and cytoskeletal proteins. We thus hypothesized that PBF is a physiological regulator of cell adhesion and its overexpression in tumours promotes cell motility via altered adhesion. Our preliminary studies have utilized TPC-1 human papillary thyroid carcinoma cells with CRISPR/Cas9-mediated PBF knockout (KO) in the analysis of cell adhesion and spreading on fibronectin-coated plates. Cell adhesion assays demonstrated that PBF-depleted cells exhibited markedly decreased cell-substrate adhesion at multiple time points up to 4 hours compared with controls. We then assessed focal adhesions, the large protein complexes that link the cell cytoskeleton to the extracellular matrix. Immunofluorescence staining of focal adhesion kinase (FAK) and paxillin revealed fewer focal adhesions with altered distribution in TPC-1 PBF KO cells compared with control cells. In particular, FAK and paxillin stained structures were smaller and shorter with reduced frequency in PBF KO cells vs controls, which displayed numerous, elongated focal adhesion structures along actin fibres. Initial live cell imaging of LifeAct-GFP and cell spreading assays also suggested that PBF KO cells had impaired cell spreading. Conversely, exogenous PBF expression resulted in a greater number of dense paxillin structures which were stabilized at focal adhesions in the lamellipodia. Altogether, these findings provide new important insights into focal adhesion dynamics in PBF-induced thyroid cancer cell motility. Further investigations are now required to better define the precise PBF interactions with cell adhesion protein complexes.

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Neuroendocrinology and Pituitary

OC3.1

CDC42: a potential therapeutic target of clinically non-functioning pituitary neuroendocrine tumours

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Background
There is no effective medical treatment available for non-functioning pituitary neuroendocrine tumours (NF-PitNETs). Recurrence (7-12%) or incomplete resection (30-45%) is a common feature. Thus, finding novel medical therapies to help the management of these tumours would be of great value. By using high-throughput mass spectrometry combined with functional characterisation, we explored novel therapeutic targets for NF-PitNETs.
Methods
Tandem mass tag-based mass spectrometry was performed on 20 frozen tissue samples (non-recurrent ($n=15$), recurrent ($n=5$)) from patients with clinically nonfunctioning PitNETs. We used RT-qPCR ($n=20$) and immunohistochemistry ($n=50$) to confirm our results. Cell viability, invasion & migration, and wound healing assays were performed in mouse gonadotroph cell lines (αT3-1 and LβT2 cells) and primary human tumour cells from NF-PitNETs.
Results
Proteomic analysis showed upregulation of 31 proteins of the CDC42 signalling pathway members in recurrent NF-PitNETs, and increased CDC42 expression was confirmed by immunohistochemistry compared to normal pituitaries (<0.0001), with the higher expression in recurrent compared to non-recurrent ($P=0.02$). Proliferative tumours (Trouillas category 1b and 2b) showed increased CDC42 gene and protein expression compared to non-proliferative tumours (1a and 2a) ($P=0.04$). Significant time- and dose-dependent decrease in cell viability was seen in αT3-1 and LβT2 cells upon treatment with CDC42 pathway inhibitors MBQ-167 ($P<0.0001$), ML141 ($P=0.0005$) and FRAX486 ($P<0.0001$). These agents also showed cytotoxic effect on primary human NF-PitNET cells ($n=18$) ($P<0.0001$). Significant inhibition was observed in ML141-treated cells in migration assays (αT3-1, $P=0.006$; LβT2, $P=0.0006$), as well as in transwell invasion assays at 24 hrs (αT3-1, $P<0.0001$; LβT2, $P=0.01$), and 48 hrs (αT3-1, $P=0.01$; LβT2, $P=0.03$).
Conclusion
Our results demonstrate that CDC42 pathway is especially upregulated in recurrent NF-PitNETs. The potent inhibitory effect of ML141 on proliferation, migration and invasion of gonadotroph cell lines and human tumour cells in primary culture points to a therapeutical effect.

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OC3.2

Long-term outcomes of non-operated non-functioning pituitary macroadenomas – results from the UK NFPA consortium

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Background
Large series of patients elucidating the natural history of conservatively managed non-functioning pituitary macroadenomas (macroNFPAs) and relevant prognostic factors are not available.
Objectives
Clarify long-term outcomes of macroNFPAs in large cohort of patients.
Methods
Multi-centre [21 UK endocrine departments-UK NFPA consortium], retrospective, cohort study of cases of (presumed) macroNFPAs offered surveillance as initial management (patients presenting with apoplexy or without follow-up excluded). Clinical/imaging/visual data were collected. Statistical analyses: Kaplan-Meier survival curves, Cox-regression.
Results
949 patients were included [549 (57.9%) men]. Median age and diameter at tumour detection were 63 years (IQR 49-75) and 17 mm (IQR 13-21), respectively. Imaging features at presentation: 15.1% only intrasellar, 55.4% suprasellar extension, 25.3% cavernous sinus extension, 24.7% >1 extensions. During median period of 3.6 years (IQR 1.3-6.6), 385 (40.6%) macroNFPAs grew, 83 (8.7%) reduced in size and 481 (50.7%) remained stable. Cumulative probabilities: growth 1.6%, 8.1%, 29.2%, 43.6% at 6 months, 1, 3, 5 years, respectively; shrinkage 7.1%, 9.6% at 3, 5 years, respectively. Fifteen (1.6%) patients developed clinical apoplexy. On multivariate regression analysis, male sex [HR 1.334;95%CI 1.052-1.693; $P=0.018$] and age [HR 1.010;95%CI 1.003-1.018; $P=0.008$] were predictors of growth, whereas presence of supra-/extrasellar extensions showed trend towards significance [HR 1.431;95%CI 0.996-2.055; $P=0.052$] (3-year probability of growth: 18% if only intrasellar, 31.2% if with extensions). Amongst 458 patients with tumours not abutting/compressing optic chiasm at presentation, 9 (2%) developed visual field defects due to first episode of enlargement and surgery led to improvement/normalisation in 8 of them.
Conclusions
In this largest to-date series of non-operated macroNFPAs, we have shown 43.6% 5-year probability of growth. Development of apoplexy is very rare. Enlargement 6 months after detection is extremely unlikely, suggesting that first surveillance imaging could be performed at one year (with visual assessment in the interim for tumours abutting/compressing optic pathways).

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OC3.3

A mutagenesis-based approach to stabilise D2 dopamine G protein-coupled receptor homomers

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The D2 dopamine receptor (D2R) is a G protein-coupled receptor (GPCR) known to have key roles in neurotransmission, hypothalamic-pituitary hormone release and glucose homeostasis. Thus, this receptor is a therapeutic target in schizophrenia, neurodegenerative disorders, endocrine tumours and even diabetes. As for many GPCRs, D2R can associate with itself as homodimers or heterodimers with distinct receptors. The balance between monomers, homodimers and heterodimers of D2R has also been implicated in several diseases. However, the lack of high-resolution dimer structures hinders our understanding of these complexes and ability to exploit these interactions therapeutically. Therefore, our aim was to stabilise D2R homomers, assess the impact on functional activity and develop pathways for high resolution structures. Molecular modelling identified residues that had the potential to stabilise and/or form disulphide bridges at the predicted homodimer interface. The impact of these mutations on homodimer stability was determined using bioluminescence resonance energy transfer, western blot analysis and super-resolution single molecule microscopy. While their impact on functional activity was assessed via agonist-mediated Gai-signalling, recruitment of a key GPCR adaptor protein, β-arrestin-2, MAPK signalling and receptor internalisation. D2R (Val96Cys) and D2R (Val96Ser/Val97Cys) mutations increased the amount and proximity of protomers within a dimer. Interestingly, these mutations reduced the efficacy of the D2R agonist quinpirole to activate Gai signalling, while promoting faster recruitment (Val96Cys) or higher basal associations (Val96Ser/Val97Cys) of β-arrestin-2. This potential bias towards β-arrestin-2 was supported by enhanced basal and agonist-induced internalization, and a 'switch' to β-arrestin-mediated MAPK signalling. Overall, these findings that modulating D2R homodimer associations and/or stability highlights a selective role in modulating interactions with β-arrestin-2, which in turn promote β-arrestin functions in directing signal activity. These modified receptors could not only form the basis of future structural studies on these homomers, but also identify new potential therapeutic targeting strategies.

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OC3.4

Characterisation of serum prolactin and mammary prolactin sensitivity at the onset of human lactation

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The onset of lactation after childbirth is a key determinant of successful breastfeeding. Copious milk secretion occurs by postpartum day 4 and is mediated by a decline in serum progesterone and high serum prolactin. However, the threshold prolactin concentration required is unclear. It is also unknown if changes in mammary prolactin sensitivity contribute to the initiation of lactation. To investigate this, we recruited 52 healthy pregnant women aged 26-42 years

following informed consent. Serum prolactin was measured before and 45min after a breastfeed on postpartum days 1-4. Mammary prolactin receptor gene (*PRLR*) expression, an index of prolactin sensitivity, was assessed by reverse transcriptase-quantitative PCR using lactating cell RNA isolated from breastmilk samples on postpartum days 1-7, and compared to RNA obtained from non-lactating mammary cells isolated from breast reduction tissue. All participants reported onset of copious milk secretion by postpartum day 4. The mean serum prolactin after childbirth was elevated at 5208 mU/l (range 1686-8400) compared to the normal pre-pregnancy range of <560 mU/l. All women had postpartum serum prolactin values >3-fold above the upper limit of the pre-pregnancy range. Serum prolactin concentrations did not significantly change during postpartum days 1-4 and showed no acute increase during a breastfeed. However, *PRLR* expression significantly increased by >90-fold in lactating cells isolated from breastmilk compared to non-lactating mammary cells ($n=4$ biological replicates, $P<0.001$). Furthermore, mammary *PRLR* expression positively correlated with postpartum duration during the first 7 days after childbirth ($R^2=0.9$, $P=0.001$). In summary, this study demonstrates that lactation onset after childbirth is associated with threshold prolactin concentrations >3-fold above the pre-pregnant normal range and is characterised by a marked increase in mammary *PRLR* expression during the early postpartum period. These findings highlight the importance of high serum prolactin combined with an acute rise in mammary *PRLR* for initiating human lactation.

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OC3.5

The effects of biochemical control and Arthropathy on Quality of Life in patients with Acromegaly: a cross-sectional study

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One of the most prevalent clinical manifestations of acromegaly is arthropathy which persists despite adequate symptom and biochemical control, and contributes to impaired quality of life. Patients with acromegaly have high psychiatry morbidity and increased prevalence of depression and poor psychological wellbeing. In a large cohort we aim to determine the effects of joint disease and disease control on quality of life in acromegaly. Eighty-five patients (45 women; median age 58) with acromegaly were enrolled in our study. Seven patients were excluded due to missing data. Joint pain was assessed using a Joint Pain 'Human Figure' and AcroQoL, EQ-5D, Hospital Anxiety and Depression Scale (HADS) questionnaires were completed by all patients. Demographic information and biochemical data were also obtained from electronic health records. Biochemical control was defined as growth hormone <1.0 mg/l and IGF-1 within the patient specific range at the time of data collection. Data are represented as medians and $P<0.05$ was considered statistically significant. Patients with uncontrolled acromegaly displayed worse QoL scores than controlled patients (AcroQoL 65.35 vs 70, $p>0.05$; EQ-5D 0.72 vs 0.74, $p>0.05$), although the difference was not statistically significant. HADS showed very high rates of anxiety and depression, 37.2% and 27.1% respectively, but no significant differences were found between the controlled vs uncontrolled group. Greater number of joints affected was significantly associated with impaired average AcroQol ($r2=0.011$, $P<0.0001$) and impaired EQ-5D quality of life scores ($r2=0.0002$, $P<0.0001$). GH and IGF-1 levels were not found to significantly correlate with number of joints affected ($r2=0.0156$, 0.0141; $p>0.05$). Quality of life and arthropathy are independent of biochemical disease control suggesting other interventions may be required to improve symptoms. Arthropathy was a significant predictor of impaired quality of life and poor psychological wellbeing highlighting that monitoring of joint disease is crucial to improve quality of life outcomes.

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OC3.6

Aryl hydrocarbon receptor-interacting protein (aip) loss causes failure-to-thrive and cardiac defects in zebrafish

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Aryl hydrocarbon receptor-interacting protein (AIP) is a highly expressed, evolutionary conserved little-known co-chaperone molecule that can bind to client proteins. Heterozygous loss-of-function mutations of AIP are associated with pituitary adenomas. Multiple lines of evidence suggest that AIP has important functions beyond the pituitary gland. Homozygous loss of AIP is lethal, with cardiac abnormalities seen in mice and failure-to-thrive seen in fruit flies and C.elegans. The mechanisms of AIP lethality are unclear. We generated *aip* loss of function zebrafish line using CRISPR/Cas9 with 29 base pair (bp) deletion in exon 2, leading to a premature stop codon. Fluorescent-labelled larval fish feed (paramecia) intake assay was conducted to measure their food intake. Heart size and functions were assessed using microscopy. In larval fish, in *situ* hybridization of atrial myosin heavy chain (*amhc*) and ventricular myosin heavy chain (*vmhc*) and H&E staining were used to characterise cardiac phenotypes. Somatotroph cells were assessed by in *situ* hybridisation for growth hormone 1 (*gh1*). There were no pituitary abnormalities noted at larval stages. The majority of $aip^{-/-}$ individuals died between 6 and 11 dpf regardless of feeding. Only 4% of $aip^{-/-}$ larvae survived until approximately 20 dpf and the remaining fish were significantly smaller, comparable to that 5 dpf larvae. The food intake assay suggested no significant difference between $aip^{+/+}$, $aip^{+/-}$ and $aip^{-/-}$ at 7 dpf, suggesting that while the intake is normal, animals are unable to absorb and metabolise nutrients. The cardiac assessment showed several cardiovascular abnormalities, including an elevated heart rate, severe pericardial oedema and the presence of ventricular hypertrophy after 4 dpf. Our findings establish the key role of AIP in cardiac development and function. Zebrafish provide an ideal model for exploring the mechanisms behind AIP-related growth failure and cardiac dysfunction and identification of potential therapeutic approaches for individuals with AIP-related disorders.

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Reproductive Endocrinology

OC4.1

Unsupervised steroid metabolome cluster analysis to dissect androgen excess and metabolic dysfunction in 488 women with polycystic ovary syndrome – results from the prospective DAISy-PCOS study

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Introduction
Polycystic ovary syndrome (PCOS) affects 10% of women and is associated with a 2-3fold risk of type 2 diabetes (T2D), hypertension, fatty liver and cardiovascular disease. Androgen excess has been implicated as a major contributor to metabolic risk in PCOS. We aimed to identify PCOS sub-types with distinct androgen profiles and compare their cardiometabolic risk.
Methods
We cross-sectionally studied 488 treatment-naïve women with PCOS from UK & Ireland, Austria and Brazil (Age 28[24-32] years; BMI 27.5[22.4-34.6] kg/m2). Standardised assessments included bloods before and during 120min oral glucose tolerance test. We quantified 11-androgenic serum steroids by tandem mass spectrometry, followed by unsupervised k-means clustering of steroid data and statistical comparison of differences in clinical phenotype and metabolic parameters.
Results
Machine learning identified three distinct PCOS subgroups characterised by gonadal-derived androgen excess (GAE; 21.5% of women; lead steroids testosterone, dihydrotestosterone), adrenal-derived androgen excess (AAE; 21.7%; 11-ketotestosterone, 11-hydroxytestosterone) and comparably mild androgen excess (MAE; 56.8%), with similar age and BMI. Compared to GAE and MAE, the AAE cluster had the highest rates of hirsutism (76.4% vs. 67.6% vs. 59.9%) and alopecia (32.1% vs. 14.3% vs. 21.7%). The AAE cluster had the highest HOMA-IR and lowest Matsuda insulin sensitivity index (all $P<0.01$) and a 2-3fold higher incidence of impaired glucose tolerance (IGT) and newly diagnosed T2D. We achieved recruitment of 27% non-white women to the UK & Ireland cohort ($n=208$), with South Asian women more likely to be in the AAE cluster compared to white women (59% vs. 35%).
Conclusion
Unsupervised cluster analysis revealed three PCOS subtypes with distinct androgen excess profiles. The AAE cluster was characterised by highest insulin resistance, IGT and T2D, implicating 11-oxygenated androgens as drivers of metabolic risk. These results provide proof-of-principle for a novel metabolic risk prediction tool in PCOS that could guide future preventative and therapeutic strategies.

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OC4.2

Maternal chronodisruption during gestation affects clock functioning in fetal tissues in a sex-dependent manner via melatonin-independent pathways

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Disruption of circadian regulation could trigger and exacerbate obesity, type 2 diabetes mellitus, and cardiovascular disease. Experiments on rats proved that the deleterious effects of chronodisruption are extremely severe, especially during early developmental stages. Only part of them could be prevented by maternal melatonin administration, suggesting that other pathophysiological mechanisms may be involved. To investigate the role of other mechanisms that might contribute to communication between the maternal and fetal circadian systems, we used PER2::LUC knock-in mice (original strain C57BL), which naturally lack melatonin. The mice carry a PER2 protein fused to luciferase, allowing for the monitoring of clock function ex vivo. Pregnant dams were exposed to either standard light conditions (LD12:12) or constant light (LL) from the first day of gestation (G0.5). Samples were collected at G17.5. Fetuses of both sexes had higher body weights in the LL group already at G17.5. Interestingly, clock function in the peripheral oscillators was impaired, with females being more affected than males. In addition, we found that clock function in the placenta and expression of the glucocorticoid-converting enzymes Hsd11b1 and Hsd11b2 were affected by maternal chronodisruption. To investigate the temporal character of the alterations, we collected samples from adult animals born to LL or LD-exposed mothers. Metabolomic analysis revealed that females born to LL-exposed mothers still differed from the control animals even in adulthood. Our data show that maternal chronodisruption affects the clock in various fetal tissues and organs of mice via melatonin-independent pathways and affects metabolism in a sex-dependent manner. The obtained results emphasize the adverse effects of artificial light during the subjective night for pregnant women.

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OC4.3

Self-administering post-cycle therapy is associated with biochemical gonadal recovery in men stopping anabolic-androgenic steroid use

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Background
Millions of men worldwide take anabolic-androgenic steroids (AAS) to boost muscle growth, but risk psychosis, cardiomyopathy, stroke and death. Users avoid stopping AAS because they are fearful of low testosterone symptoms including sexual dysfunction, depression and suicidality. To avoid these symptoms, men often illicitly self-medicate a 2–12-week course of drugs including selective oestrogen receptor modulators to boost testicular function when stopping AAS (post-cycle therapy; PCT). The endocrine consequences of PCT have not been studied previously, but are important since PCT might paradoxically impair AAS recovery.
Methods
Multivariable analysis of 641 men attending a single addiction clinic in Glasgow between 2015-2022. Men ceasing AAS within 36 months, with or without PCT, underwent assessment including a single, non-fasting random blood test. Normalised reproductive hormones (combination of reference range serum luteinising hormone, follicle-stimulating hormone, and total testosterone levels) was used as a surrogate of biochemical gonadal recovery.
Results
Seventy-three-percent of men illicitly administered PCT during AAS cessation. Odds of biochemical recovery during multivariable analysis were: (1) higher with PCT (OR = 3.80) vs no-PCT ($P=0.001$), in men stopping AAS 3 months previously; (2) reduced when two (OR = 0.55), three (OR = 0.46) or four (OR = 0.25) AAS were administered vs one drug ($P=0.009$); (3) lower with AAS >6 vs ≤ 3 months previously (OR = 0.34, $P=0.01$); (4) higher with last reported AAS >3 months (OR = 5.68) vs ≤ 3 months ($P=0.001$). PCT use was not associated with biochemical recovery in men stopping AAS >3 months previously.
Conclusions
This is the largest endocrine study of AAS cessation, revealing for the first-time independent factors associated with recovery from AAS-induced hypogonadism. Surprisingly, we observed that self-administered PCT is associated with gonadal recovery in men stopping AAS <3 months. PCT remains illicit, potentially dangerous and unproven. Interventional studies are needed to determine whether PCT modulates gonadal recovery in men motivated to stop their AAS addiction.

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OC4.4

Intranasal kisspeptin: a novel, effective and non-invasive approach to stimulate reproductive hormones in patients with reproductive disorders

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Background
Kisspeptin is a potent regulator of GnRH neurons with potential to treat reproductive and psychosexual disorders. However, administration is limited to the subcutaneous or intravenous routes. These invasive routes limit clinical development. Herein, we comprehensively examine the translational potential of intranasal kisspeptin administration for the first-time using rodent, human and pharmaceutical studies.
Methods
First, we conducted *rodent studies* in adult mice to investigate whether intranasal kisspeptin-54 administration could stimulate reproductive hormone release, as well as experiments to elucidate possible mechanisms. Thereafter, we sought to translate these findings into humans: healthy men ($n = 12$) and a patient group of women with hypothalamic amenorrhoea (HA) ($n = 5$) completed a randomised, double-blinded, crossover, placebo-controlled study investigating the effects of intranasal kisspeptin-54 (doses: 3.2-25.6nmol/kg [healthy men] and 12.8nmol/kg [women with HA] vs placebo) on reproductive hormone secretion over 4hrs. Finally, we undertook *pharmaceutical studies* to evaluate the chemical stability of kisspeptin-54 in solution for nasal delivery.
Results
Rodent studies: we demonstrate that intranasal kisspeptin-54 robustly and dose-dependently stimulates LH release in mice. To provide mechanistic insight, we show that intranasal administration of fluorescently-tagged kisspeptin-54 binds to the olfactory epithelium and that GnRH neurons located in the olfactory bulb express kisspeptin receptors. *Human studies*: in healthy men, intranasal kisspeptin dose-dependently increased serum LH at doses 6.4-25.6nmol/kg ($P < 0.01$ all doses vs placebo) with maximal rises at 30mins. Likewise, in women with HA, intranasal kisspeptin acutely increased serum LH ($P = 0.004$ vs placebo) with maximal stimulation from 30mins. *Pharmaceutical studies*: Kisspeptin-54 in solution remained within pharmaceutically accepted limits for stability for 60days at 4°C, demonstrating realistic pharmaceutical potential.
Conclusion
We identify robust clinical effects and provide mechanistic and pharmaceutical data for intranasal delivery as a novel, non-invasive and effective kisspeptin administration route for the management of reproductive disorders that would likely be preferable to patients and clinicians alike.

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OC4.5

Luteinising hormone receptor signalling is reliant on formation of distinct multi-receptor complexes

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Luteinising hormone (LH) and the luteinising hormone receptor (LHR) have key roles in steroidogenesis and ovulation, thus are central targets for fertility treatment. The LHR is a G protein-coupled receptor that predominantly signals through Gαs, although under conditions of high ligand concentration and/or high receptor density, as occurs during the mid-cycle LH surge, can also signal via Gαq/11. Yet, how LHR delineates signal pathway activation to coordinate pleiotropic physiological roles remains unknown. GPCR di/oligomerisation is an important mechanism regulating receptor activity. Whilst mouse studies have demonstrated the physiological relevance of multi-receptor complexes for the LHR in males, the role of distinct LHR complexes in coordinating the complexities of LHR signalling and female reproduction remains unknown. Based on previous super-resolution imaging, molecular modelling predicted multiple transmembrane (TM) interfaces used in formation of multi-receptor LHR complexes. From this, peptides were designed against specific LHR transmembrane domains to allow disruption of different LHR complexes. By inhibiting specific transmembrane domain interactions singularly, and in combination, we have demonstrated that inhibiting formation of different LHR complexes has distinct effects on downstream signalling. Inhibiting TM1,2,4,5 and 6 together results in a 50% loss in cAMP signalling, whilst inhibiting TM1 or TM5 alone results in a 22% or 12% loss of cAMP, respectively. It has been proposed that membrane trafficking can position GPCRs in microdomains rich in signalling partners. Using single particle tracking we have demonstrated that following LH treatment LHR moves slower than untreated receptor, travels less total distance than untreated receptor and is more constricted in its movements, suggesting activated LHR is trafficked to specific membrane micro-compartments. Overall, we have demonstrated that formation of different LHR complexes is critical for LHR function, and that treatment with LH may constrict receptor movement to specific membrane microdomains prior to internalisation.

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OC4.6

Tool development: Characterization of novel follicle-stimulating hormone receptor (FSHR) Inhibitors

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Follicle stimulating hormone (FSH) is a heterodimeric glycoprotein hormone, crucial for regulating female reproduction. Its actions are mediated through FSHR, a Class A G protein-coupled receptor (GPCR), which primarily couples to Gs/cAMP/PKA pathway to modulate ovarian follicle growth, granulosa cell proliferation, and estrogen production. In addition to dogmatic functions of FSH in reproduction, there is increasing evidence that FSH can act on extragonadal tissues. Specifically, that elevated FSH levels experienced during perimenopause/menopause may directly act on bone, adipose and brain, contributing to increased susceptibility to the development of co-morbidities including osteoporosis, changes in adipose tissue distribution and Alzheimer's disease, respectively. Inhibiting FSH/FSHR therefore is therapeutically enticing, with potential for a non-steroidal method of contraception and/or preventing the development of menopause-related co-morbidities. The aim of this study therefore was to develop and characterize novel AI generated FSHR inhibitors. 84 small molecule compounds (SMCs) were generated by AI and screened for their ability to inhibit FSH-dependent cre-luciferase activity in HEK 293 cells expressing FSHR. 3 potential inhibitors exhibited over 90% inhibition of FSH-dependent cre-luciferase activity, were taken forward for further analysis. Using the live kinetic Glo sensor cAMP assay, all 3 inhibitors were shown to display concentration-dependent inhibition of FSH-dependent cAMP accumulation, achieving $>90\%$ inhibition at 100μM and partial inhibition at 20μM. Interestingly, the inhibitors showed different potencies for inhibiting FSH-dependent ERK phosphorylation, suggesting different functional profiles. Analysis of inhibitor effects on ovarian function suggested little effect of the inhibitors on FSH-dependent ovarian follicle growth, supporting a potential therapeutic role in non-steroidal contraception. Finally, assessment of selectivity to FSHR suggested little cross-reactivity with the related glycoprotein hormone receptor, luteinizing hormone receptor. This study highlights 3 novel FSHR inhibitors that are promising candidates for potential development as therapeutic agents for potential targeting menopause-related co-morbidities and/or non-steroidal contraceptives.

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Adrenal and Cardiovascular

OC5.1

Urine steroid metabolomics as a diagnostic tool in endocrine hypertension

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Background
Hypertension affects more than 30% of the adult population worldwide and is a major cardiovascular risk factor. Identifying secondary causes of hypertension is key to offering targeted treatment and mitigating adverse health outcomes. We tested the performance of urine steroid metabolomics (USM), the computational analysis of 24-hour urine steroid metabolome data by machine learning, for diagnosing endocrine hypertension.
Methods
Mass spectrometry-based multi-steroid profiling was used to quantify the excretion of 27 steroid metabolites in 24-hour urine samples from 1400 hypertensive adults with and without endocrine causes (351 retrospectively and 1049 prospectively collected). Data were analysed by generalised matrix learning vector quantisation, a prototype-based algorithm of supervised machine learning, using the retrospective cohort for training and the prospective for validation.
Results
We included 610 patients with primary aldosteronism (PA; 110 retrospective, 500 prospective), 126 with phaeochromocytoma-paraganglioma (PPGL; 82 retrospective, 44 prospective), 83 with Cushing's syndrome (CS; 48 retrospective, 35 prospective), and 581 with primary hypertension (PHT; 111 retrospective, 470 prospective). Of the prospective patients with PHT, 188 had low renin levels (low-renin PHT). USM demonstrated high accuracy in identifying CS cases (area under the receiver-operating characteristics curve [AUC-ROC] 0.93), which showed higher urinary excretion of glucocorticoid and glucocorticoid precursor metabolites. USM yielded moderate accuracy in differentiating PHT from PA (AUC-ROC 0.73); however, the performance improved considerably when comparing PA cases to low-renin PHT (AUC-ROC 0.86), with the major aldosterone metabolite – 3α,5β-tetrahydroaldosterone – being the most discriminatory. USM could not reliably differentiate PHT from PPGL (AUC-ROC 0.57).
Conclusions
Urine steroid metabolomics is a non-invasive candidate test for the accurate diagnosis of hypertension secondary to cortisol and aldosterone excess, and can improve diagnosis and delivery of appropriate treatment in affected individuals.

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OC5.2

Gain-of-function mutation F278C in MC2R results in reduced beta-1-arrestin recruitment and increased cAMP implicating impairment of S280 phosphorylation

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The adrenocorticotrophin hormone (ACTH) receptor, also known as the melanocortin-2-receptor (MC2R), is a key mediator of cortisol synthesis in the adrenal gland. Over 40 loss-of-function MC2R mutations have been described to give rise to familial glucocorticoid deficiency type-1 (FGD1). In contrast, to date only one naturally occurring gain-of-function mutation, F278C, has been identified in a patient with ACTH-independent Cushing's syndrome. Previous work has demonstrated that F278C results in enhanced cAMP generation and impaired desensitisation and internalisation compared to wild-type MC2R receptor. Herein using kinetic biosensors in a naïve cell culture system, we build upon previous findings that the F278C mutation results in increased cAMP signalling. Additionally, we show direct interaction of MC2R with beta-1-arrestin (ARRB1), a protein involved in the sequestration of phosphorylated GPCRs away from the cell surface and that the F278C mutation has impaired recruitment of ARRB1. We have further interrogated this mutation by modifying the downstream putative phosphorylation-site S280 and show very similar trends to that of the F278C mutation, this aligns with the hypothesis that F278 is involved in the phosphorylation of residue S280. In summary, our current data adds to the mechanistic reasons of how naturally occurring human MC2R mutation (F278C) leads to ACTH-independent Cushing's Disease.

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OC5.3

Imaging of adrenal aldosterone synthase expression in patients with primary aldosteronism – a first-in-human study with [^{18}F]aldoview PET-CT

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Background
Primary aldosteronism (PA) is the most common potentially curable cause of secondary hypertension and is a risk factor for cardiovascular morbidity and mortality. For patients with unilateral disease adrenalectomy can be curative. However, PA remains substantially underdiagnosed due the complex diagnostic pathway required to identify patients with unilateral disease, and the difficulties in accurate lateralization of the affected adrenal gland. Specific and selective imaging of aldosterone synthase with PET-CT could provide a non-invasive readout of aldosterone production from both adrenals and allow patients with suspected PA to be better stratified for surgery or medical intervention. To achieve this, we have developed [^{18}F]AldoView – the first highly selective aldosterone synthase PET tracer. Here we report the results of the first-in-human imaging with [^{18}F]AldoView.
Methods
The PET ligand is a highly selective antagonist of aldosterone synthase with fluoride in its primary structure which enables labelling without structural modifications. [^{18}F]AldoView was synthesized in accordance with Good Manufacturing Practice. Four patients (1F,3M) diagnosed with PA (RAA, saline infusion confirmatory test) with unilateral excessive aldosterone secretion confirmed by cross sectional imaging and Adrenal Venous Sampling were imaged with [^{18}F]AldoView PET-CT prior to adrenalectomy.
Results
[^{18}F]AldoView showed rapid clearance from background tissues and substantial uptake in the abnormal adrenal gland. The adrenal lateralisation index, measured as the SUVmax ratio between the two adrenals 35-45 min post-injection, was 6:1, 11:1, 4:1, and 7:1, suggesting it is markedly more selective relative to results reported with alternative PET tracers. Patients tolerated [^{18}F]AldoView well and had no side effects.
Conclusion
PET/CT imaging with [^{18}F]AldoView in this preliminary report of the first four patients has provided highly promising results and suggests that this highly selective tracer has potential to improve the stratification of patients with unilateral PA.

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OC5.4

Mild weight loss and activation of RAAS in gene-edited mice with a E958A knock-in mutation in the AF2-LBD domain of the mineralocorticoid receptor gene

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The mineralocorticoid receptor (MR) has a modular domain structure containing a C-terminal ligand-binding domain (LBD) that consists of 11 α-helices

(designated H1 to H12) organized in an antiparallel helical sandwich. The LBD undergoes a conformational change upon aldosterone binding such that H12 forms a stable interaction with helices 3, 4 and 5 to create an AF-2 domain, a hydrophobic cleft on the surface of the LBD, which serves as a docking platform for transcriptional coactivators. In the human MR, as in other nuclear receptors, replacement of a highly conserved glutamic acid with alanine in helix 12, eliminates interactions with LxxLL motif-containing co-activators (SRC-1, PGC1α and tesmin) but has little impact on ligand-binding. To determine the functional significance of the MR AF-2, *in vivo*, we have used CRISPR/Cas9 gene-editing technology to introduce the equivalent AF-2 mutation, E958A, into exon 12 of the mouse MR gene in a C57Bl/6 genetic background. These mice, bred to homozygosity (MRE958A), are viable without the fatal sodium wasting, seen for MR null and MR DBD mutant mice. This argues that intact AF-2 function in mice is not obligatory for MR-mediated sodium transport. Initial evaluation however shows a significant weight difference between both male and female wildtype and MRE958A mice. Metabolic cage analysis showed increased food and water intake in the MRE958A mice potentially as a potential compensation for mild salt and fluid loss. Both plasma and urinary aldosterone levels were markedly elevated and renal renin mRNA levels increased in MRE958A mice, that was further exacerbated on a low sodium diet. Given previous evidence for the importance of the MR LBD/AF2-coregulator interaction in mediating ligand-dependent transactivation, our finding of only a subtle physiological phenotype in the MRE958A mice is unexpected. This suggests that novel non-AF2 mediated mechanisms may play a role in MR-mediated transactivation.

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OC5.5

Identification of micrornas targeting the mineralocorticoid receptor with therapeutic potential in vascular cognitive impairment

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Hypertension is the most important risk factor in the development of cerebrovascular diseases including vascular cognitive impairment (VCI). Aldosterone is a key regulator of blood pressure, acting via the mineralocorticoid receptor (MR) in the kidney to promote sodium/water reabsorption. Elevated aldosterone, as in primary aldosteronism (PA) is a risk factor for cerebrovascular disease. In addition to its traditional role, the MR is expressed throughout the brain and vasculature, with potential as a dual target in VCI. The MR is partially regulated by non-coding microRNAs, which bind the 3' untranslated region of genes for repression. MicroRNAs are packaged within extracellular vesicles (EVs), which can be manipulated therapeutically. This project seeks to deliver MR-specific microRNAs with therapeutic benefits in VCI. Using a combination of predictive and validated databases, 74 microRNAs were identified as binding the MR-3'UTR. This included miR-19a-3p and miR-124-3p, highlighted in a prior review of circulating microRNAs in stroke. Data from the previous ENSAT-HT study measured 20 MR-specific microRNAs in healthy, primary hypertensive and PA individuals (1). Levels of 4 MR-specific microRNAs were significantly elevated in PA plasma compared to normotensive/primary hypertensive individuals, including a 4-fold increase in miR-19a-3p. Validation of microRNA binding was performed by dual luciferase reporter assay and manipulation with precursor microRNAs. MR binding of miR-19a-3p and miR-124-3p was confirmed, with a significant decrease in reporter expression. EVs were loaded with precursor miR-19a-3p or miR-124-3p via electroporation. MicroRNA levels of miR-124-3p show a significant 4.5-fold increase in rat neuronal cells following 6-hour incubation with pre-miR-124-3p loaded EVs. MicroRNAs miR-19a-3p and miR-124-3p are promising candidates for targeting the MR. Future studies will assess neuroprotective effects in models of VCI.

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OC5.6

11βHSD1 inhibition improves cardiac function compared to standard therapy in a translational pig mode through regulation of extracellular matrix

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Glucocorticoids (GCs) protect cardiomyocytes immediately after myocardial infarction (MI), but GCs subsequently regenerated within the heart by 11β-hydroxysteroid dehydrogenase 1 (11βHSD1) are detrimental during infarct repair, with functional outcomes post-MI improved in mice lacking 11βHSD1. Pharmacological 11βHSD1 inhibition (AZD8329 50mg/kg, 11βHSD1i) was compared to standard clinical therapy (SCT) in a translational pig model (female, 11βHSD1i $n = 11$ vs SCT $n = 9$). MI was induced in Goettingen mini-pigs by temporary coronary occlusion followed by reperfusion, and magnetic resonance imaging was conducted. Fresh frozen tissue and fixed cross-sections of left ventricle were collected, with ethical approval, 28d after MI. Although scar size did not differ between groups, ejection fraction was improved 28d post-MI in 11βHSD1i compared to SCT ($P<0.05$). Mass spectrometry imaging on frozen sections (12 μm) identified 11βHSD1i in infarct scars of 11βHSD1i-treated pigs, aligning with immunostaining for activated fibroblasts. Proteomic analysis of border zone (BZ) tissue highlighted extracellular matrix (ECM) organisation (FDR-corrected $P^*<0.05$) as main pathways modified by 11βHSD1i vs SC, showing collagen processing enzymes (P4HA2, PCOLCE, $P^*<0.05$) and ECM proteins (FN1, VTN, LTBP1, MATN4, $P^*<0.05$) were downregulated in the BZ by 11βHSD1i vs SCT. Collagen processing enzyme lysyl oxidase's mRNA expression was also reduced in the BZ of 11βHSD1i-treated pigs, relative to SCT ($P<0.05$). While total infarct collagen (picrosirius red) and transcript abundance (qPCR) of Collagen I or III did not differ between groups, polarised light microscopy revealed a trend for decreased thick collagen in scars of 11βHSD1i-treated pigs. Finally, brain natriuretic peptide, marking heart failure, was reduced in BZ ($P^*=0.05$), and collagen I ($P=0.05$) was downregulated in the remote myocardium of 11βHSD1i-treated pigs, consistent with reduced wall stress. These data provide the first evidence of 11βHSD1i cardiac protection in a translational model, and support a role of fibroblasts and alteration of collagen processing as the mechanism underlying this effect.

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Metabolism, Obesity and Diabetes

OC6.1

Reduction of SGLT2 protein levels inhibits cortisol secretion through regulation of cytokine secretion

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Background
Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of oral anti-diabetic medications that improve glycaemia by reducing the amount of glucose being absorbed in the kidneys. SGLT2 inhibitors have been proven to improve blood pressure, cardiovascular health and kidney disease. Despite their beneficial clinical effects, their exact mechanism of action is not fully explored. The aim of this project was to investigate the effect of SGLT2 inhibitors in cortisol secretion and action, a hormone secreted by the adrenal glands and activated by the enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11βHSD1), which can cause hyperglycaemia and insulin resistance when in high concentration.
Methods
SGLT2 knockout mice were generated on a C57/BL6 background using CRISPR/Cas9. Cortisol, cytokines and 11βHSD1 levels were measured in plasma and tissue in high-fat-fed male SGLT2−/− (knockout) mice and SGLT2+/+ (wild type-WT) mice chronically treated with the SGLT2 inhibitor dapagliflozin. Human kidney cells (HK2) were treated with cytokines found to be elevated in SGLT2-/- and dapagliflozin treated mice.
Results
Both WT dapagliflozin-treated and SGLT2-/- mice demonstrated same levels of glycosuria. However, glucose tolerance and insulin secretion was more pronounced in the latter. Cortisol secretion in plasma, and 11βHSD1 expression in liver and adipose tissue, was significantly reduced only in SGLT2-/- mice. Cytokines interleukin-6 (IL-6), leptin and Transforming growth factor beta (TGF-β) were significantly inhibited in plasma in SGLT2-/- mice, while anti-inflammatory peptides FGF-21 and IL-10 were increased. HK-2 cells treated with ascending concentrations of these IL-6, leptin and TGFβ demonstrated an increase in SGLT2 expression at gene level, while a decrease was observed when treated with IL-10 and FGF21.

Conclusion
SGLT2 inhibition appears to regulate cortisol secretion by reducing its tissular activation in the liver and adipose tissue. This effect may be mediated by a reduction in inflammatory cytokines and an improvement in glucose tolerance and insulin secretion.

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OC6.2

An hif-fective connection? unravelling the link between hif1α, diabetic neuropathy, and obesity

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Obesity, a complex metabolic disorder characterised by excessive adipose tissue accumulation, is associated with numerous health complications. This study aimed to investigate the molecular mechanisms underlying obesity, focusing on the role of hypoxia-inducible factor 1 alpha (HIF1α). Our findings establish a novel link between HIF1α and the pathogenesis of obesity-related conditions. We uncovered a connection between HIF1α and diabetic neuropathy, a prevalent obesity-associated complication. Our results demonstrate that HIF1α levels play a role in the development of neuropathic pain associated with diabetes. Utilising HIF1α knockout mice, we observed a substantial reduction in pain behaviours, with the mechanical withdrawal threshold significantly reduced by ~48% (***p, $n=6$) in DMOG-treated mice when compared to DMOG-treated HIF1αKO and vehicle-treated wild-type mice. highlighting the pivotal role of HIF1α in pain sensitivity modulation. Mice on a high-fat diet had ~50% (***p, $n=6$) reduced heat withdrawal latency and mechanical withdrawal threshold from week 3 onwards when compared to wild-type and HIF1αKO mice. Proteomics analysis identified 387 differentially expressed genes, including 259 upregulated and 128 downregulated genes, with STRING and DAVID analysis showing mitochondrial ATP production as a top affected function. SeaHorse analysis confirmed the reduced ATP production in hypoxia-modelled neurons compared to DMOG-treated HIF1α knockout controls. On average ATP production was 199.5 ± 35.5 pmol/min in treated HIF1α knockout compared to 107.7 ± 12.0 pmol/min (* $P=0.04$, $n=5$) in hypoxia-induced neurons, basal respiration was also decreased in hypoxia-induced neurons at 157.0 ± 20.4 pmol/min compared to 283.8 ± 48.7 pmol/min of DMOG-treated HIF1α knockout controls (* $P=0.04$, $n=5$). Targeting HIF1α emerges as a promising therapeutic approach for effectively managing obesity-associated disorders, encompassing diabetic neuropathy. The continual exploration of the intricate interplay between HIF1α and obesity-related pathologies holds vast potential for the development of future therapeutic strategies.

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OC6.3

Sex hormone contribution to sex differences in a mouse model of beta cell endoplasmic reticulum (ER) stress

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The KINGS mouse harbours a mutant *Ins2* which drives beta cell ER stress, however only males develop diabetes. Since diabetes incidence is lower in women and ER stress is implicated in human diabetes, we investigated the influence of oestrogen and testosterone in mediating sex differences in the KINGS mouse. To investigate the influence oestrogen (E2) and testosterone removal on glycaemic control, male ($n=4$-6) and female ($n=9$) KINGS mice underwent pre- or post-puberty gonadectomies. In a separate study, KINGS males were administered oestrogen from 3-weeks ($n=5$-7). Glycaemic control was measured through non-fasted blood glucose (NFBG) measurements. Direct beta cell effects of sex hormone removal/administration were investigated through insulin secretion assays using isolated islets and assessing beta cell ER stress using immunofluorescence. Female KINGS ovariectomy mildly increased NFBG but did not cause diabetes, despite increasing beta cell ER stress (10wk BiP fluorescence (AU): Ovariectomy:29.1±1.2, Sham:21.9±1.7, $P<0.05$) and impairing islet glucose stimulated insulin secretion (ng/islet/h at 20mM glucose: Ovariectomy:0.10±0.03, Sham: 0.15±0.05, $P<0.05$). Oestrogen administration in KINGS males prevented diabetes (6-week NFBG: E2:11.2mM±1.0, Vehicle:17.5mM±2.3, $P<0.05$) and was found to reduce beta cell ER stress (BiP fluorescence (AU): E2:40.6±1.7, Vehicle:48.7±1.8, $P<0.05$) and improve islet glucose stimulated insulin secretion (ng/islet/h at 20mM glucose: E2:0.02±0.003, Vehicle: 0.004±0.001, $P<0.05$). Orchidectomy in male mice similarly prevented the development of overt diabetes (10-week NFBG: Orchidectomy:10.4mM±1.1, Sham:25.7mM±2.2, $P<0.05$). Oestrogen was found to have protective effects on the beta cell through reducing beta cell ER stress and improving glucose stimulated insulin secretion. Whilst oestrogen administration rescued male KINGS mice from developing diabetes, ovariectomy was not associated with overt diabetes in female KINGS mice. This suggests that oestrogen is not solely responsible for driving sex differences in diabetes, and indeed testosterone also seems to be involved.

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OC6.4

Human brown adipose tissue activity is regulated by the parasympathetic nervous system

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Brown adipose tissue (BAT) is a therapeutic target for obesity and associated metabolic diseases, due to its role in non-shivering thermogenesis. BAT activation is mediated through sympathetic stimulation, but parasympathetic regulation of human BAT has not been demonstrated previously. We undertook RNA sequencing of human white and brown primary adipocytes to identify novel pathways regulating BAT. CHRM2 (encoding the muscarinic acetylcholine receptor 2) was the most differentially expressed gene (~50-fold higher in human brown than white adipocytes) and was not expressed in murine brown or beige adipocytes. In addition, immunohistochemistry revealed higher CHRM2 expression in human BAT than WAT. To identify parasympathetic regulation of BAT *in vivo*, 15 healthy volunteers (26.4±1.3 years, BMI 22.2±0.4 kg/m^2) received oxybutynin (a CHRM antagonist) 15mg daily or placebo for 4 days in a randomised double-blind crossover study. At the end of each phase, participants were housed in a warm room (23-24°C) for 1 hour, followed by mild cold exposure (16-17°C) for 3 hours to activate BAT. BAT activity was measured using ^{18}F-fluorodeoxyglucose-positron emission tomography magnetic resonance scanning (^{18}F-FDG-PET/MR) during cold exposure. Supraclavicular skin temperature and energy expenditure were measured during warm and cold conditions. Oxybutynin reduced ^{18}F-FDG uptake by BAT by ~20% ($P<0.01$) and BAT volume by ~25% ($P<0.05$) without altering BAT fat fraction. Energy expenditure increased following cold exposure only during the placebo phase. Supraclavicular skin temperature during warm and cold exposure were similar between phases. Cold exposure increased free fatty acid and noradrenaline levels similarly during placebo and oxybutynin phases, indicating adequate and equal sympathetic stimulation on both phases with cold exposure. These data suggest that the parasympathetic system activates human BAT through CHRM2 and reveals novel species-specific differences in the regulation of BAT. Further work is required to determine the mechanisms through which CHMR2 activates human BAT.

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OC6.5

Increased risk of obesity programmed by in utero exposure to maternal obesity: the effects of miR-505-5p in the hypothalamus

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In utero exposure to maternal obesity programs an increased risk of obesity. Animal models have shown that offspring obesity is often preceded by increased food intake, however, the mechanisms that mediate these changes are not understood. Using a mouse model of maternal diet-induced obesity we observed increased intake specifically of a high-fat pellet in adult offspring of obese mothers. Through small RNA sequencing, we identified programmed over-expression of miR-505-5p in the hypothalamus of offspring of obese mothers that is established in the fetus and remains to adulthood and confirmed in vitro that fatty acid exposure increases expression of miR-505-5p in hypothalamic neurons. Pulsed SILAC analysis demonstrated protein targets of miR-505-5p are enriched in pathways involved in fatty acid metabolism. These include key components of

neuronal fatty acid sensing pathways. Over-expression of miR-505-5p decreased neuronal fatty acid uptake and metabolism in neurons in vitro. Importantly, intracerebroventricular injection of a miR-505-5p mimic in mice resulted in increased intake specifically of a high-fat pellet. Collectively these data suggest that maternal obesity induces over-expression of miR-505-5p in offspring hypothalamus, resulting in altered fatty acid sensing and increased intake of high-fat diet. This represents a novel mechanism by which exposure to obesity in pregnancy programs obesity in offspring.

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OC6.6

Low carbohydrate diets in Type 1 diabetes – defining the degree of glycaemic control and nutritional ketosis

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Background
Carbohydrate-restricted diets in type 1 diabetes mellitus (T1DM) are highly controversial. A commonly held concern is that a low carbohydrate diet may more readily result in conversion to diabetic ketoacidosis – one of the most severe complications of poorly managed T1DM. Of note, there is no clear evidence for this phenomenon. We evaluated metabolic profiles in patients with T1DM who had self-selected carbohydrate-restricted diets.
Methods
We analysed data from a three-day evaluation completed by 12 T1DM patients adhering to low- or very-low carbohydrate diets (LCDs or VLCDs respectively) and 3 T1DM patients following regular carbohydrate counting diets (RCCDs). Participants completed a food diary, noted daily insulin usage and measured diurnal blood/interstitial fluid glucose and blood ketones at set daily metabolic intervals.
Results
Participants were divided into three groups according to mean carbohydrate intake: VLCD (<50g carbohydrates/day) $n=6$, LCD (50–130g carbohydrates/day) $n=6$, and RCCD (>130g carbohydrates/day) $n=3$. Data from the three-day metabolic profile evaluation demonstrated significantly raised beta-hydroxybutyrate concentrations (BOHBs) between the VLCD/LCD groups compared with the RCCD group ($P=0.004$). However, the mean daily BOHB concentrations in the VLCD and LCD groups were lower than expected and ranged from 0.3-1.15mmol/l. Further, VLCD/LCD groups had lower daily mean blood/interstitial fluid glucose concentrations compared to the RCCD group ($P=0.021$). The reduced carbohydrate intake was also associated with lower insulin doses, a lower variance of glucose and hence a more stable glycaemic profile ($P=0.01$).
Conclusion
The data obtained suggests that adherence to VLCDs/LCDs in T1DM can facilitate an improved and less variable glycaemic profile. Importantly, these changes occur in a manner that does not mediate concerning supraphysiological increases in BOHB concentrations. The results obtained warrant further research in the form of randomised controlled trials to assess the long-term safety and sustainability of this dietary approach.

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Thyroid

OC7.1

A copper-based metabolite of disulfiram upregulates sodium iodide symporter (NIS) gene expression to enhance thyroidal uptake of radionuclides *in vivo*

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Introduction
New approaches to improve radioiodide (RAI) uptake are urgently required in RAI-refractory thyroid cancer. We previously identified disulfiram as a leading candidate to induce sodium iodide symporter (NIS) activity and promote RAI uptake. *In vivo*, DSF is metabolised to diethyldithiocarbamate (DDC) which binds metal ions. Here, we aimed to gain a mechanistic understanding of how DSF and it's related metabolite $Cu(DDC)_2$ impact NIS activity.
Methods
NIS function was monitored by RAI (^{125}I) uptake assays. Global gene expression changes in response to $Cu(DDC)_2$ were appraised via *in vitro* RNAseq analysis. Technetium-99m pertechnetate (^{99m}Tc) uptake was used to evaluate NIS function in wild-type BALB/c mice.
Results
The ability of DSF to increase RAI uptake in TPC-1 (3.1-fold; $P<0.01$) and 8505C (4.9-fold; $P<0.001$) cells was potentiated by combination with Cu^{2+} to 5.1- and 18.9-fold increases, respectively. Similarly, $Cu(DDC)_2$ was highly effective at increasing RAI uptake (up to 8-fold;250nM; $P<0.001$) in multiple thyroid cell types and induced NIS protein expression, whilst methylated-DDC lacking Cu^{2+} had no effect. Interestingly, a potent transcriptional effect of $Cu(DDC)_2$ was revealed via NIS mRNA induction in TPC-1 (8.5-fold; $P<0.001$) and 8505C (104.8-fold; $P<0.001$) cells. RNA-Seq analysis of $Cu(DDC)_2$-treated 8505C cells revealed altered expression of NIS transcriptional regulators, including *PAX8* (+4.02-fold; $P=0.009$), *CREM* (+1.97-fold; $P=0.003$), *SMAD3* (-1.66-fold; $P=0.012$) and *NKX2-1* (-1.93-fold; $P=0.026$). Intraperitoneal administration of $Cu(DDC)_2$ in wild-type BALB/c mice significantly induced thyroidal uptake of ^{99m}Tc after 30 min (~40% increase;3mg/kg dose; $P<0.001$), as well as increasing thyroidal NIS (1.9-fold; $P<0.01$), thyroid peroxidase (1.8-fold; $P<0.001$) and thyroglobulin (1.3-fold; $P<0.05$) mRNA expression. Importantly, there was a significant positive correlation between thyroidal ^{99m}Tc uptake and NIS mRNA levels ($r_s=0.448$, $P=0.0169$) in $Cu(DDC)_2$-treated mice.
Discussion
Our study demonstrates that a copper-disulfiram metabolite induces a transcriptional response to increase NIS activity *in vitro* and *in vivo*, with clinical potential to improve RAI-refractory thyroid cancer treatment.

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OC7.2

Examining latest costs and prescribing on Liothyronine (T3) by dose levels with respect to the 2017 Competition and Market Authority (CMA) investigation into liothyronine prices and the implementation of 2023 British Thyroid Association (BTA) guidance for appropriate patients suggesting Liothyronine daily dose levels of 5-10mg at possible split dose twice day

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Background
CMA showed price paid for liothyronine tablets rose from £15.15 in 2009 to £258.19 in 2017; a £100 million fine against suppliers was made public December 2021. BTA published guidance on use of liothyronine for appropriate patients in May 2023 suggesting daily dose 5-10mg at possible split twice day. This report investigated link between amounts and costs of T3 prescribing for different dose levels over the last 6 years.
Method
Monthly primary care prescribing data for liothyronine, levothyroxine and NDT by dose levels was analysed to examine change from 2016 to 2022. The monthly rolling 12month total/average was used to identify specific moments. Outcomes included number of GP practices issuing prescriptions, number of prescriptions, actual costs, mgT3, and the cost/prescription &/mg T3
Results
Liothyronine prescriptions fell by 30% then in 2020 started to grow reaching 61,000 in 2022 still 18% below 2016. In 2020 % of 5 & 10 mg prescriptions started to rise from 7% to 30%. In 2019 average cost/item started to fall reaching £146/prescription in 2022 37% of the 2016 value, 20mg fell by 75% to £101/prescription (£0.11/mgT3), 10 mg by 27% to £255/prescription (£0.47/mgT3) and 5mg by 32% to £241 (£0.64/mgT3). Total annual cost fell 70% to £9m/year. % of practices prescribing liothyronine fell from 49% of total to 36%. Levothyroxine cost/prescription fell 47% from £2.94 to £1.57, as total increased by 9% to 30.7 million so total costs fell 42% to £52m/year. NDT costs/prescriptions increased from £207 to £440, total reduced by 44% to 2384 prescriptions, so total costs increased to £1 million.
Conclusion
Liothyronine cost/prescription/mgT3 have fallen significantly but remain 10 times higher than 2009 levels. Lower dose Liothyronine are more than double the

costs of higher dose, so significant cost pressure remains against compliance with latest BTA guidance.

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OC7.3

Influence of tyrosine availability on TSH-dependent cell proliferation and gene transcription in rat FRTL-5 thyroid cells

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Tyrosine availability critically influences thyroid hormone synthesis, and thyroid disorders, such as hyperthyroidism, affect 1% of humans. In contrast, nearly 10% of mature/senior cats develop hyperthyroidism, but colourpoint breeds with mutations in the tyrosinase gene (e.g. Siamese) show reduced risk of developing hyperthyroidism, potentially due to increased availability of tyrosine (related to coat colouration). To establish how tyrosine availability can alter thyroid function, we used the well-established rat FRTL-5 thyroid cell line and investigated how manipulating tyrosine concentrations affected cell proliferation, gene expression and Thyroid Stimulating Hormone (TSH) responsiveness in vitro. FRTL-5 cells were grown in modified Coon's F12 media with variable concentrations of tyrosine, phenylalanine or glycine, to create conditions of depleted, very low, moderate or high tyrosine conditions (range 0 to 140μM). Cell morphology remained consistent, regardless of tyrosine conditions. Furthermore, cell proliferation (as determined by crystal violet assays) was not significantly affected by tyrosine conditions. However, TSH-stimulated cell proliferation was dramatically inhibited in conditions of depleted, very low or moderate tyrosine. Increased phenylalanine availability did not compensate for the lack of tyrosine. These effects were reversible, upon return to tyrosine-replete conditions. Gene expression analyses (using multiplex RT-qPCR) revealed that tyrosine availability did not affect basal gene expression of any thyroid cell marker investigated, but the absence of tyrosine significantly *inhibited* TSH-stimulated *Tg* (thyroglobulin) and *Tpo* (thyroid peroxidase) expression, and significantly *enhanced* TSH-stimulated *Slc26a4* (Pendrin) and *Duox2* (Dual oxidase 2) expression. These data show that tyrosine availability can have direct effects on TSH-stimulated cell proliferation and gene expression in FRTL-5 thyroid cells, and reveals that genes associated with thyroid hormone synthesis (*Tg, Tpo, Slc26a4, Duox2*) are sensitive to tyrosine concentrations. If these changes are reflected *in vivo* in humans and cats, pharmacological or dietary manipulation of tyrosine availability could influence thyroid responsiveness and help prevent hyperthyroidism.

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OC7.4

The effectiveness of radioactive iodine vs thyroidectomy for paediatric grave's disease: a systematic review and meta-analysis

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Introduction
Definitive treatment for pediatric Grave's disease includes radioiodine ablation (RAI) or thyroidectomy. The aim of this systematic review and meta-analysis was to compare the cure and relapse rates of RAI vs surgery as definitive therapy in children with Grave's disease.
Methods
A comprehensive search on Cochrane library, EMBASE, PUBMED and ClinicalTrials.gov for English articles published on definitive treatment of Grave's disease in children since 1985 to 2022 was performed. The data was extracted and analyzed for treatment outcomes, adverse outcomes, risk of bias (ROB) and evidence summated using the GRADE instrument.
Results
Twenty-eight (26 retrospective and 2 prospective) studies with a total of 2571 children (F2057:514M) and a mean age of 13.15 years, with a mean follow up of 8 years were included. Studies were at risk of low to moderate risk of bias. Analysis suggested better cure rates at 12 months for thyroidectomy (95%) compared to RAI 81% (OR 0.9; 95% CI 0.8–1.00); (pheterogeneity = 0.01; I2 = 39%). Recurrence rates was higher in RAI group (11.4% vs 8.7%; OR 1.22; 95% CI: 0.26-5.77); (pheterogeneity = 0.002; I2 = 73%). In subgroup analysis of patients from 16 studies who underwent surgery, total thyroidectomy was more effective than subtotal thyroidectomy in preventing recurrent hyperthyroidism in 0.7 VS 7.8%; (*P* 0.001; moderate quality evidence). Hypothyroidism rates after RAI and surgery were similar (~ 70%). There were no significant adverse outcomes reported such as secondary malignancy or quality of life after RAI. Following total thyroidectomy, adverse effects seen were permanent hypoparathyroidism at 0.4% and temporary recurrent laryngeal nerve palsy at 5.4%.
Conclusion
Thyroidectomy is more effective than radioiodine therapy in effecting cure in Graves' disease in children following failed remission. However, access to thyroidectomy may not be universally available and RAI is an option in these children.

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OC7.5

Thyroid cancer referral pathways: findings from an inner-city tertiary thyroid centre

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Background
Absence of effective clinical indicators for thyroid cancer, which has an excellent prognosis, means community ultrasounds (US) can be important in identifying risk. Where cytology is definitive it should be reviewed by appropriate MDT specialists. This study aimed to examine the outcomes from two-week-wait (2WW) referrals.
Methods
To achieve these aims, we retrospectively reviewed 293 patients referred on the 2ww pathway to an inner-city tertiary thyroid centre (01/09/2021-31/08/2022). Electronic patient records were examined for demographics, US results (highest graded nodule), and cytology.
Results
Following application of exclusion criteria, 262 patients were analysed. The mean (SD) age of the cohort was 49 (±14.7) years: 80.9% (n =212) were female. 12.6% (n =33) had a known multinodular goitre (MNG). The majority were referred on the basis of community US results (49.6%, n =130); 8.5% (n =11) of referrals did not include the scan results. 87.7% (n =114) of these scans were repeated by our thyroid MDT radiologists (Table 1). The following community US scans were amended to U1/U2 classifications: U3 49.4% (n= 39), U4 41.2% (n = 7) and U5 58.3% (n = 7). Of the patients referred on the pathway, 25.6% (n =67) underwent fine needle aspiration (FNA): 43.3% (n =29) yielded cytology ≥Thy3. The incidence of Thy5 nodules in the entire cohort was 5.0% (n =13): 1.1% (n =3) had Thy4 nodules.
Conclusion and Discussion
Criteria for thyroid cancer two week wait referrals needs to be addressed given the low yield of results necessitating treatment. The role of community ultrasounds should be considered as part of the strategy.

Table 1: Ultrasound Assessment of Thyroid Nodules

BTA Classification	Frequency (%) as per Community Ultrasound Results (n)	Frequency (%) as per Community Ultrasound Results (n)
U1	0.0 (0)	11.2 (24)
U2	8.5 (11)	54.0 (116)
U3	60.8 (79)	25.6 (55)
U4	13.1 (17)	5.1 (11)
U5	9.2 (12)	4.2 (9)

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OC7.6

Shallow whole genome sequencing (swgs) as an aiding tool in monitoring of thyroid cancer

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Introduction
Liquid biopsies have revolutionised cancer care, from accurate diagnosis to guiding treatment and surveillance. Here, we used shallow Whole Genome Sequencing (sWGS); a cost-effective and easy-to-perform test to explore concordance of copy number alterations (CNAs) between formalin-fixed paraffin-embedded (FFPE) tissue extracted DNA and circulating cell-free DNA (cfDNA) in patients with Thyroid Cancer (TC) during different stages of the disease.
Aim
To explore the utilisation of sWGS as an aiding tool in the monitoring of TC by looking at concordance of CNAs between FFPEs and cfDNA during follow up.
Methods
FFPE and cfDNA of 23 patients during different stages of TC (pre-operative, remission, progression, new metastases and recurrence) were examined for the presence of CNAs using the Ion ReproSeq PGS™ platform.
Results
Twelve FFPE DNA samples had clear CNAs on sWGS. We applied the same test to the relevant patients' cfDNA looking for CNAs. At the time of writing, all remission cfDNA samples ($n = 8$) were negative for CNAs. One patient had matching CNAs in FFPE DNA and cfDNA during progressive disease. There were 2 further patients with disease progression but without clear CNAs in cfDNA. Further sWGS is underway on the remaining cfDNA samples of patients with positive CNAs on FFPE DNA.
Discussion
Almost half of FFPE DNA showed no clear CNAs, probably due to tumour heterogeneity and/or poor-quality DNA. Absence of CNAs in cfDNA correlates with remission although low mutant DNA fraction in cfDNA might have contributed to absent CNAs in the 2 patients with progressive cancer. The presence of cfDNA CNAs correlated with progression in one patient. Further sWGS results for the remaining cfDNA are to follow.
Learning points
1. sWGS is cost-effective and easy-to-perform test.
2. sWGS can potentially be used to monitor the status of TC during follow up.

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Oral Poster Presentations

Neuroendocrinology and Pituitary

OP1.1

Gene methylation status contributes to delayed puberty

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Self-limited delayed puberty is a condition that is frequently familial with strong genetic determinants. It has been linked to coding region sequence variation by next generation sequencing of affected individuals, identifying genetic regulation of gonadotropin-releasing hormone (GnRH) pathways underlying this condition. However, the role of epigenetic modifiers of human pubertal timing is underexplored. The Hypothalamic-pituitary-gonadal (HPG) axis is unique as it is active in three phases of life: foetal, infancy and then from puberty onwards. In-between these phases of life it is dormant. This is a process highly likely to be regulated by changes in DNA methylation. We have completed DNA methylation analysis, using the Infinium Methylation EPIC array, for patients with delayed puberty who had no identified genetic cause for the condition. Quality control, annotation of CpG sites and differential methylation was completed in R Studio. This has revealed dysregulated methylation in CpG sites linked to important genes known to play a role in the control of puberty and growth. Specifically, dysregulated CpG sites were identified in both VCX and NRXN2, by analysing both differentially methylated positions (DMPs), using the software dmpFinder, and differentially methylated regions (DMR), using the software bumphunter. Key genes involved in upstream regulation of GnHR such as KISS1, TAC3, KMT2A and SIRT1 also showed increased methylation in individuals with delayed puberty. Genes associated with differentially methylated positions were then analysed to identify cellular pathways that were dysregulated. Over representation analysis identified multiple KEGG pathways previously associated with growth dysfunction as significantly altered. These included the cAMP pathway ($P=8.85$x10-08), the neuroactive ligand-receptor interaction pathway ($P=1.63$x10-05) and focal adhesion pathway ($P=1.63$x10-05). Our results suggest that changes in methylation of key regulatory genes contribute to the phenotype of self-limited delayed puberty in a cohort of patients.

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OP1.2

Optimisation of molecular imaging for pituitary tumours using a radioactive phantom

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Background
Image reconstruction is a key step for the accurate interpretation of positron emission tomography (PET) scans. Nuclear medicine phantoms play a critical role in this process. However, existing phantoms (based on simple geometric shapes) do not reflect the complexity of sellar/parasellar anatomy. We therefore created a novel pituitary phantom and examined the impact of image optimisation on the detection of microadenomas, using 11C-methionine PET scans from patients with Cushing Disease who had previously undergone surgery.
Methods
Using radioactive 3D-printing, a bespoke pituitary phantom was created as previously reported (Gillett, 2023). The phantom replicated pituitary glands harbouring tumors of differing sizes (2, 4 and 6 mm diameters) and radioactive concentrations (2×, 5× and 8× the background normal gland). The anatomical phantom, housing the normal gland and embedded tumour, closely approximated the attenuation properties of surrounding bone and soft tissue. Following identification of optimal reconstruction parameters, these were retrospectively applied to PET scans from a cohort of patients with surgically-confirmed microadenomas, and assessed in blinded fashion by expert readers.
Results
Consistent with our previous findings, the optimal parameters for molecular pituitary imaging used a Bayesian penalised likelihood (BPL) iterative reconstruction algorithm, with time of flight, point spread function correction, and regularisation (β) parameter values of 400 or 100 (for tumours <4 mm diameter). These parameters were then applied retrospectively to preoperative scans from a cohort of patients with pituitary corticotroph microadenomas, in whom subsequent transsphenoidal surgery had confirmed the location of the tumour. In each case, reader confidence in identifying the correct location of the tumour was increased using the optimised reconstruction parameters. Importantly, no false positive calls were made using a negative control.
Conclusions
We have shown how a novel pituitary phantom can enhance detection of small corticotroph microadenomas using molecular PET imaging.

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OP1.3

Biochemical control does not improve functional impairment in people with acromegaly

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Acromegaly, a chronic disorder of excessive growth hormone secretion, leads to functional limitation and impaired mobility most commonly due to arthropathy. Patients with biochemically controlled acromegaly have reported persistent impairment in prior studies. We aimed to compare the functional differences in patients with biochemically controlled acromegaly to those with uncontrolled disease by means of validated questionnaires. Between March 2017 and May 2022, patients over 18 years old, diagnosed with acromegaly were recruited to fill out validated questionnaires at a tertiary hospital in this cross-sectional study. Exclusion criteria were co-morbid inflammatory arthritis, recent musculoskeletal trauma (<3 months), active cancer, and impaired cognition. Data on the activities of daily living (ADL) and sport function subsections of the Knee injury and Osteoarthritis Outcome Score (KOOS), and the Health Assessment Questionnaire (HAQ) were collected. Patient demographics and biochemical data were also collected. Biochemical control of acromegaly was defined as a growth hormone (GH) level of <1.0 mg/l alongside an insulin-like growth factor-1 (IGF-1) within range at the time of data collection. Data are presented as medians and interquartile ranges (IQR). Of the 85 patients (median age 58 years (IQR 52, 68), 52.9% females, GH 0.6 mg/l [0.2, 1.5], and IGF-1 24.9 nmol/l [17.2, 36.8]), seven patients had missing biochemical data, resulting in 39 patients (50%) with control and 39 without. There was functional impairment (KOOS-ADL controlled 89.7% vs. uncontrolled 86.8%, $P=0.63$; KOOS-sport function 65% vs. 70%, $P=0.84$; and HAQ 0.25 vs. 0.25, $P=0.41$) across both groups; the impairment was equally severe in those with and without control. Age, gender, GH, and/or IGF-1 did not predict impairment in our cohort. Despite adequate biochemical control of acromegaly, patients reported ongoing functional impairment across multiple domains of activity. Longitudinal data on biochemical burden are needed to draw further conclusions.

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OP1.4

Ambulatory dynamic assessment in endocrinology: Insights and possibilities

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Rhythms and change are fundamental properties of all living things, having evolved to allow adaptation to life on earth. Rhythmicity can be observed both in behaviour and internal biology of all mammals including humans. Hormonal secretion patterns that occur at circadian and or ultradian frequencies occur commonly in the endocrine system but for practical and pragmatic reasons clinicians tend to sample and attempt to interpret single time point measures. These results can often be difficult to interpret. In this presentation I will demonstrate sophisticated sampling and measurement techniques that permit blood free and high-resolution measurement of hormone and metabolism in real world contexts. I will present ambulatory dynamic profiles of 7 corticosteroids from $n = 214$ volunteers. I will demonstrate how mathematical and machine learning techniques can be used to extract and interpret important features from these dynamic profiles and how this information could be used to improve diagnosis and management, providing specific examples of Cushing's, primary aldosteronism, and primary adrenal insufficiency. I will also show pilot experimental methods that allow simultaneous ambulatory profiling of melatonin, glucocorticoids, catecholamines and metanephrines. Finally I will show data from $n = 11$ healthy participants demonstrating the integration of passive wearable devices that contextualise biological data, and how, taken together, this could represent the future of personalised endocrinology.

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Metabolism, Obesity and Diabetes

OP2.1

Insulin resistance in macrophages impacts cholesterol biosynthesis and interferon gene expression and reduces foam cell formation capacity

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Background
Insulin resistance and ageing are risk factors for the development of type 2 diabetes and atherosclerosis. Insulin signalling in macrophages affects their inflammatory responses and foam cell formation capacity, yet the mechanisms linking these remain unclear. Recent evidence has emerged linking macrophage lipid metabolism and inflammatory response such as an interferon-cholesterol pathway flux axis. Insulin has been shown to directly regulate cholesterol biosynthesis in liver and brain. SHIP2 is a negative regulator of insulin mediated PI(3)K signalling pathway which is affected in insulin resistant patients.
Methods
Hematopoietic SHIP2 knock-down mice (h-SHIP2KD) were aged for 50 weeks. Bone marrow derived macrophages (BMDM) were compared to their aged cre expressing control litter mates.
Results
BMDM from aged h-SHIP2KD mice were shown to be insulin resistant through lack of acute phosphoAkt-S473 induction by insulin. Transcriptome array profiling revealed the differential expression of more than 600 genes by more than 2-fold, FDR-adj P value <0.05). Hallmark pathway analysis showed interferon immune responses were the top regulated pathways. A selection of interferon responsive genes were confirmed by RT-qPCR in separate experiments. Further interrogation of the array data revealed significant up-regulation of genes involved in cholesterol biosynthesis in the aged insulin resistant h-SHIP2KD BMDM which were also confirmed by qPCR, and Oil red O staining revealed increased lipid content in the aged insulin resistant h-SHIP2KD cells. Furthermore, when challenged acutely with insulin, young insulin-responsive BMDM also show significant changes in cholesterol biosynthesis and interferon gene expression. Oil red O staining after incubation with acetylated LDL revealed aged h-SHIP2KD BMDM showed significant resistance to foam cell formation when compared to controls.
Conclusion
We propose a novel unifying mechanism, in which insulin affects macrophage inflammatory responses through insulin's effect on macrophage cholesterol metabolism.

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OP2.2

An acute upregulation of hepatic de novo lipogenesis does not attenuate the partitioning of polyunsaturated fatty acids into oxidation pathways

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Background
Intrahepatic triglyceride (IHTG) accumulation, a cardiometabolic disease risk factor, is greater in individuals consuming saturated-fat (SFA) compared to polyunsaturated-fat (PUFA) enriched diets. We have demonstrated that compared to SFA, PUFA are preferentially partitioned into oxidation pathways, which may, in part, explain the divergence in IHTG accumulation. However, it remains unclear if this preferential handling is maintained when hepatocellular metabolism is shifted toward fatty acid (FA) esterification and away from oxidation, such as when hepatic *de novo* lipogenesis (DNL) is upregulated.
Aim
To investigate whether dietary-induced upregulation of hepatic DNL influences the partitioning of dietary FAs.
Methods
20 healthy volunteers (11 females) underwent a fasting baseline visit followed by two postprandial study days (PSD), 2-weeks apart. Prior to each PSD, participants consumed an isocaloric high-sugar diet (to promote hepatic DNL) for 3-days. On the PSD, participants consumed an identical standardised test meal that contained a ^{13}C-labelled FA (SFA ([U^{13}C]palmitate) or PUFA ([U^{13}C]linoleate)), in random order, to trace the fate of dietary FA. Blood and breath samples were collected over the 6h postprandial period and ^{13}C enrichment in breath CO_2 and plasma lipid fractions were measured using gas chromatography/mass-spectrometry.
Results
Compared to the baseline visit, fasting plasma triglyceride concentrations and hepatic DNL were significantly ($P<0.05$) increased after consumpting the high-sugar diet. Appearance of ^{13}C in expired CO_2 and tracer recovery were significantly ($P<0.05$) higher after consumption of the meal containing [U^{13}C] linoleate compared to [U^{13}C]palmitate ($5.1\pm0.5\%$ vs. $3.7\pm0.4\%$), respectively. Incorporation of ^{13}C into the plasma triglyceride and non-esterified FA pool was significantly ($P<0.001$) greater for [U^{13}C]palmitate compared to [U^{13}C] linoleate.
Conclusion
Our findings demonstrate that the increased partitioning of SFA into esterification pathways, compared to PUFA, is maintained during dietary-induced DNL upregulation. This may reveal important mechanistic insights regarding SFA in cardiometabolic disease risk.

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OP2.3

Vitamin B12 deficiency alters leptin DNA methylation and lipid metabolism in the human placenta

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Background
Maternal B12 deficiency is linked with adverse metabolic disorders in infants. B12 has a potential epigenetic role which could influence placental dysfunction and fetal metabolism. Adipokines such as leptin and adiponectin play a major role in placental development by regulating lipid metabolism. Alterations in in-utero programming develop risk to obesity and metabolic diseases in offspring. B12 deficiency in mothers has been linked with higher cord triglyceride and lower HDL levels. Here, we aim to assess the adaptation of placental adipokine promoter methylation due to low B12 and determine the consequences of these epigenetic changes on gene expression and lipid metabolism.
Methods
Human placental explants (derived from 10 healthy pregnant women) and BeWo trophoblastic cell line were cultured for 7 days in CMRL or custom-made Ham's F12 media, respectively, supplemented with sufficient (500nM-Control) or low B12 concentrations (25pM-low B12). Expression of lipid metabolism genes was detected using qRT-PCR. CpG methylation was measured using pyrosequencing.
Results
Placental explants and BeWo cells deficient in B12 demonstrated increased gene expression of nuclear transcription factors regulating fatty-acid (FA) synthesis (SREBF1), adipogenesis (PPARγ, CEBPα) and significantly altered the gene expressions of FA (FASN, ACACA, ACLY, ELOVL6), triglycerides biosynthesis (AGPAT2, GPAM, SCD, DGAT1, DGAT2) and FA oxidation (LDLR, ACADM, ACADS, ACSL1, SLC25A20) compared to control ($P<0.05$). Low B12 showed significant hypomethylation of specific CpG sites in the leptin promoter and an increase in gene expression. However, we found that the adiponectin gene was not expressed, and there were only slightly elevated methylated CpG sites in the adiponectin promoter region.
Conclusion
Our novel data highlights that low B12 has a key role in altering lipid metabolism which might be via leptin gene promoter methylation in placenta. Thus, indicating maternal B12 deficiency during placental development could lead to metabolic defects such as dyslipidaemia in infants.

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OP2.4

iPSC-derived hepatocytes as a novel tool for Ornithine Transcarbamylase Deficiency (OTCD) modelling and drug screening

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Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle disorder (UCD) with a prevalence of one in 60-70,000 in humans. It is mainly caused by mutations in the *OTC* gene, which encodes the enzyme ornithine transcarbamylase. Patients with OTCD present disturbed urea cycle function and ammonia accumulation in the bloodstream, downstream leading to a range of symptoms, including developmental delay, cerebral oedema, coma, and death. We developed a human hepatocyte model recapitulating the OTCD phenotype in-a-dish. In healthy induced pluripotent stem cells (iPSCs), the OTC mutation D175V (Asp175Val) was introduced by CRISPR gene editing. Genotype confirmation was performed by Sanger sequencing, whilst iPSC pluripotency and differentiation of iPSCs towards hepatocyte-like cells (HLCs) by qPCR and immunocytochemistry. Expression of urea cycle-related markers were determined by qPCR and western blotting, whilst urea secretion by biochemical assays. Following direct iPSC differentiation, we generated iPSC-derived HLCs expressing comparable levels of the hepatocyte maturity markers albumin, alpha-1-antitrypsin, and HNF4alpha to primary human hepatocytes. To characterise our HLC model, expression of the urea cycle-related enzymes OTC, ASS1, ASL, CPS1, and ARG were measured, revealing higher expression levels compared to iPSCs (negative control) and HepG2 hepatocellular carcinoma cells. Supporting these data, stimulation of urea cycle with NH4Cl and ornithine resulted in increasing urea secretion in a time-dependent manner, and this was significantly higher when compared to HepG2 cells. Consistent with successful confirmation of D175V mutation in CRISPR-derived HLCs, mRNA and protein levels of OTC were significantly lower compared to their wild-type isogenic controls, accompanied by decreased urea secretion. In conclusion, we have developed an iPSC-derived hepatocyte model that recapitulates human OTCD phenotype *in vitro*. This technology provides a framework for the development of human metabolic disease models and highlights the superiority of iPSCs as an effective platform for metabolic disease modelling and hit-lead drug screening.

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Reproductive Endocrinology

OP3.1

Are we giving enough attention to blood pressure control in turner syndrome? : Data from the international turner syndrome (I-TS) registry

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Introduction
Cardiovascular disease is the commonest cause of death (absolute-excess-risk:41%) in Turner Syndrome (TS). Hypertension is a major risk for circulatory-disease (up to 60%) and a key modifiable-risk factor of aortopathy, ischemic heart disease and stroke in TS. There is no current consensus for hypertension diagnosis/management in TS.
Methods
Retrospective multi-centre observational study of patients aged ≥18 years, included in the I-TS registry (2020-2022) utilising registry and participating centre collected data.
Results
Eleven international-centres participated, including 184 patients; [median age 28 (range 18-71) years]. Hypertension was recorded in 13% (24/184) with median age 27(range 10-56) years, systolic-blood pressur(SBP) 150 (range 125-270) mmHg, and diastolic-BP(DBP) 90(range 60-136)mmHg at diagnosis. Hypertension was diagnosed in 69.2% aged ≤40 years and 92.3% aged ≤50 years. Karyotype 45,X ($P=0.024$) was significantly associated with hypertension (Table 1). Age of estrogen comencement ($P=0.508$), daily estrogen ($P=0.719$) and progesterone ($P=0.352$) doses, and route of HRT ($P=0.568$) were not associated with hypertension. None of TS-specific-comorbidities [aortic disease: 39.1% ($P=0.125$), renal anomalies: 20.8% ($P=0.585$)], nor TS-associated-morbidities [dyslipidaemia: 40% ($P=0.14$)], were associated with hypertension. Hypertension control was suboptimal; 38.1% and 52.6% respectively had SBP and DBP above 130/80 mmHg, including 50% (4/8) of patients with aortopathy. Management included angiotensin-converting-enzyme inhibitors (ACEi) (62.5%), angotensin-receptor-blockers(25%) and beta-blockers(25%).

Table 1: Hypertension Vs no-hypertension

Characteristic	Hypertension	No hypertension	P values
Median age at data collection	45 (range 18-67) years	28 (range 18-71) years	0.012
Body-mass-index	28.4 (range 20.6-43.9) Kg/m2	24 (range 14.2-34.5 Kg/m2	0.005
Monosomy, 45,X	15 (62.5%)	61 (38.1%)	0.024

Conclusions
Hypertension was common in TS. Young-onset disease with high prevalence of TS-specific/associated morbidity was observed. Overweight/obesity and 45,X karyotype were notable risk factors for hypertension. The frequency of sub-optimal BP control highlights the importance of increased awareness and TS-specific consensus guidance on management.

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OP3.2

Abnormal uterine bleeding (AUB) and COVID-19: investigating associations and potential mechanisms

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Women with COVID-19 and Long COVID (symptoms >4 weeks) have reported AUB. We investigated (i) the association between COVID-19/Long COVID and AUB and (ii) ovarian sex hormones across the menstrual cycle in women with Long COVID. Two studies were completed with ethical approvals and consent. Firstly, a retrospective online survey 'The Covid-19 Pandemic and Women's Reproductive Health' was conducted March-May 2021 with UK participants >18 years old (n =26,710). Those who had menstruated in the last year (n = 12,579) were asked about menstrual frequency, regularity, volume, duration and grouped by COVID status. Multivariable analyses adjusted for hormone use, pre-exiting gynaecological conditions, socioeconomic status and multiple comparisons. Previous acute COVID-19 (n =2017) or Long COVID (n =1048) resulted in an increased relative risk of reporting frequent vs. normal cycles (<24 days) (OR=1.3[1.06-1.6], P=0.01 and OR =1.27[1.01-1.59], P=0.03 respectively), subjectively heavier vs. normal flow (OR=1.38[1.17-1.63], P=0.0001 and OR=1.94[1.59-2.36], P<0.0001) and prolonged duration (>8 days) (OR= 1.65[1.08-2.54], P=0.02 and OR=2.26[1.46-3.51], P=0.0003) when compared with no COVID (n =9423). COVID-19 vaccination alone was not associated with AUB. Secondly, women with Long COVID (n =10), regular menstrual cycles (24-38 days) and no exogenous hormone use provided peripheral blood samples +/- endometrial biopsies during the proliferative, secretory and menstrual phases. Control samples were collected before December 2020, matched for age and parity. Comparing serum from those with Long COVID and controls, there were no significant differences in estradiol, progesterone or testosterone across the cycle measured by ELISA/Immunoassay and LC-MS/MS. In endometrial tissue from those with Long COVID vs controls, *PGR, PGR-B, ESR1* and *AR* measured by qRT-PCR were not significantly different. COVID 19 and Long COVID were associated with increased reports of AUB. Long COVID did not significantly affect ovarian sex hormone levels in those with regular cycles and AUB in may result from localised endometrial dysfunction.

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OP3.3

Characterisation of a novel N terminally FLAG-tagged FSHR knock in mouse model to understand the physiological roles of FSHR oligomerisation

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The G protein-coupled receptor (GPCR), follicle stimulating hormone receptor (FSHR) plays a critical role in ovarian function and reproduction, with multiple functions in follicle growth, maturation, survival, and steroid hormone production. Yet how FSH/FSHR mediates these pleiotrophic physiological roles remains unknown. Numerous studies indicate GPCRs can regulate and diversify their actions through receptor-receptor association and the formation of dimers/oligomers. Moreover, our recent data in heterologous cell lines expressing FSHR suggests that differences in signal amplitude may in part be mediated by modulating FSHR homomerisation. However, the physiological significance of FSHR oligomerisation in coordinating ovarian functions remains unknown. This study therefore aimed to characterise a novel N-terminally FLAG-tagged knock-in FSHR mouse model, to understand the physiological roles of FSHR oligomerisation in modulating ovarian functions. Phenotypic characterisation of FLAG-FSHR mice revealed that ovarian and uterine weights were comparable to wild type (WT), suggesting FSH-mediated oestrogenic actions were maintained in the FLAG-knock in mice. Histological analysis of ovaries showed the presence of follicles at all stages of development and corpora lutea in WT and FLAG-FSHR mice, indicating intact follicle development and ovulation. Breeding studies confirmed the fertility of FLAG-FSHR mice, showing comparable litter sizes and interbreeding intervals to WT animals. As these data suggested that the insertion of the FLAG tag did not affect FSHR-ovarian functions, analysis of FSHR homomerisation in granulosa cells was conducted. Super-resolution imaging via PD-PALM revealed ~40% of FSHR were basally associated, with ligand-dependent differences observed in the number and subtype of FSHR monomer, dimer and oligomer populations. These data support the utilisation of this novel FLAG-FSHR mouse model for monitoring endogenous native FSHR oligomerisation, providing an effective tool to elucidate the role of FSHR complexes in ovarian function.

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OP3.4

Exploring the sexual dimorphic development of human external genitalia

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Hypospadias is among the most common congenital malformations with a mean prevalence of 19.9 per 10,000 live births in Europe. The cause of many cases of hypospadias remains unclear but likely results from a combination of genetic susceptibility and environmental factors. Although rodent studies have provided great insights into external genitalia morphogenesis, extrapolations to the human genitals is challenging given significant anatomic and morphogenetic differences. With this study, we provide novel data on the regulation of sex-specific development of the prenatal human genital tubercle (GT). Total RNA from 83 GTs (9-19 gestational weeks (GW), n = 40 males and 43 females) from human fetuses obtained from normally progressing electively-terminated pregnancies (REC 15/NS/0123) were sequenced (NextSeq 500 Illumina). Following raw reads alignment to the human genome (GRCh38), filtration and normalisation, statistically-significant differentially expressed genes (DEGs) were assessed using EdgeR (FDR<0.05). This was followed by ongoing spatial transcriptomics analysis (GeoMx®) based on transversal sections from sex-analogous GT regions. Combining morphometric data from 136 male and 128 female fetuses, GT weights diverged at around 15 GW, 2 weeks later than divergence in anogenital distance, a morphometric readout of androgens action. Samples segregated according to age and sex, accounting for ~51% and 11% of total variation in gene expression, respectively. More transcript changes were sex-related in 2nd than 1st trimesters (1,242 *vs* 118 DEGs). Males had a larger number of sex-specific DEGs between 1st and 2nd trimesters than females (7,722 *vs* 6,545 DEGs). Gene Ontology enrichment analyses based on age- (9,163 DEGs) and sex- (1,136 DEGs) related DEGs (filtered with logFC>1) showed significant enrichment of biological processes such as "response to corticosteroid", "response to steroid hormone", "extracellular matrix organization" and "epidermis development" (with age only for this last). These data represent early but important steps towards better understanding of sex-dependent human external genitalial development.

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Thyroid

OP4.1

Management of thyroid nodules in patient with phosphatase and tensin homolog gene (PTEN) mutation

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Introduction
Phosphatase and tensin homolog gene (PTEN) gene encodes a lipid phosphatase that plays a central role in cell-cycle processes. PTEN hamartoma tumour syndrome (PHTS), caused by the mutation of the PTEN gene, is a diverse multi-system disorder. PHTS is characterised by the hamartomatous growths, increased risk of breast, thyroid, and renal cancers. In terms of thyroid presentation of PHTS, there is up to 75% risk of multinodular goitre and the lifetime risk for the thyroid cancer is around 1 in 3. Papillary pathology is more common than follicular. Management pathways for the PHTS related thyroid nodules remain unclear.
Methods
We studied 10 patients with PHTS from the Imperial College London Endocrinology Clinic. The PHTS-related thyroid involvement was summarised. We focused on the thyroid nodule presentation, treatment, and surveillance.
Results
Of the recruited 10 patients, half of them were female with average age of 45. 1 patient had hypothyroidism at the time of the diagnosis. 9 patients showed thyroid changes on ultrasound scan (7 benign multinodular goitre, 1 autoimmune thyroiditis and 1 follicular thyroid carcinoma) and 3 of them received fine needle aspiration cytology (FNAC) for U3 nodules on the scan. 5 patients received partial/total thyroidectomy. Patients without thyroidectomy are receiving annual ultrasound surveillance. Other organ involvement included: macrocephaly 5 cases, lipoma 4 cases, colon polyps/adenomas 5 cases, breast nodules 4 cases and renal cysts/tumours 2 cases.
Conclusion
We followed the current guideline of annual thyroid ultrasounds starting at the time of PHTS diagnosis. However, whether these patients should have thyroid FNA is controversial, as follicular lesions can be difficult to distinguish via FNA. A more proactive approach to thyroidectomy may be required, considering the lifetime risk of thyroid cancer in PTHS patients.

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OP4.2

Primary thyroid sarcoma: a case report

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Background
Undifferentiated pleomorphic sarcoma (UPS) of the thyroid is rare. It is often identified in its advanced stage, with distant metastasis, and has poor prognosis. This paper presents one of the less than 30 cases that have been documented ever since it was first identified in 1989. In the Philippines, there is no published report of a primary thyroid sarcoma.
Case Presentation
The author describes a 73-year-old female who presented with a rapidly enlarging neck mass, dysphagia, and weight loss. CT scan revealed a complex enhancing mass in the right thyroid gland measuring 16.5cm x 12.5cm with amorphous calcifications. She underwent tumor debulking, tube gastrostomy, tracheostomy, and radiation therapy. Biopsy revealed a malignant tumor exhibiting high-grade cellular features: storiform pattern and irregular fascicles with variable cellularity. She was discharged well after the initial admission, but succumbed two months after, exhibiting the dismal course and prognosis of this rare thyroid cancer.
Learning Points
There is still no consensus for the management of thyroid sarcoma but surgery plays a central role; this involves thyroidectomy plus excision of involved tissue with or without neck dissection. The recommendation for surgical margins of head and neck sarcomas is to do a complete tumor resection with as wide a margin as is feasible, with the least morbidity possible. Since surgical treatment alone gives poor results, adjuvant radiotherapy and/or chemotherapy is often utilized even if chemotherapy's role for UPS remains unknown. The few existing studies on the advantages of chemotherapy detect no differences in overall survival.
Conclusion
Primary thyroid sarcoma is a rare malignancy that shares similar features with anaplastic thyroid cancer. The mainstay of treatment is surgery, radiotherapy, and clinical management of the malignancy's complications; a multi-disciplinary team composed of surgical specialists and clinicians is crucial for the improved survival of these patients.

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OP4.3

Prevalence, predictors and rhythm outcome of Atrial fibrillation (AF) in patients with Graves hyperthyroidism

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Background
Graves disease is an autonomous condition characterised by interaction of the TSH receptor with autoantibody(TRAb). It is well recognised that atrial fibrillation (AF) is a consequence of hyperthyroidism but the prevalence, predictors and outcomes of AF in patients with Graves hyperthyroidism is not completely known.
Method
We analysed a prospective database of Graves disease patients over a 16 year period from October 2007 till June 2023 with the aim of estimating the prevalence of AF and to analyse factors that predict its development. In addition, we performed statistical analyses to assess if echocardiographic parameters were related to conversion to sinus rhythm.
Results
AF was observed in 48 (6.4%) patients out of 749 new patients with hyperthyroidism due to Graves disease. The independent predictor of AF were older age (OR 1.21), higher FT4 levels (OR 1.03), male sex (OR 1.58) and current smokers (OR 2.86). Poor Left ventricular function and higher atrial diameter on echocardiography were significant predictors of persistent or permanent AF.
Discussion
The results above showed that almost 1 in 16 people with hyperthyroidism presents with AF. This analysis has identified patients at higher risk of developing and remaining in AF. A close interaction between endocrinologists and cardiologists is needed to improve the management of these patients.

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OP4.4

Incidental thyroid nodules on CT Angiography in patients presenting with acute stroke: incidence and clinical outcomes from a regional stroke centre

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Background
CT Angiography (CTA) is a frequently used modality of imaging for assessment and diagnosis of patients presenting with acute stroke. There is a paucity of data on management guidelines for the presence of incidental thyroid nodules found on CT Angiography in patients presenting with acute stroke.
Methods
A retrospective analysis was conducted on 2092 patients presenting with acute stroke, identified through the Sentinel Stroke National Audit Programme (SSNAP) audit from January 2019 through to December 2021.
Results
From the cohort, 1046 patients admitted with acute stroke subsequently had a CTA performed. Of these, 79 patients had incidental thyroid nodules noted, corresponding to a prevalence of 7.5%. Around half of these patients, 37 underwent formal thyroid ultrasonography (US). Thyroid nodule size ranged from 2mm to 8 cm, 18/79 (22%) were bilateral. Further US results revealed that one patient (2.7%) had no discernible nodules, twenty two (59.5%) labelled as U2, 12 (32.4%) as U3, two (5.4%) as U4 and none as U5. For the remaining 42 patients not receiving US, 28 patients had no reason documented for not perusing further investigations, 8 patients were deceased in the short period following acute stroke.

Five (6.3%) patients had thyroid surgery, based on subsequent FNA cytology: 1 had follicular variant of papillary thyroid carcinoma, 2 with follicular thyroid carcinoma, 1 papillary thyroid carcinoma, 1 benign histology.
Conclusions
In this study, incidental thyroid nodules were identified in 7.5 % of post-stroke patients undergoing CTA. The risk of malignancy was small at 6%. The presence of incidentally noted thyroid nodules on CTA in the work up of stroke has to be balanced in the context of an acutely unwell patient and the appropriateness of further investigations. We are establishing a pathway locally to guide stroke physicians as to guide onward appropriate referral to specialist care.

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Adrenal and Cardiovascular

OP5.1

Nocturnal metyrapone administration for cortisol suppression in macs: tolerability and impact on metabolic outcomes

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Background
Mild autonomous cortisol secretion (MACS) in patients with adrenal incidentalomas has been associated with elevated cortisol levels during the nocturnal period resulting in a disturbed cortisol rhythm. We hypothesised that administration of nocturnal metyrapone, an 11-beta-hydroxylase inhibitor, previously shown to restore cortisol rhythm in MACS patients, could reduce metabolic complications in this patient group.
Methods
In this controlled, retrospective, longitudinal study we evaluated the tolerability and metabolic effects of nocturnal metyrapone administration in MACS. The study included all patients ($n = 15$) who were initiated on metyrapone treatment, 250mg-500mg at 6pm and 250mg at 10pm, for MACS at a tertiary endocrinology centre between 2015 and 2022. Age and sex-matched controls were selected from patients with adrenal incidentalomas and non-suppressed overnight dexamethasone suppression tests (ONDST). Metabolic risk factors, including mean arterial blood pressure (MAP), HbA1c, non-HDL cholesterol, and weight, were assessed at baseline and after 1 year.
Results
Metyrapone was well tolerated by 82% of patients, with no occurrences of adrenal crises. Among the metyrapone-treated group ($n = 6$), MAP decreased from 106 mmHg to 92 mmHg after 1 year, demonstrating a statistically significant difference in improvement compared to the control group ($P = 0.041$). There were 4 patients on metyrapone in whom MAP improved by greater than 10mmHg as opposed to only one control patient.
Conclusion
Our findings highlight the potential of metyrapone in controlling metabolic risk factors associated with MACS, as evidenced by the decrease in MAP compared to the control group. This study, albeit small, provides data to power a larger controlled clinical trial for further investigation into the broader metabolic outcomes of metyrapone administration in MACS. Importantly, the well-tolerated nature of metyrapone and the absence of significant events such as adrenal crises support its clinical utility.

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OP5.2

Sex differences in the hypothalamus-pituitary-adrenal axis during stress

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Background
The hypothalamus-pituitary-adrenal axis (HPA) controls the neuroendocrine response to psychological and physiological stress. The balance of the hormones synthesised and secreted by these organs is tightly regulated. However, there are intrinsic differences in the relative expression of these hormones depending on sex, which can influence the magnitude of the endocrine response to stressors or the response to pharmacological treatments. Herein, we performed a study investigating the stress response, including HPA genes of interest to identify novel pathways differentially regulated in male and female mice, which can be affected during stress.
Methods
mRNA was extracted from the hypothalamus, pituitary and adrenal gland of 30-week-old male and female C56Bl/6J mice for qPCR analyses. Plasma corticosterone concentration was measured using an ELISA kit at baseline and after exposure to stressors, including overnight fasting (16h), exercise to exhaustion and the administration of synthetic ACTH[1-24] (tetracosactrin, Synacthen®).
Results
mRNA studies identified pathways that are differentially regulated between male and female mice, including steroidogenesis, the melanocortin system, gonadotropin-releasing hormone pathway, growth, energy balance and blood pressure regulation. Plasma corticosterone levels increased in both males and females after overnight food withdrawal, exercise and ACTH[1-24] stimulation. However, these responses were larger in female animals.
Conclusion
Herein we identify sex-dependent HPA dimorphism to stress including differential mRNA expression in male compared to female mice as well as enhanced corticosterone responses in females. These findings reinforce the necessity to conduct research studies on both sexes and awareness of stressors applied to ensure consistency of data as well as efficacy and safety of newly developed drugs.

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OP5.3

Adrenal insufficiency can be associated with biallelic mutations in porphyria genes

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Adrenal insufficiency (AI) is life-threatening and can present alone or in combination with other co-morbidities. Acute porphyria attacks can also be serious, resulting in permanent disability or death and symptoms can be similar to AI. Previous literature describing hormonal perturbations in porphyria suggest an association between the two conditions. We were referred a family with 4 individuals with porphyria and AI, the clinical picture included global developmental delay, convulsions, nystagmus, darkening of the skin, high ACTH and low cortisol. Whole exome sequencing, array Comparative Genomic Hybridization and whole genome sequencing ruled out variants in known AI-causing genes, leaving a homozygous mutation, p.Glu339Lys, in PPOX as a possible cause for both conditions. To investigate the mechanism, we created PPOX-knockdown (KD), human adrenocortical cells (H295R). Proliferation was lower in PPOX-KD cells at 72 hours and mitochondrial respiration was diminished, possibly due to toxicity of porphyrin precursors. GSH/GSSG ratio, a marker of oxidative stress, was lower in KD cells suggesting increased ROS in these cells. CYP11A1 expression was unaltered whereas STAR and CYP17A1 were significantly lower in PPOX-KD cells. Finally, and definitively, knockdown of $>60\%$ reduced cortisol output by 2.2-fold ($P < 0.01$) at baseline and 1.9-fold ($P < 0.0001$) in forskolin stimulated cells. A further 6 families with AI and mutations in CPOX ($n = 3$) and HMBS ($n = 3$), genes causing porphyrias, have been identified. Unexpectedly, the heterozygous parents are asymptomatic, manifesting neither porphyria nor AI, suggesting that the level of enzyme function is key for both phenotypes. Reduced PPOX activity may cause AI through a reduction in the level or activity of steroidogenic CYP450 enzymes, toxicity of intermediate porphyrins and/or the increased oxidative stress these may cause. The above cases demonstrate an association between AI and biallelic mutations in porphyria genes, we therefore suggest that adrenal function should be monitored in all individuals with porphyria.

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OP5.4

Adrenal responses with peak and cumulative hyperthermia from marathon running

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Aims
Exertional hyperthermia stimulates the hypothalamic-pituitary adrenal axis, increasing the availability of free cortisol in body fluids and opening a window onto physical stress for novel biosensing technologies. This study aimed to determine the impact of prolonged endurance exercise on relationships described for shorter activity bouts, by characterising interactions between salivary indices of glucocorticoid activity, serum total cortisol response and thermal strain.
Methods
Core body temperature (Tc) was measured 5 min^{-1} in 32 recreational runners completing Brighton Marathon 2022 (4 female, 28 male). Peak Tc (Tcpeak) was determined and cumulative hyperthermia calculated as the area under the temperature-time curve for Tc > 38 °C (AUCTc38). Saliva and blood were sampled at rested baseline and within 30 min of finishing, for later analysis by commercial radioimmunoassay and in-house LCMS/MS.
Results
Runners finished the marathon in 240 ± 41 min, attaining Tcpeak 39.3 ± 0.45 °C. There was significant ($P < 0.05$) elevation in serum cortisol (397 ± 137 vs 1109 ± 278 nmol.L^{-1}) and salivary cortisol (12.3 ± 10.9 nmol.L^{-1} vs 52.0 ± 39.2 nmol.L^{-1}), cortisone (15.5 ± 11.0 vs 64.7 ± 39.3 nmol.L^{-1}) and 11-dehydrocorticosterone. Salivary analytes mutually correlated to a high degree ($r > 0.75$, baseline and post-marathon), whereas serum cortisol correlated less robustly at baseline and showed weakening linear associations with salivary analytes post-run: only the relationship to salivary cortisol remained significant ($r = 0.57$). At higher thermal strain, changes in the ratio of salivary cortisol:cortisone, but not serum cortisol, varied positively with Tcpeak and AUCTc38 ($r > 0.45$).
Conclusions
Prolonged exercise disrupted close relationships between serum and salivary cortisol and Tc response, which are otherwise preserved in studies of shorter exercise duration and lower cumulative thermal stress. Increasing tissue temperature may skew the balance of salivary glucocorticoids towards cortisol, with production appearing to exceed inactivation. This could potentially confound attempts to monitor physical performance with biosensors according to the site and fluid sampled.

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Bone and Calcium

OP6.1

Sclerostin but not Dickkopf-related protein 1 predicts bone mass and markers of bone turnover in older adults

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Sclerostin (SOST) and Dickkopf-related protein 1 (DKK1) are antagonists of Wnt signalling, inhibiting osteoblast activity and indirectly stimulating osteoclast activity. SOST and DKK1 antibody therapy leads to increases in bone mass and bone formation. However, reported associations between plasma SOST and DKK1 concentrations and measures of bone mass and turnover are conflicting. This study in healthy older men and women ($n = 379$; median 74.1 [IQR 71.5-77.0]y) investigated associations between plasma SOST and DKK1 and (a) BMD and BMC at the hip and femoral neck, (b) markers of bone turnover and Wnt signalling (C-terminal telopeptide (CTX), Procollagen 1 N-terminal Propeptide (P1NP), bone alkaline phosphatase (BAP), osteoprotegerin and soluble receptor activator of nuclear factor-K-B ligand (OPG, sRANKL) and (c) hormonal regulators (parathyroid hormone (PTH), 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), 25 hydroxy vitamin D (25(OH)D), intact and c-terminal Fibroblast Growth Factor 23 (iFGF23, cFGF23) and KLOTHO. Associations were analysed by univariate (model 1) and multivariate linear regression with adjustment for height, weight and age (model 2) or renal function (CKD-EPI eGFR; model 3). Plasma SOST was positively associated with BMD and BMC at both sites (all $P < 0.001$) and negatively with CTX, P1NP and BAP (all $P < 0.01$). Associations with DKK1, OPG and RANKL were non-significant. SOST was negatively associated with $1,25(OH)_2D$ ($P = 0.002$) and positively with cFGF23 and iFGF23 ($P < 0.001$ and 0.025). Associations with PTH, 25(OH)D and KLOTHO were non-significant. Model 2 provided similar results. Adjustment for eGFR attenuated associations with $1,25(OH)_2D$ ($P = 0.06$) and iFGF23 ($P = 0.07$). Plasma DKK1 was negatively associated only with cFGF23 in univariate and multivariate models. In conclusion, plasma SOST but not DKK1 was positively associated with bone mass and negatively with markers of bone formation and resorption, suggestive of lower rate of bone turnover. This was independent of body size and renal function.

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OP6.2

Measuring FGF23 in patients treated with burosumab

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Burosumab has become available as a treatment for children with X-linked hypophosphatemia (XLH) and is a recombinant fully human IgG1 against FGF23. By binding to the active FGF23, burosumab inhibits its effect and symptoms (growth retardation, rickets, enthesiopathy, low phosphate) may improve, however, not in all children. Concomitantly paediatricians are keen to measure FGF23, in treated children, to avoid overtreatment with burosumab, associated with potential calcification risk. Samples from treated patients were sent for c-terminal FGF23 analysis as part of the clinical request. On suspicion of an assay interference, the clinician/patients authorised the analysis of the samples further. Control samples were provided fully anonymised as leftover material from the clinical laboratory. FGF23 was measured using cFGF23 (Immutopics, detecting both intact and c-terminal fragment) and iFGF23 (DiaSorin) immunoassays. Antibodies used for western-blot were anti-human IgG-Fc and anti-human cFGF23 (186-206). Serial dilution demonstrated a positive interference of burosumab in the cFGF23 assay and a negative interference in the iFGF23 assay. We immunoprecipitated burosumab using magnetic beads. IgG and iFGF23 were present in the precipitated fraction but only iFGF23 was detectable in the supernatant. In neither compartment was cFGF23 detected. Supernatants were submitted to FGF23 total assay and elevated concentrations were observed (RR: < 100RU/mL). Only iFGF23 was detected by western-blot suggesting that either there is no free cFGF23 or the technique is not sensitive enough to detect the circulating cFGF23 fragments. The presence of sufficient circulating intact FGF23 and absence of cFGF23 in treated patients could explain the persistence of some symptoms of XLH. In future, we may be able to correlate outcome with circulating concentrations of free iFGF23. The changes in efficacy of Burosumab in older children and adolescents may partly reflect a requirement for an increased dose of burosumab to fully capture iFGF23.

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OP6.3

A case of hypophosphatasia presenting during pregnancy

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A 28 year old female was referred to endocrinology after routine bloods during first trimester of pregnancy demonstrated a low alkaline phosphatase (ALP) of 14U/l (range 30-130U/l). Calcium, phosphate and vitamin D were normal. There is no past medical history, no fragility fractures, no dental concerns and height was normal (157.5cm). Her only family history was her mother lost her teeth prematurely. Biochemical testing showed a raised copper level of 26.0µmol/l (range 11-25µmol/l) which may be pregnancy related. PLP (pyridoxal 5′-phosphate) was raised at 423.65nmol/l (range 20-140nmol/l) and PLP:PA ratio significantly raised at 15.13. Genetic analysis confirmed hypophosphatasia (HPP) with a heterozygous pathogenic mutation in ALPL gene variant c.382G > A p.(Val128Met). HPP is a rare genetic disorder characterised by defective mineralisation of bones and teeth due to ALP deficiency. The ALPL gene encodes the tissue non-specific isoenzyme of ALP (TNSALP) and gene mutations reduces activity of ALP. This leads to extracellular accumulation of PLP which further reduces skeletal mineralisation. The features are highly variable in their expression and range from a perinatal lethal form, to presenting in child or adulthood. It can cause fragility fractures, joint pain and dental issues known as odontohypophosphatasia. Management includes genetic counselling, analgesia

and enzyme replacement therapy with asfotase alfa (Strensiq). This replaces the missing enzyme and promotes bone mineralisation. It is not widely available and is reserved for those with severe disease, or who develop HPP at a younger age. Strensiq has been shown to reduce the PLP:PA ratio and improve functional outcomes. In summary, this is an unusual case of HPP presenting in the first trimester of pregnancy in an asymptomatic individual but who may be at risk of developing odontohypophosphatasia in the future. This patient had an uncomplicated pregnancy and delivered a healthy baby who does not have HPP.

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OP6.4

HDR syndrome (hypoparathyroidism, deafness and renal dysplasia) Unveiled: A rare cause of profound hypocalcaemia and seizure

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Background
HDR syndrome also known by the eponym Barakat syndrome, is a rare, autosomal dominant disorder characterized by the triad of hypoparathyroidism, sensorineural hearing loss, and renal abnormalities. It is caused due to mutation (haploinsufficiency) in GATA3 gene on chromosome 10p with a wide spectrum of phenotypic variations.
Case presentation
A 33-year-old lady presented to emergency department with an episode of tonic-clonic seizure and a one-week history of paraesthesia-tingling and numbness over face and upper limbs. Her past medical history was notable for sensorineural deafness since childhood. She had a family history of first-degree relatives with congenital deafness and one sibling with renal dysfunction. She had no head and neck surgeries in the past. Laboratory investigations revealed severe hypocalcaemia (adjusted calcium-1.36 mmol/l) along with mild hypomagnesemia, hyperphosphataemia with low vitamin D levels and inappropriately low PTH (1.2 pmol/l). Renal function tests were normal, but CT abdomen revealed a severely contracted left kidney with focal scarring. She was administered intravenous calcium gluconate for correction and then treated with oral calcium with alfacalcidol. The patient was then followed up after four weeks in the clinic where she reported paraesthesia. There was a reduction in calcium level (1.94 mmol/l) requiring further up-titration of calcium and alfacalcidol. A genetic testing was done which showed that she was heterozygous for a pathogenic GATA3 variant. Her performance status improved significantly after correcting calcium levels. The first-degree relatives of the patient were then referred for cascade genetic testing for HDR syndrome.
Conclusion
This case underscores the significance of recognizing diverse clinical expressions in adults with rare genetic disorders with variable penetrance and highlights the necessity of thorough evaluations and interdisciplinary consideration. To better comprehend the varied phenotypic spectrum of HDR Syndrome, further research is essential to refine clinical management and improve patient outcomes.

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RET and Endocrine Cancer

OP7.1

Investigating the functional kinome in Multiple Endocrine Neoplasia Type 2

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Introduction
The age of onset and severity of thyroid disease in MEN2 kindreds can be variable, resulting in wide intrafamilial heterogeneity, despite the same oncogenic driver *RET* pathogenic variant being present. Our study sought to investigate the RET kinomic landscape in MEN2 to discover new biomarkers and to provide further mechanistic insights into malignant disease progression, focussing on paediatric cases.
Methods
Peripheral blood and thyroid tissue samples were obtained from 23 children and 10 adults diagnosed with different germline *RET* pathogenic variants (cysteine rich region C609Y, C620G, C634G/R/S, intracellular pathogenic variants V804M, S891A and M918T) and healthy controls. Matching thyroid tissue was obtained from pre-emptive risk-reducing thyroidectomies in children with MEN2A and adult and paediatric patients undergoing primary surgery for medullary thyroid cancer. Kinetics of tyrosine, serine and threonine phosphorylation in protein lysates from peripheral blood mononuclear cells and thyroid cells were analysed using Pamgene technology (PamStation 12).
Results
Functional large scale kinome and integrated analyses revealed differentially active kinases between healthy controls, MEN2A and MEN2B patients. Using network analysis, protein-protein interaction databases and cumulative functionality predictors we generated a range of biomarkers, which imply multi-kinase alterations in a genotype specific manner leading to different disease outcomes. We further validated these markers in primary paediatric patient thyroid tissue excised before frank cancerous transformation. Direct RET kinase activity was comparable between mutation types, but downstream specificity and subsequent kinase activity segregated by mutation type. Interestingly, cysteine rich mutants were more similar to M918T than V804M or S891A, suggesting that genotype-phenotype linkage may be due to substrate specificity rather than standalone RET kinase activity.
Conclusion
Together our data demonstrates that, as a kinase hub, pathogenic variants in *RET* lead to diverse outcomes in primary patients, providing rationale for targeting RET protein to prevent malignant transformation or disease progression in MEN2A and MEN2B.

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OP7.2

Peptide receptor radiotherapy (prrt) for well- differentiated metastatic paraganglioma and phaeochromocytomas (ppgl)

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Introduction
Pheochromocytoma and Paraganglioma (PPGL) are neuroendocrine tumours arising from chromaffin cells in the adrenal medulla or ganglia in the autonomic nervous system. ~40% of PPGL arise due to germline mutation (commonly SDHx) and sporadic tumours frequently have causative somatic mutations. 15-20% of PPGL behave in a malignant manner. ~95% PPGL express somastostatin receptors and are GaDOTATATE avid. Lutathera® is a commercially available PRRT. There is little known about the effectiveness of PRRT in PPGL. This report summarises our experience with PRRT in malignant PPGL.
Methods
Using electronic patient records, radiological, biochemical and clinical behaviour of metastatic PPGLs treated with PRRT (typically 4 cycles, 7.4GBq 177-Lutetium Dotatate) was documented.
Patient characteristics and key findings
Twelve patients were treated for metastatic PPGL, 9 of whom had a known tumour syndrome, 8 of which were SDH- mutation-related. 66% were secretory. Commonest sites of metastases were bone and lung. Mean duration of follow up after PRRT was 18 months. Five patients demonstrated stability at a range of 6 to 50 months, one of whom demonstrated features of regression at 6 months. Three patients progressed at 3 months and were referred for alternative treatment. Two have not yet undergone post-treatment surveillance imaging. One patient had grade 1 CTCAE criteria for toxicity after third cycle due to marrow suppression,

with full recovery at twelve-months (1). There was no indication of renal impairment.
Limitations
This was a small series without a control group.
Conclusion
PRRT is well tolerated therapy. In this cohort of patients, with a mean of 18.8 months of surveillance, 42% showed stability. As clinical experience increases, NETTER-P will hopefully inform practice in terms of where PRRT is best placed in the malignant PPGL treatment algorithm (2).
1 CTCAE v5.0 US Department of Health and Human Services, Nov 2017.
2 NETTER-P Study ongoing-NCT04711135.

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OP7.3

Penetrance of MEN2A-causing RET mutations in clinically unselected population is very low – important implications for clinical practice

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Background
MEN2A-causing RET variants are considered highly penetrant, and early prophylactic thyroidectomy is recommended to prevent the development of Medullary thyroid cancer (MTC). However, existing risk estimates may be exaggerated due to their reliance on clinically selected patients, leading to unnecessary surgeries. To address this, we conducted a comprehensive study of 450,000 clinically unselected individuals to evaluate the risk of MTC with pathogenic RET variants.
Methods
We analysed whole exome sequencing and deep phenotype data on 450,000 people from clinically unselected UK biobank cohort. We defined variant pathogenic if it is previously reported in *MEN2A* cases and fulfilled the American college of medical genetics criteria. To identify MTC cases, we utilised self-reported, cancer registry, general practice, and hospital records data. We use two definitions of MTC: definitive (medullary histology) and potential (thyroid cancer, thyroid surgery or thyroid replacement).
Results
Our analysis identified 193 carriers (age range 56-86) with 18 distinct pathogenic RET variants. Of these, 7 were high/moderate-risk variants according to the American Thyroid Association (ATA) guideline, and 11 were low risk variants. The risk of definitive MTC was found to be extremely low at 1.6% (3/193, 95% CI 0.3-4.5). The risk remained similarly low at 6.7% (13/193, 95% CI 3.6–11.2) for much broader potential MTC definition. The penetrance of potential MTC for carriers with high/moderate risk variants was slightly higher but still low at 16.0% (4/25 95% CI 4.5-36.1). V894M variant was the most common with 111 carriers and had very low risk of definitive MTC (0.95%).
Conclusion
This largest study to date involving clinically unselected individuals, challenges the current understanding of MTC penetrance associated with *MEN2A*-causing RET mutations. Our findings strongly advocate for a reconsideration of the prevailing approach of early prophylactic thyroidectomy when these pathogenic variants are incidentally detected before the onset of MTC.

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OP7.4

Primary ovarian failure after 131I-metaiodobenzylguanide (MIBG) therapy

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131I-metaiodobenzylguanide (MIBG) therapy, initially introduced in the 1980s, has emerged as a first-line to treatment of malignant phaeochromocytomas. Its other notable use has been in treating neuroblastomas occurring in childhood serving as an adjuvant prior to surgery or chemotherapy. An observed known late consequence of MIBG therapy is Primary ovarian failure (POI), characterised by menstrual irregularities over a period of 4 months associated with high Follicular stimulating hormone (FSH$>$40 iu/l.) In our study, we conducted a comprehensive review of MIBG therapy within our radionucleotide database, spanning from 2008. Through stringent gender (female) and age ($<$40) criteria, we identified a subset of 56 patients, ultimately narrowing down to a cohort of 5 patients. Our investigation revealed that 3 out of 5 developed POI consequent to mIBG therapy between 2013 and 2022. The clinical indication was for managing metastatic phaeochromocytoma and paragangliomas. Average age was 35 years. The administered activity of I-131 mIBG during each cycle ranged between 6484-10256 Mbq. Remarkably, 1 patient underwent a single cycle of mIBG, while 1 patient received 2 cycles and another 3 cycles. The onset of oligomenorrhoea, was detected around 4 months following first therapy dose. Subsequent diagnosis of POI was made around 6 months post-treatment. FSH levels at diagnosis were available for 2 patients, measuring 100 IU/l and 85 IU/l. respectively. In conclusion, despite the limited scale of our study, we identified a significant incidence of POI following MIBG therapy. POI is a devastating complication to women of child bearing age. At present patients are not consented about this prior to treatment and such patients are not routinely offered fertility preservation. As renal excretion of the radioisotope is in the bladder, we postulate that introducing intervention, like urinary catheterisation, may mitigate the risk but further research is warranted in this area.

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Late Breaking Abstracts Respectively

OP8.1

Real-world experience with 11C-methionine PET co-registered with MRI in the management of acromegaly – Insights from a single reference centre 12 year observation

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Background
11C-methionine positron emission tomography (Met-PET) is a potentially important imaging adjunct in the diagnostic workup of pituitary adenomas, including somatotroph tumours. Met-PET can identify residual or occult disease and make definitive therapies accessible for a subgroup of patients who would otherwise require lifelong medical therapy. However, data on its use is still limited to small case series. Here, we report the currently largest single centre experience (n = 61) in acromegaly.
Methods
189 cases of acromegaly were referred to our national Met-PET service in the last decade. We have reviewed outcomes in the 61 patients managed exclusively by our multidisciplinary team (single centre, single surgeon). The patients were referred for the following indications: Occult de novo tumour (n =3, 4.9%), occult residual (n =14, 23.0%), indeterminate MRI (n =38, 62.3%) and (radio-) surgical planning (n =6, 9.8%).
Results
33/61 patients (54.1%) underwent PET-guided surgery. 24/33 patients (72.7%) achieved complete biochemical remission following (re-)surgery. IGF-1 levels were reduced to $<$2xULN (upper limit of normal) in 6 of the remaining 9 cases, 3 of whom achieved levels of $<$1.1xULN compared to mean pre-operative levels of 2.4xULN (SD 0.8) for n =9. In 4 patients with persistent or suspected residual disease, repeat PET was performed and led to further surgery in two cases, while the other two were referred for fractionated radiotherapy. Of the operated patients, only 3 developed single new hormonal deficits (gonadotropic insufficiency). There were no cases of neurovascular complications post-surgery.
Conclusion
In patients with persistent/recurrent acromegaly or occult tumours, Met-PET can potentially facilitate further targeted intervention (surgery/radiosurgery). This led to complete remission in the majority of cases (24/33) or significant improvement with comparatively low risk of complications. Met-PET should therefore be

considered in all patients who are potential candidates for further (radio-)surgical intervention, but present no clear target on MRI.

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OP8.2

Subcutaneous Levothyroxine as an alternative long-term treatment for refractory hypothyroidism: A case report

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Background
Refractory hypothyroidism poses a clinical dilemma, with great difficulty to treat. Novel cases have targeted intramuscular (IM) levothyroxine (LT4) as a potential treatment for cases resistant to oral LT4. We discuss a patient who became intolerant of IM LT4 after 18 years of treatment, thus SC LT4 was initiated as alternative management.
Case Presentation
35-year-old female with diagnosed Schmidt's Syndrome and refractory hypothyroidism, was developing worsening side effects associated with IM LT4. She was initially diagnosed with hypothyroidism at 13-years-old, and remained hypothyroid despite escalating doses of oral LT4. Patient compliance was ensured, and common causes of resistant hypothyroidism excluded. Nasogastric investigation confirmed thyroxine malabsorption. She finally achieved euthyroid status at age of 18 with titrating regime of fortnightly IM LT4. This was maintained for 18 years. Unfortunately, scar tissue developed around injection sites, resulting in increased pain and difficulty of continued IM administration. An alternative management was thus sought. SC LT4 injections were trialled with success, and she has remained euthyroid on SC LT4 1200 micrograms every 12 days, for the last six years with minimal side effects.
Discussion
First-line treatment for hypothyroidism is oral LT4. Most patients require 1.6-1.8 microgram/kg dose to maintain euthyroid state. However, many cases in the literature note resistance to oral treatment ie. 'refractory hypothyroidism'. The most reported treatment for refractory hypothyroidism is IM LT4, however IV LT4 is also recognised. Very few cases note the success of subcutaneous thyroxine to treat refractory hypothyroidism, and only one discusses its efficacy and safety over multiple (two) years. Our case highlights the benefit of SC LT4 injections over longer duration, which include ease of self-administration, safety, efficacy and reduced pain after chronic intramuscular injection use.
Conclusion
We wish to highlight SC LT4 as a safe, effective and alternative chronic treatment for refractory hypothyroidism.

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OP8.3

Unsuspected autonomous adrenal cortisol excess and primary aldosteronism accurately diagnosed by NP59 scanning after discordant adrenal vein sampling

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Introduction
Adrenal vein sampling (AVS) is considered gold-standard for diagnosis of unilateral primary aldosteronism (PA), and necessary pre-surgery. Imaging-AVS discordance may occur in up to 30-40% of PA-AVS series, and presents a diagnostic dilemma which may preclude surgery. Lateralization by AVS is defined as the ratio of aldosterone concentrations normalized by cortisol from each adrenal vein, and is thus sensitive to any pathologic asymmetry in cortisol production. Unsuspected primary adrenal cortisol excess may explain cases of imaging-AVS discordance. Dynamic nuclear adrenal imaging could solve AVS-imaging discordance.
Methods
Retrospective study from the Calgary-AVS database, 2017-2023. Included patients had 1) biochemical and clinical presentation of PA with adrenal mass, 2) technically successful AVS with lateralization results discordant to cross-sectional imaging, and 3) dexamethasone-suppressed NP59-iodocholesterol adrenal scintigraphy. Concordance between cross-sectional imaging, AVS, and NP59 lateralization data was examined, as well as PASO-related outcomes for patients who ultimately underwent surgery.
Results
The database yielded 25 cases meeting the inclusion criteria. Despite discordant lateralization on AVS, functional lateralization with NP59 scanning was concordant with CT imaging in 80% of cases (20/25). 13 cases subsequently underwent surgical adrenalectomy (guided by CT-NP59 results) – in 62% of cases (8/13) the diagnosis after pathology and final biochemical and clinical outcomes was cortisol producing adenoma in bilateral (persistent) primary aldosteronism, while the final diagnosis in the remaining 38% of cases (5/13) was cortisol/aldosterone co-secreting adenoma with complete biochemical response. All cases had pre-operative low/suppressed ACTH with rise post adrenalectomy.
Conclusions
In cases of hypertension with adrenal mass and hyperaldosteronism, subtle cortisol excess may not be clinically recognized or meet biochemical thresholds of cortisol excess, yet may jeopardize the reliability of AVS, leading to treatment inertia, or inappropriate contralateral adrenalectomy. Functional nuclear imaging can be used to solve apparent discordance between adrenal anatomical abnormalities and unexpected AVS lateralization results.

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OP8.4

Fixing black holes in traditional clinical training: 360o virtual reality emergency simulations

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National training surveys demonstrate that medical trainees feel under-prepared for practice and under-prepared for managing emergencies, such as diabetic ketoacidosis (DKA). It is challenging for traditional clinical training to guarantee first-hand exposure to all medical emergencies as they occur at random and often out-of-hours, resulting in only minority of students witnessing many emergencies first-hand. It is unfeasible for most universities to provide in-person simulation across all medical emergencies, through timetabling and logistical pressures, as well as the recurring costs of facilitator and actors. Simulation suites, such as those used in aviation, are impracticably expensive. This gap in ward-based training demands an alternative, realistic and scalable form of simulation. Virtual reality (VR) combined with 360o filming provides an immersive simulation experience, which is interactive and realistic. Through our 360o VR scenarios, we re-created real life emergency scenarios across medical emergencies, including DKA. These simulation scenarios make students feel as though they are 'really there' and use branching pathways to empower student to make decisions which determine patient outcomes- something that could never happen in real life. Our scenarios have been integrated into the MBBS curriculum and delivered to over 700 Year 5 and Year 6 undergraduate students who experience these scenarios within VR headsets, can interact through time-pressured questions, and gain individualised feedback within the headsets. The sessions are delivered within simulation style de-briefs, combining individual and group activities. Unlike traditional in-person simulation, we deliver these scenarios to 60 students in 1 hour sessions and all students actively partake in their own emergency simulation. Feedback has been overwhelmingly positive with students objectively and subjectively enjoying and feeling engaged with the sessions. We found that 92% of students enjoyed the sessions, 93% felt engaged, 97.5% felt it met their learning requirements, feeling significantly more confident in identifying and managing the conditions presented.

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Featured Clinical Case Posters

CC1

Primary unilateral macronodular adrenal hyperplasia (pumah) with concomitant glucocorticoid and androgen excess due to kdm1a activation and constitute mc2r activation

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Clinical vignette: We investigated a 33-year-old woman diagnosed during pregnancy with a 7cm unilateral adrenal mass associated with severe ACTH-independent glucocorticoid and androgen excess, a steroid phenotype usually indicative of adrenocortical carcinoma. Pregnancy had been achieved with in-vitro fertilisation on the assumption of underlying PCOS. Neonatal death occurred soon after emergency delivery due to foetal growth arrest at 26 weeks gestation. Histopathology after post-pregnancy unilateral adrenalectomy showed tumour-like macronodular adrenocortical hyperplasia. Postoperatively, the clinical and biochemical phenotype resolved. The contralateral adrenal had normal size and morphology. The patient spontaneously conceived three months later and delivered a healthy baby. Workup: Germline mutations in ARMC5 were excluded. We performed whole-exome sequencing on four representative hyperplastic cortical nodules. We detected germline variants p.G46S and p.R269Dfs*7 in KDM1A and p.M255I in the gene encoding for the ACTH receptor (MC2R). Copy number variation analysis showed clonally related nodules and demonstrated an additional somatic loss of the KDM1A wild-type allele on chromosome 1p36.12 in all nodules. RNA-sequencing on a representative nodule showed low/absent expression of KDM1A and a high expression of the gene GIPR compared to 52 adenomas and 4 normal adrenals, suggesting a similar pathogenic mechanism as recently described in primary bilateral macronodular adrenal hyperplasia associated with food-dependant Cushing Syndrome. Functional in vitro analysis of the MC2R variant demonstrated constitutive activation of receptor activity. Sanger sequencing confirmed germline KDMIA p.R269Dfs*7 variant in the father and both KDM1A p.G46S and MC2R p.M255I variants in the mother. Clinical assessment of the parents showed no features of glucocorticoid or androgen excess.
Conclusion
We present the first case of primary unilateral macronodular adrenocortical hyperplasia (PUMAH) associated with Cushing's syndrome and concomitant androgen excess and suggest pathogenic mechanisms involving KDM1A and MC2R.

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CC2

Late presentation of complete androgen insensitivity syndrome: a case report

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We report a late presentation of complete androgen insensitivity syndrome (AIS) in a phenotypic female. The patient presented with primary amenorrhoea at age 37, after ten years of heterosexual marriage. She experienced monthly pelvic pain and breast tenderness but no menstrual bleeding. Her family history was significant for primary amenorrhoea in two of her three sisters. Physical examination revealed Tanner 2 breast development, reduced axillary and pubic hair, and normal external female genitalia. Her Testosterone was raised (38 nmol/l, 0.5-1.9 for females) with high LH (17 IU/l, 1.8-11.8). The rest of her synacthen test for cortisol and 17 OH progesterone and anterior pituitary hormones were within the reference ranges. Pelvic ultrasound revealed a shallow blind-ended vagina of 3 cm and an absence of uterus and ovaries. MRI scan confirmed the absence of intraabdominal uterus and ovaries and revealed gonadal structures at the external orifices of the inguinal canal. She had osteopenia at the spine, femoral neck, and hip on bone densitometry. Genetic testing confirmed 46 XY karyotypes. Fluorescence sequence analysis of the patient's DNA found her to be hemizygous for an in-frame deletion (c.2077_2079delAAC) in exon 4 of the Androgen Receptor gene, resulting in abnormal Androgen Receptor protein, confirming complete AIS. The patient was offered gonadectomy with long-term hormone replacement treatment but chose regular ultrasound surveillance. Bone health was addressed by vitamin D supplementation, as her level of total vitamin D was undetectable. Genetic counselling has been provided to the couple. The case demonstrated the challenges in diagnosing and managing AIS in phenotypic females presenting many years after puberty.

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CC3

"A case of metastatic insulinoma: a real challenge to manage"

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Background
Insulinomas are the commonest functional neuroendocrine tumours (NETs) but metastatic insulinomas are rare (incidence $<2\%$) and their management can be challenging. We report a case of metastatic insulinoma requiring multiple treatment modalities to achieve biochemical control.
Case presentation
A 77 year old healthy female was admitted with severe spontaneous hypoglycaemia (glucose 1.8mmol/l) due to endogenous hyperinsulinism [insulin 530pmol/l (range 12-50pmol/l); C-peptide 0.58nmol/l (range 0.34-1.8nmol/l)]. Subsequent investigations revealed a well-differentiated grade 2 pancreatic insulinoma (Ki67-12%) with multiple bulky liver metastases. She responded well to diazoxide, but within 3 months her severe hypoglycaemia recurred. Dexamethasone and subcutaneous octreotide were unhelpful. An interval scan showed significant disease progression, therefore NET MDT recommended Lutetium-177 peptide-receptor-radionuclide-therapy (PRRT). Following the first dose, she had hypoglycaemic seizures, requiring two weeks on ITU for continuous 50% dextrose, glucagon infusions and nasogastric feeding. We used Pasireotide as a bridging therapy to step her down from ITU. Pasireotide was stopped after a month and she remained hypoglycaemia-free and completed 4 cycles of PRRT. After PRRT, there was an excellent radiological response. Unfortunately, within 3 months, she had biochemical relapse with severe hypoglycaemia. A trial of low dose Everolimus failed due to neutropenic sepsis. Reintroduction of Pasireotide was not helpful. She remained an inpatient for over 2 months, requiring dextrose and glucagon infusions and continuous PEG feeding. Bland embolisation was ineffective due to her liver disease burden. Following further MDT discussion, we used Theraspheres SIRT (Boston Scientific) (selective internal radiation therapy). Within a week, her hypoglycaemic episodes improved, her infusions were then stopped and she was subsequently discharged from hospital. Her PEG feeds are being weaned and she is in biochemical remission.
Conclusion
The management of metastatic insulinoma is very challenging. Multiple treatment modalities are often required in parallel. PRRT and SIRT both have a role in achieving biochemical control.

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CC4

A rare cause of hypercalcemia, unmasked by over-the-counter vitamin D supplementation

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Background
Mutation in the CYP24A1 gene can have variable phenotypes including infantile hypercalcemia and adult-onset hypercalcemia, hypercalciuria, nephrocalcinosis, or nephrolithiasis. CYP24A1 gene mutation is a rare but important cause of PTH-independent hypercalcemia.

Case presentation
We describe a case of a 67-year-old gentleman who presented with lethargy, fatigue and weight loss. He was found to have PTH-independent hypercalcemia with acute renal impairment. His biochemistry was as follows: adjusted calcium of 3.13 mmol/l (Reference Range (RR) 2.20-2.60)), PTH 0.7 pmol/l, phosphate 1.32 mmol/l, Vitamin D 134 nmol/l and creatinine 249 umol/l. His past medical history included Type 1 diabetes. At the time, he was taking over-the-counter vitamin D3 spray (up to 36,000 units/weekly), which he started during the Covid pandemic. He was initially managed with intravenous fluids and advised to stay off any vitamin D supplementation and keep well hydrated upon discharge. He was extensively investigated but no malignancy was identified. During the follow-up, his calcium level normalised and his renal function improved. His PTH-related peptide level was reassuringly undetectable but 1,25(OH)2D3 level was inappropriately high at 158 nmol/l (RR 55-139). A 24-hour urine calcium output was raised at 13.3 mmol/day (NR 2.5-7.5). Genetic analysis for a possible CYP24A1 mutation was requested but no mutation was identified. As our level of suspicion remained high, we went on to measure the level of 24,25 dihydroxy vitamin D. A raised 1,25:24,25 dihydroxy vitamin D ratio of 64 was found in keeping with 24- hydroxylase deficiency.
Discussion
The COVID era saw the zealous use of vitamin D supplements which can potentially unmask CYP24A1 mutations with milder phenotypes. The use of a 1, 25:24, 25 dihydroxy vitamin D ratio can be a useful diagnostic tool in patients suspected of CYP24A1 mutations, with negative genetics.

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CC5

A case of an ACTH-secreting phaeochromocytoma: Biochemical response to metyrapone suggests the presence of a glucocorticoid-driven positive feedback loop

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Phaeochromocytoma-driven Ectopic ACTH Syndrome (EAS) is rare. We report the case of a 31-year-old female, who presented with abdominal pain and vomiting. She had clinical features of severe Cushing's syndrome (proximal myopathy, bruising, refractory hypertension and acute confusion). Admission investigations revealed hypokalaemia (2.1mmol/l [3.5-5.5mmol/l]) and a 4.5cm left adrenal lesion with a 'bulky' right adrenal on CT abdomen. She was diagnosed with hypertension (requiring 4 antihypertensives) 11 months prior, during the third trimester of pregnancy (remained refractory post-delivery without screening for secondary causes). Further investigations included non-suppression of cortisol on overnight (2649 nmol/l) and low-dose dexamethasone suppression tests (2231 nmol/l), ACTH 472 ng/l (0-46ng/l), plasma metanephrines 1.55nmol/l (<0.51nmol/l) and normetanephrines 16.9nmol/l (<1.18nmol/l). There was no pituitary lesion on cross-sectional imaging. An FDG PET/CT revealed increased uptake in both adrenals without uptake elsewhere, leading to a diagnosis of phaeochromocytoma-induced EAS. There was intense avidity of the left adrenal lesion on Ga68-DOTATATE PET/CT. Metyrapone and phenoxybenzamine were commenced and uptitrated in anticipation of urgent adrenal surgery, for which she remained an inpatient. She progressed well with resolution of confusion, normokalaemia and normotension (using less antihypertensives [5 to 2 agents]). Her ACTH showed stepwise (weekly) reductions in response to cortisol normalisation due to metyrapone treatment (472,338,188,136,113,85,29 ng/l). There were also reductions in plasma metanephrines (0.82nmol/l), normetanephrines (11.26nmol/l) and tumour size (4.5 to 3.5cm on MRI scan). The patient underwent an uncomplicated left adrenalectomy with subsequent normalisation of clinical and biochemical parameters. Histology confirmed a phaeochromocytoma (no atypical features) however ACTH staining is pending. There are important observations to derive, including that young patients with hypertension should be screened for secondary causes. The metyrapone-associated pre-operative effects were possibly mediated through the attenuation of a glucocorticoid-driven positive feedback loop on the ACTH-secreting phaeochromocytoma.

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CC6

Cyclical Cushing's Syndrome Causing Hypokalaemia in A Marathon Runner

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Cyclic Cushing's syndrome (CCS) is a rare condition that involves recurring episodes of hypercortisolaemia, alternating with normocortisolemia at intervals ranging from a few days to several years. To diagnose CCS, it is necessary to demonstrate three cortisol peaks and two troughs. CCS is mostly seen in females and can be Adrenocorticotropic hormone (ACTH)-dependent or independent2. The common causes of CCS are Cushing's Disease (55%), ectopic ACTH syndrome (26%), and adrenal tumours (11%). Around 18% of functioning adrenal incidentalomas exhibit cyclic autonomous cortisol production. We present a case of a 51-year-old marathon runner referred for evaluation of hypokalaemia (2.3 nmol/l) and bradycardia (38 beats/minute) associated with abdominal bloating, knee swelling, polyuria, lethargy, and weight loss of 2-3 kg in 1 week. The first episode was reported in July 2021, followed by further episodes in April 2022, and September 2022 each lasting for 1 week and he resumed marathon running after each episode. He was symptom-free on initial assessment without any clinical features to suggest Cushing syndrome. His potassium, and cortisol were normal with mildly elevated prolactin(420mU/l). Overnight Dexamethasone Suppression Test (ONDST), aldosterone renin ratio, and 24-hour urinary cortisol levels done while symptomatic, showed potassium 2.7 nmol/l, random cortisol level of 1728nmol/l, 24-hour urine cortisol (237 nmol/d), ACTH (453 ng/l) and post ONDST cortisol (361 nmol/l) suggesting ACTH-dependent Cushing's Syndrome. MRI pituitary confirmed pituitary macroadenoma abutting the chiasm. He awaits transsphenoidal resection of pituitary macroadenoma with potassium supplements and thromboprophylaxis coverage for increased VTE risk associated with Cushing's Syndrome. This case report highlights that though most patients present with typical clinical features, a minority of CCS patients present without clinical signs initially. Due to a lack of persistent high cortisol levels and variable clinical presentation, CCS is particularly challenging to diagnose.

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CC7

Use of osilodrostat alongside 11C-Methionine PET CT in pituitary-dependent Cushing's disease may improve radiological detection and lead to better outcomes

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Introduction
Pituitary – dependent Cushing's disease accounts for approximately 80% of endogenous Cushing's syndrome but a target lesion is only detectable on MRI in 60% of cases. 11C-methionine PET CT improves detection of indeterminate pituitary lesions. Osilodrostat is a novel steroidogenesis inhibitor which reduces cortisol levels with resultant rise in ACTH and may further enhance the sensitivity of 11C-methionine PET CT in difficult cases.
Case presentation
A 42 year-old woman presented with central weight gain, hypertension and proximal myopathy. Initial investigations were consistent with ACTH-dependent Cushing's disease including raised morning cortisol (599 nmol/l) and failure to suppress following 1mg dexamethasone (219 nmol/l), with raised 24 hr urinary free cortisol (1907 nmol/l), midnight salivary free cortisol (26.2 nmol/l) and elevated ACTH (55.3 ng/l). Inferior petrosal sinus sampling (IPSS) showed central:peripheral ratio > 2.0 thus excluding ectopic ACTH. MRI pituitary did not demonstrate a clear surgical target and medical management was commenced with metyrapone, which was switched to osilodrostat due to inability to optimise cortisol levels and poor tolerability. Serum and free cortisol levels normalised by week five of osilodrostat (12mg/day). ACTH increased on osilodrostat and after 11 weeks of treatment, 11C-Methionine PET CT was performed (ACTH 135 ng/l, cortisol 145 nmol/l). A methionine-avid lesion was identified in the posterior-lateral pituitary and trans-sphenoidal resection was performed. This achieved biochemical cure with serum and free cortisol levels in the normal range and return of diurnal variation on cortisol day curves post-operatively.
Discussion
This case illustrates the diagnostic and management challenges in pituitary - dependent Cushing's disease without a clear lesion on initial imaging. Adjunctive use of 11C-methionine PET CT can enhance imaging sensitivity for indeterminate lesions and additional ACTH stimulation through downregulation of the steroidogenesis pathway by osilodrostat may further improve detection.

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CC8

Hungry Bone Syndrome: a state of deficit

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A 51 year old female presented with an Adjusted Calcium (Adj Cal) of 1.68mmol/l (Ref: 2.20-2.60 mmol/l), raised PTH 24.2 pmol/l (1.6-6.9 pmol/l) and raised Alkaline phosphatase (ALP). She had a background of type 2 intestinal failure secondary to surgical complications resulting in stoma formation. She reported peri-oral tingling, joint stiffness, cramps and generalised pain over several months which left her requiring the use of a wheelchair for mobilisation. There was proximal myopathy, QT prolongation and Chvostek's sign was elicited on examination. She was managed with bolus and infusion intravenous 10% calcium gluconate therapy. Blood results showed undetectable Vitamin D for the prior 2 years. Her Adj Cal levels showed a steady decline for the past year with nadir levels on this admission. 300,000 units of intramuscular Vitamin D was administered to bypass gut absorption. along with daily oral calcium (sandocal) and 1-OH vitamin D (alfacalcidol) supplementation. During her admission the patient required daily infusions of 100ml 10% calcium gluconate to keep her adjusted calcium levels >1.9 mmol/l. A spot urine calcium performed excluded pathological loses at the kidney and a DEXA scan showed evidence of osteomalacia with a T score of -3.1 at the femoral neck. A diagnosis of hungry bone syndrome secondary to prolonged Vitamin D deficiency was made. She was discharged on daily calcium infusions and 3 monthly 25-OH vitamin D injections after a 2 month inpatient stay. Management will be guided by her Adj Ca and ALP with repeat DEXA scanning. The patient's symptoms improved, improving her quality of life and suitability for stoma reversal surgery. We present this case to highlight the consequences of prolonged, severe hypovitaminosis D, the reversibility of the condition and the management of a "hungry bone" case in the absence of preceding parathyroid surgery.

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CC9

Spontaneous recurrent non-insulin dependent hypoglycaemia associated with malignant phyllodes tumour of the breast: a rare case report

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We present the case of 78-year-old female admitted to our hospital in January 2023 with recurrent hypoglycaemic episodes during fasting periods, particularly overnight and early morning. The patient had impaired hypoglycaemia awareness and cognitive decline. The only past medical history was of hypertension treated with bendroflumethiazide and amlodipine. During hospital stay, she experienced multiple hypoglycaemic episodes. Biochemical investigations revealed non-insulin-dependent hypoglycaemia, as evidenced by suppressed serum insulin ($<$ 7 pmol/l) and C peptide ($<$ 50 pmol/l) at a laboratory glucose of 2.6 mmol/l. IGF-1 levels were marginally low at 4.1 nmol/l (4.4 – 21.8 nmol/l), IGF-2 levels at the upper limit of normal at 28 nmol/l (upper range 28.4 nmol/l) and the IGF-1:IGF-2 ratio was 6.9 (normal <10). Other biochemical parameters were normal. Clinical examination revealed a large mass in the right breast, confirmed on central core biopsy as a malignant phyllodes tumour with extensive stromal overgrowth in the form of undifferentiated spindle cell sarcoma. Staging imaging did not reveal metastasis. Despite high-dose dexamethasone (8 mg/day) and diazoxide (50 mg twice a day), the patient continued to experience hypoglycaemia. Subsequently, she underwent a right mastectomy, leading to complete tumour removal with discontinuation of dexamethasone and diazoxide post-operatively. Flash glucose monitoring (Free Style Libre 2) was used following surgery, revealing no evidence of hypoglycaemia following tumour resection. This case report presents a rare instance of spontaneous recurrent non-insulin dependent hypoglycaemia linked to a malignant phyllodes tumour in the breast. The key clinical lesson is that the combined use of dexamethasone, diazoxide, and flash glucose monitoring enabled safe domiciliary management. However, complete resolution of troublesome hypoglycaemia required surgical resection of the tumour. The exact mechanisms underlying hypoglycaemia in such cases are not fully understood. While IGF-2 secreting sarcomas have been reported, our patient exhibited normal IGF-2 levels

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CC10

Graves' thyrotoxicosis presenting with coexistent Familial Dysalbuminaemic Hyperthyroxinemia- challenges and pitfalls of discrepant thyroid function tests

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Familial Dysalbuminaemic Hyperthyroxinaemia (FDH) is characterised by mutant albumin with increased affinity for thyroxine, and to a lesser extent triiodothyronine, giving falsely elevated fT4 and fT3 levels in standard assays. This may lead to inappropriate management of euthyroid patients, and complicate diagnosis and management of thyroid disease in patients with coexistent FDH. We report a case of Graves' thyrotoxicosis complicated by underlying FDH. A 41-year-old woman presented with a history of symptomatic hyperthyroidism. Clinical examination showed tremor, tachycardia, diffuse goitre, and signs of thyroid eye disease. Biochemistry confirmed hyperthyroidism (TSH $<$ 0.01, free T4 80.9, free T3 30.8) due to Graves thyrotoxicosis (TRAb antibody level 22.2). Neck Ultrasound showed a diffusely enlarged heterogenous and hypervascular thyroid gland. The patient underwent total thyroidectomy as definitive treatment after initial biochemical control was achieved with thionamide treatment. Thyroid function on replacement dose Levothyroxine 125 mg daily, showed discrepant results with a high T4(26.6 pmol/l) with non-suppressed TSH(0.72 mU/l). Assay interference was excluded. FDH was suspected and genetic analysis a showed heterozygosity for the c.725G$>$A p (Arg 242 His) pathogenic variant in the ALB gene, confirming FDH. While FDH may have contributed to the magnitude of elevation of the initial T4 and T3 on presentation, the diagnosis of Graves' disease was secure given symptomatic hyperthyroidism, suppressed TSH, elevated TRAb and clinical symptoms and signs of thyroid eye disease. This case highlights difficulties in assessing thyroid status in patients with autoimmune thyroid disease and coexisting FDH, which may potentially result in inappropriate therapy. A high index of suspicion of underlying FDH as a cause for discordant thyroid function tests remains the cornerstone of diagnosis with TSH levels being the most reliable biochemical marker of thyroid status in patients with coexistent autoimmune thyroid disease.

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Poster Presentations

Adrenal and Cardiovascular

P1

Urinary steroid profiling by ultra-high-performance liquid-chromatography tandem mass spectrometry: Method Validation and comparison to GC-MS

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Gas chromatography mass spectrometry (GC-MS) is the gold standard for urinary steroid profiling. Our established GC-MS method quantifies mineralocorticoids, glucocorticoids, and androgens. GC-MS assays require chemical derivatisation and long run times, rendering them unsuitable for high-throughput analysis. Our aim was to develop and validate a high-throughput urinary steroid profiling method using ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-LC-MS/MS). Chromatography and mass spectrometry parameters were optimised for 29 urinary steroids. Steroids were extracted from 200 μL of urine after the isotopically labelled internal standards were added. Samples underwent hydrolysis to remove sulfate and glucuronide conjugates. Unconjugated steroids were extracted using a C18 96-well plate solid-phase extraction cartridge. Steroid separation was achieved using a Waters HSS T3 column (1.8 μm 1.2 x 50 mm) with a water and methanol (0.1 % formic acid) gradient maintained at a 0.6 ml/min flow rate, on a Waters Acquity UPLC system coupled to a Waters TQ-XS mass spectrometer. The method was validated, determining the linear calibration range, assay imprecision, accuracy, reproducibility, recovery, and matrix effects. Furthermore, quantification was compared to GC-MS. Steroids were quantified across the large concentration ranges observed in the urine metabolome (0.5-3000 ng/ml). Lower limits of quantification ranged from 0.5 to 10 ng/ml. Accuracy, measured as percentage bias was $< \pm 15\%$, and imprecision, measured as percentage variance was $< 15\%$ for all steroids measured at three concentrations (30, 200, and 700 ng/ml). Mean recovery was 89% (range 61-131%) with acceptable matrix effects. The total run time was 22 minutes. A comparison of GC-MS and UPLC-MS/MS revealed similar quantitation for all steroids. We have developed a powerful tool for the comprehensive profiling of 29 urinary steroids using UPLC-MS/MS. Compared to the GC-MS method, this assay reduced sample preparation and run time whilst maintaining the resolution, allowing for greater sample throughput.

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P2

Comparison of aldosterone measurements during saline suppression tests by immunoassay and liquid chromatography tandem mass spectrometry methods

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Background
Primary aldosteronism is an increasingly recognised cause of hypertension, caused by excess aldosterone secretion. Screening and confirmatory tests such as saline suppression tests (SST) require accurate measurements of aldosterone and use of appropriate cut-offs. Many laboratories have chosen liquid chromatography tandem mass spectrometry (LC-MSMS) methods as issues of poor specificity have been reported for immunoassay methods. During the validation of a LC-MSMS method at Glasgow Royal Infirmary (GRI), comparison with the existing IDS-iSYS immunoassay showed a 35% negative bias, requiring re-evaluation of the aldosterone renin ratio and SST cut-offs.
Method
Paired specimens from SST ($n=55$) referred to GRI for aldosterone were analysed by immunoassay (IDS-iSYS) and LC-MSMS methods. Samples with baseline $Aldo_{LC\text{-}MSMS} > 210$ pmol/l (equivalent to $Aldo_{IA}$ 300 pmol/l) were excluded. Clinical information was obtained for all patients. Interpretation of SST varies between centres but several studies quote an immunoassay aldosterone ($Aldo_{IA}$) of < 190 pmol/l as an appropriate response. From sample comparison $Aldo_{IA} = 190$ pmol/l equates to $Aldo_{LC\text{-}MSMS} = 120$ pmol/l.
Results
Concordant results were recorded for 37/42 patients and 5/42 were discrepant. Two patients had potential false positives by IA resulting in unnecessary investigations. Three patients were potentially false negatives by IA, all of which required alterations to their medical management. One of these patients also had a false negative $Aldo_{IA}$ baseline result. An additional patient not included as the baseline $Aldo_{LC\text{-}MSMS} = 174$ pmol/l, underwent unnecessary adrenal vein sampling due to possible false positive IA results, pre and post SST.
Conclusion
This data highlights the variability in performance of the immunoassay method compared to the LC-MSMS method. Unfortunately definitive outcomes were not available for the patients in this cohort but potential false positive and false negative results were reported. False positive confirmatory tests put the patient at risk of unnecessary invasive procedures such as adrenal vein sampling.

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P3

Assessing the Impact of Residual Adrenal Function on the prevalence of adrenal crises and intercurrent infections

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Objective
Determinants of why only a subset of patients with adrenal insufficiency (AI) experience recurrent adrenal crises (AC) and intercurrent illnesses are not well understood. This study aimed to identify whether residual adrenal function (RAF), defined by the peak response to a provocative test undertaken before commencing glucocorticoids, may help explain differences in prevalence.
Design and Methods
Patients with AI who previously were enrolled in the European Adrenal Insufficiency Registry (EU-AIR) were invited to participate in this parallel study (RAF study). The EU-AIR was a prospective observational study, collecting data on glucocorticoid dosage, episodes of intercurrent illness and AC in patients with AI irrespective of aetiology. Peak cortisol level to stimulation was collected from the hospitals electronic records.
Results
The cohort comprised 203 patients, of whom 114 had documented peak cortisol measurement on stimulation. This sub-cohort were of mean age 53.8+/-15.6, 71M/43F, 9 PAI and 105 SAI. Mean follow-up was 5.5+/-2.4 years. Over this period there were 457 intercurrent illnesses and 131 SAEs. Only four episodes of AC in two patients were recorded during the study period. Comparison of patients with peak cortisol of ≤ 200 nmol/l ($n=52$) or > 200 nmol/l ($n=62$) showed no statistical difference for mean number of intercurrent illnesses ($P=0.16$) or SAE per year ($P=0.79$). Using the lower cut-off value of 125 nmol/l, patients with peak cortisol of ≤ 125 (32 patients) or > 125 (82 patients) on stimulation showed no statistical difference for mean number of intercurrent illnesses ($P=0.90$) or mean number of SAE per year ($P=0.43$).
Conclusion
In this prospective study we found no evidence to support the degree of RAF in patients with AI to be a determinant of the rate of occurrence of intercurrent illnesses or SAEs. Why a subset of patients experience repeated intercurrent infections and adrenal crises, but others do not remains elusive.

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P4

Implementation and impact of perioperative guidelines and the steroid emergency card for the management of adrenal insufficiency and prevention of adrenal crisis

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Background
Peri-operative guidelines (POG) published early 2020, were followed by the NHS National Patient Safety Alert (NatPSA) and launch of the NHS Steroid Emergency Card (SEC) in Aug 2020. The NatPSA was sent to all NHS health and care providers. This survey was undertaken to assess the implementation and impact of both.
Methods
A pilot survey was undertaken at Endocrine Nurse Update 2022 and amended survey emailed to the SfE membership. 106 participants responded to the first question with 84 completing the remaining questions. Respondents were a mix of Doctors and Nurses from the UK.

Key Outcomes
59% of responders agreed the POG had made it easier to give advice on steroid management vs 9% who disagreed. IV infusion of Hydrocortisone is used in perioperative care but less than IV/IM bolus. 61.5% of local guidelines incorporated the POG guidelines, 16.9% "did not know" and 21.7% reported "No" to incorporation into local guidelines. 53% of respondents reported local Trust strategies to implement the NatPSA alert however 33.7% of respondents were not aware of the local NatPSA strategy. Confidence that patients received the SEC was high: >70% in primary and secondary adrenal insufficiency, vs 58% in tertiary. 41.7% confirmed their Trust had an alert system to identify inpatients on glucocorticoid treatment. 11.9% did not know.
Conclusion
Findings of this survey suggest the POG have been helpful in clinical practice. Whist there has been good uptake of the NatPSA in some organisations, this survey demonstrates a need for Trust's to improve processes in order to ensure safe practice for patients with adrenal insufficiency is implemented. Communication of NatPSA needs to improve, alongside organisations communication and compliance of the NatPSA. As endocrine clinicians we should be leading this work in our organisations.

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P5

Salivary Steroid Profile: the simultaneous quantification of androgens, glucocorticoids, and mineralocorticoids in human saliva

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Steroid profiling of biological fluids has been used for clinical and diagnostic research since the 1950s. Most methods focus on blood and urine, however, more recently saliva analysis has been employed as a non-invasive, simple to collect sample for the diagnosis of conditions such as Cushing's and androgen excess. Despite its ease of collection, saliva remains an underutilised biofluid. To investigate the use of salivary steroid profiling for endocrine research, we aimed to develop and validate a liquid chromatography-tandem mass spectrometry method to quantify salivary androgens, glucocorticoids, and mineralocorticoids. Furthermore, we aimed to investigate the correlations between urine, serum, and salivary steroids. Twenty steroids were included in the assay. Calibrants and samples were spiked with isotopically labelled internal standards and extracted via supported liquid extraction (SLE) using methyl-tertbutyl ether. Steroids were separated on a Phenomenex Luna Omega C18 column (1.6 µm, 100 Å, 2.1 x 50 mm), using a methanol and water (0.1% formic acid) linear gradient on an Acquity UPLC chromatography system with post-column infusion of ammonium fluoride. Quantification was performed on a Waters TQ-XS mass spectrometer using electrospray ionisation in positive ion mode. The method was clinically validated. The lower limit of quantification of the assay was $\leq$0.2 ng/ml for all steroids. Assay precision at low, medium, and high (0.2, 0.5, and 1 ng/ml) spiked QCs resulted in a variation of $\leq$20%. Calibrations were linear from 0.02-10 ng/ml with correlation coefficients (R2) of $\geq$0.98. Matrix effects, analyte recovery, reproducibility, and carryover demonstrated acceptable validation outcomes. Ten healthy participants provided matched saliva, serum, and urine to investigate correlations between the biofluids. 10 of the 20 steroids were detectable in saliva from healthy volunteers. In the future, this method will be used to obtain a healthy control reference cohort and investigate endocrine conditions.

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P6

Initial impact of a virtual pathway to evaluate patients with evidence of mild autonomous cortisol secretion

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Background
Adrenal incidentalomas (AI) are common, with approximately 40% of these demonstrating evidence of mild autonomous cortisol secretion (MACS). MACS has been associated with increased morbidity and mortality, and some patients with MACS may benefit from medical therapy or adrenalectomy, so all require further evaluation. Given the large numbers of patients involved, this has potentially significant resource implications for outpatient endocrinology services. To standardise and enhance the evaluation of patients with MACS, we developed a virtual pathway that systematically assesses symptoms, biochemistry, and end-organ impact of patients with MACS.
Methods
Retrospective data collection was conducted on 391 patients with AI and evidence of MACS (cortisol between 50-138 nmol/l on ONDST), before and after the introduction of a virtual 'MACS testing' pathway. Completion of relevant biochemistry (including ACTH and DHEAS), completion of HbA1c screening and DEXA scans conducted in each group were documented.
Results
A total of 391 patients were included (53% female, median age of 69 $\pm$ 10 years (SD)). Mean cortisol on ONDST was 76.5 $\pm$ 20 nmol/l. 53.2% of these were assessed via the virtual MACS pathway, whilst the rest had individualised clinician-led assessment in clinic. Both groups had comparable baseline demographic characteristics. Following implementation of the pathway, there was a significant increase in patients undergoing tests for ACTH (77% increase), DHEAS (76% increase), HbA1c (46% increase), and 24-h urinary cortisol (74% increase). Additionally, the referred group had a 3% higher utilisation of DEXA scans. Most patients following the MACS pathway did not require an endocrinology outpatient appointment.
Conclusions
Within our cohort of patients with AI and MACS, implementation of a systematic virtual pathway resulted in significant increase in completion of key diagnostic investigations. Such a pathway facilitated standardised assessment and virtual review of results, resulting in reductions in the need for clinic appointments for this large cohort of patients.

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P7

Presentation and management of adrenal tumours over time: a real-life experience from a UK tertiary care centre

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Background
Adrenal tumours are found in 3-7% of adults. The European guidelines on management of adrenal incidentalomas (first published in 2016 and recently updated) have standardised the management of these patients, but evidence of guideline impact on clinical care is lacking.
Methods
Retrospective review of the mode of presentation, radiological characteristics and final diagnosis of a large cohort of patients with adrenal tumours referred to a UK tertiary centre between 1998 and 2022.
Results
We included 1398 patients (55.7% women; median age 60 [interquartile range, IQR, 49-70] years; n=407 evaluated before and n=991 after implementing the guidelines). Incidental discovery was the most frequent mode of presentation (63.7%). Overall, 14.6% patients had bilateral tumours and 30.7% had tumours $\geq$4 cm (median 2.9 cm (IQR 1.9-4.7)). Unenhanced CT Hounsfield Units (HU) were available for 763 patients; of these, 32.9% had heterogeneous tumours or HU>20. After standardised work-up, the most common diagnoses were adrenocortical adenoma (ACA, 55.9%), phaeochromocytoma (13.3%), adrenocortical carcinoma (10.6%), and metastases of an extra-adrenal primary cancer (5.7%). Reassuringly, nearly half of the patients (47.5%) referred for indeterminate lesions were eventually diagnosed as having ACAs. At multivariable regression analysis, HU>20 or heterogeneous tumour was most powerful in discriminating malignant from benign lesions (adjusted Odd Ratio, OR, 29.57), followed by discovery during cancer surveillance (OR 10.56), tumour size $\geq$4 cm (OR 6.10) and presence of hormonal or localising symptoms (OR 3.30). Following the publication of the guidelines, the proportion of follow-up visits in patients with non-functioning ACAs decreased from 89.6% to 69.9%, while the proportion of patients discharged from the clinic increased from 4.3 to 25.3% (P<0.05).

Conclusion
We provide an extensive retrospective review of patients referred and worked-up for adrenal tumours. The implementation of the European 2016 guidelines positively impacted clinical practice, reducing the number of unnecessary investigations and surgeries.

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P8

A conundrum of steroid absorption and metabolism in the treatment of diamond blackfan anaemia

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Background
Diamond Blackfan anaemia (DBA) is a condition caused by mutations in ribosomal protein genes. After the first year of life, the mainstay of treatment is corticosteroids whilst red blood cell transfusions are used for patients who do not respond.
Case
We present a case of a 20-year-old woman with a history of DBA (RPS19 mutation), initially treated with courses of prednisolone, who aged 3 developed steroid-induced adrenal insufficiency. Aged 4, hydrocortisone replacement was commenced. At age 19, there was a loss of clinical response of the DBA to increased hydrocortisone doses. Prednisolone 40mg daily failed to induce a clinical response and it was noted that there were no cushingoid features despite a prolonged course. A prednisolone challenge resulted in serum prednisolone level <5 mg/l with non-suppressed ACTH. Urinary steroid profiling showed metabolised prednisolone at 15-40% of the expected levels, suggesting malabsorption. A hydrocortisone absorption curve was normal. A methylprednisolone challenge resulted in ACTH suppression to 4ng/l at 3 h. Treatment with steroids was preferred over a transfusion strategy due to patient preference and finding of severe hepatic iron loading. A course of high dose methylprednisolone (64mg per day) was commenced, resulting in improvement of haemoglobin from 105g/l to 142g/l and reticulocyte count from 46 x109/l to 149 x109/l. The dose has since been weaned to 36mg/20mg on alternate days.
Discussion
This case demonstrates isolated malabsorption of prednisolone but improved absorption and clinical response with methylprednisolone. The mechanism behind this is not clear but there are no previously known methylation defects in DBA. Finding a suitable steroid has prevented transfusion-dependence for now. A future challenge may be the choice between high doses of methylprednisolone or transfusion-dependence if the disease becomes uncontrolled on low doses of methylprednisolone.

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P9

Evidence of mild autonomous cortisol secretion in patients with adrenal incidentaloma is associated with increased cardiometabolic morbidity and relative risk of cardiovascular disease, compared to those with non-functional adrenal incidentalomas

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Background
Mild autonomous cortisol secretion (MACS) is a common finding in patients who have an adrenal incidentaloma (AI). Evidence suggests patients with MACS are at risk of cardiovascular morbidity, but there is not yet a consensus on the management of this cohort. Our study assesses the cardiovascular risk of patients with MACS, compared to patients with non-functioning AIs.
Methods
Data were collected retrospectively between 2019-2022. Inclusion criteria were patients with AI and an overnight dexamethasone suppression test (ONDST) cortisol between 50-138 nmol/l. Patients with AI and ONDST cortisol <50 nmol/l were the comparator group. Cardiovascular co-morbidities and medications were collected. Relative Risk (RR) of cardiovascular disease was calculated using the QRISK3 algorithm. Statistical analysis was conducted using PRISM v9.3.1.
Results
391 patients (47% male), median age 69 ± 10 years (SD) were identified with MACS. 630 patients were included in the non-MACS group (median age 63 ± 12 years, 43% male). 70.8% of MACS had hypertension, vs 51.5% of the non-MACS group ($P<0.0001$). 43.5% of the MACS group were on more than one antihypertensive vs 24.8% ($P<0.0001$). 66.8% of MACS patients were on statin therapy vs 49% ($P<0.0001$ for both). 35% of the MACS group had T2DM vs 20% of the non-MACS group ($P<0.0001$). 25% of MACS patients had IHD vs 9.8% ($P<0.0001$). Mean QRISK3 score was 27 ± 13% in the MACS group, compared with 16 ± 10% in age/sex matched healthy controls ($P<0.0001$). RR for MI/stroke was 2.0 in the MACS group and 1.6 in the non-MACS group ($P=0.0004$).
Conclusions
Within our unselected cohort of patients with MACS, there was higher prevalence of hypertension, T2DM and IHD, and increased RR for MI/stroke, compared with the non-MACS AI group. Our data suggest a need for consideration and optimisation of cardiometabolic morbidity when managing patients with MACS, in line with recent guidelines.

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P10

Iatrogenic Cushing's syndrome and Avascular necrosis of femoral heads following a drug to drug interaction of antiretrovirals and fluticasone inhaler

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Background
Fluticasone is an inhaled steroid commonly used for asthma with low systemic bioavailability (~9%). We present a case of significant Iatrogenic Cushing's syndrome when fluticasone was used simultaneously with antiretroviral therapy.
Case
27-year-old man was diagnosed with HIV in 2021. His antiretroviral therapy was simplified to GENVOYA (elvitegravir/cobicistat/tenofovir/alafenamide/emtricitabine) at the same time as starting a new inhaler for his asthma (Relvar-fluticasone furoate/vilanterol). Two months later, he presented with profound tiredness, weight gain and bilateral hip pain. He was profoundly Cushingoid. Investigation confirmed significant adrenal insufficiency (9am cortisol <22 nmol/l) and his DEXA scan confirmed osteoporosis. MRI showed bilateral avascular necrosis of femoral heads and he is now awaiting bilateral hip replacements. An alternative antiretroviral regime (BIKTARVY -bictegravir/tenofovir alafenamide/emtricitabine) was prescribed. His inhaler was changed to beclomethasone and his hydrocortisone replacement was tailored based on cortisol day curves.
Discussion
Cobicistat is a CYP3A4 inhibitor (a pharmacokinetic 'booster'), given in HIV to increase bioavailability of antiretroviral medications. Fluticasone (a synthetic inhaled glucocorticoid) is metabolised via the CYP3A4 pathway. Co-prescription results in significant increases in the bioavailability of fluticasone and exogenous systemic steroid exposure causing Cushing's syndrome with concomitant adrenal suppression. The degree of Cushing's was unnoticed and caused profound clinical sequalae including destructive bone disease with lifelong consequences. This significant drug-drug reaction was not highlighted on electronic system as antiretroviral medications are prescribed on alternate system.
Conclusion
1. Patients on CYP3A4 inhibitors therapy, including anti-retroviral therapy, should avoid inhaled steroid fluticasone. Beclomethasone, less dependent on CYP3A4 for metabolism, should be the alternative.
2. Any additional medication prescribed for HIV patients should be checked with drug interaction database* or discussed with a specialist HIV pharmacist
3. Patients should be advised to consult their HIV team for any new medication prescribed.
*(https://www.hiv-druginteractions.org/),

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P11

Healthcare professionals' knowledge of adrenal insufficiency: a quantitative and qualitative study

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Objective
We sought to assess the knowledge of adrenal insufficiency among undergraduate healthcare students and pharmacy staff.
Methods
We undertook a cross-sectional UK-wide survey of final year undergraduate student knowledge of AI before and after an online educational intervention. Universities were recruited through the Council of Medical Schools, Council of Pharmacy and Dean of Health Council, whereby surveys were sent out to undergraduates through e-mail. Pre/post intervention data were imported into SPSS for analysis. Qualitative analysis of HCP knowledge was undertaken by semi-structured interviews (2 focus groups, comprising 8 pharmacy staff). Interviews were transcribed and entered into the NVivo system, and analysed using the Theoretical Domains Framework.
Results
The main themes which emerged included concerns on knowledge, memory, attention, decision processes, and environmental context and resources. In total, 9 surveys were returned, 16.7% stating that they confidently recognised the symptoms, increasing to 100% after intervention. Pharmacy staff correctly identified the risk of long-term steroid use in patients, with recognition of sick day rules. Knowledge varied where patients were on multiple steroid medications. All undergraduate respondents indicated the need for additional training before the intervention. Pharmacy staff noted difficulty in remembering what to do in the management of certain patients. Increase from 80% to 100% was noted in knowing where to go for information about AI after the intervention. Responses included pharmacy staff noting that AI is "scary because it's different".
Conclusions
The study highlights areas where targeted intervention may be undertaken to reduce AI-related morbidity and mortality, and demonstrates that an online educational intervention has the potential to improve clinical practice. Our data demonstrate the importance of regular education through in-person teaching and additional e-learning. Clear and concise checklists should be made available for all HCPs. Such a cross-disciplinary approach would encourage consistency in management and reduce errors.

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P12

Service evaluation suggests variation in clinical care provision in adults with congenital adrenal hyperplasia in the UK and Ireland

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Background
The Congenital adrenal Hyperplasia (CAH) Adult Study Executive (CaHASE) identified poor metabolic outcomes and reduced quality of life in CAH. CaHASE2 was recently established to examine the current status of CAH care. We surveyed clinical practice in the UK and Ireland, and awareness and use of the International CAH (I-CAH) Registry.
Methods
We undertook an anonymised online survey targeting clinicians providing care for patients with CAH. Respondents were asked questions relating to biochemical monitoring, glucocorticoid replacement, management of comorbidities and use of the I-CAH Registry.
Results
Among 65 respondents, 42% reported management of patients with CAH within specialist clinics, whilst the majority managed in General Endocrinology clinics. Clinical assessment frequency was similar in both settings, with review every six months in 37% of specialist and of general services. Notable differences were identified regarding treatment and use of biomarkers. Modified-release hydrocortisone and combination glucocorticoid regimens were utilised more frequently in specialist clinics (62% vs 13%; $P=0.001$). Androstenedione was measured in 70% of specialist clinics compared to 55% in general services ($P=0.44$). Renin assessment was greater in specialist than general clinics (81 vs 58%, $P=0.25$). In specialist clinics, reliance on ACTH (30%) and DHEA-S (44%) was high, indicating limited concordance with management guidelines. There was no consensus on optimal timing of monitoring biochemistry, with 57% of respondents not considering recent glucocorticoid dose timing. Semen analysis was offered in 56% of specialist clinics compared to 34% of general services. 26% of respondents in specialist clinics used the I-CAH registry; 34% of those in general clinics were unaware of the registry, compared to 19% in specialist services.
Conclusions
This survey suggests marked heterogeneity in clinical care of CAH. Future initiatives are required to raise awareness of the I-CAH registry, enabling clinical outcome assessment to standardise CAH management.

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P13

Hyponatraemia and falls in the elderly due to hypoaldosteronism

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A third of people over the age of 65 and half of those over 85 fall at least once a year. Aside from the human cost, the cost to the NHS is an estimated £2 billion/year and 4 million bed days (2014 figures). Hyponatraemia in the elderly is associated with falls, fractures, morbidity and mortality. Previous studies have demonstrated decreased activity of renin-angiotensin-aldosterone system with increasing age. More recent studies have suggested dysregulation of aldosterone secretion with advancing age, with high aldosterone levels as a potential cardiovascular disease risk factor. We investigated the status of the renin-angiotensin-aldosterone system in 20 elderly patients (7 males and 13 females) aged 66-92 (mean age 82) referred with hyponatraemia who had also experienced falls. All had supine and standing blood pressure measurement. Only 5 patients were receiving medications recognised to affect renin and aldosterone levels. The results suggested that dysregulated aldosterone secretion in the elderly can result in symptomatic hypoaldosteronism:

	Range (systolic/diastolic)	Mean (systolic/diastolic)
BP supine (mmHg)	70-180/50-90	128/72
BP standing (mmHg)	60-170/50-90	110/68
BP drop (mmHg)	0-40/0-20	18/6
Sodium (mmol/l)	113-131	123

Plasma renin activity ranged between 0.1-8.6 nmol/l/h (mean 1.3) and aldosterone <50-289 pmol/l (mean 107). The postural drop in blood pressure provides a possible explanation of the association of hyponatraemia with falls. The suggestion is supported by the improvement of all abnormalities on treatment with fludrocortisone:

	Range (systolic/diastolic)	Mean (systolic/diastolic)
BP supine (mmHg)	95-180/60-90	133/76
BP standing (mmHg)	95-170/55-90	133/74
BP drop (mmHg)	0-20/0-10	3/3
Sodium (mmol/l)	127-143	136

Our findings suggest an accelerated deterioration in the ability to secrete aldosterone in response to recognised stimuli (dysregulation) in extreme old age, with significant adverse consequences. The therapeutic effect of fludrocortisone provides an effective treatment for this difficult patient group.

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P14

Evaluation of inpatient hyponatremia: if formal recognition (coding) of hyponatremia makes a difference in management and outcomes

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Introduction
Hyponatremia is a common electrolyte disorder in clinical practice. We did a retrospective analysis of 100 patients admitted between Jan 2019 to June 2019

with moderate hyponatremia (Na-125-129 mmol/l) to see if there was a difference in management and outcome of the patients who were formally coded as hyponatremia and those who were not coded as such.

Results

Mean age was 74 years in the coded group ($n=50$) and 79 years in the non-coded group ($n=50$). Male patients were 38% and 22% respectively in coded and non-coded groups. Volume status was assessed in 72% of the patients in both groups. Drug reviews were done in 64% of the patients in the coded group and 40% in the non-coded group. Serum osmolality was measured in 42% of the patients in coded group and 18% in non-coded group. 24% of the patients in the coded group were measured for urine osmolality/urinary sodium and 16% respectively in the non-coded group. Cortisol was measured in 28% of the coded patients whereas in the non-coded group, only 8% of the patients were checked for cortisol. TSH was checked in 46% of the patients in both groups. 8% of patients with hyponatremia in both groups were treated inappropriately. In the coded group, 8 patients died in the hospital (16%). 12 patients died in the hospital (24%) in the non-coded group. 2 patients had inpatient falls in the coded group. In the non-coded group, the percentage of inpatient falls was 10% (5 patients).

Conclusion

Coded diagnosis implies that the diagnosis has been identified on a senior clinician review and documented as such on the post-take ward round or discharge letter. Coding of hyponatremia and hence senior recognition is associated with better medication reviews, more investigations including osmolalities and cortisol measurements and slightly better outcomes.

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P15

Genetic aetiology of primary adrenal insufficiency in Sudan

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Primary adrenal insufficiency (PAI) in children is usually congenital with more than 25 causal genes with overlapping phenotypes. Genetic diagnosis helps to guide management and genetic counselling but can be challenging in resource limited settings. The most common genetic aetiologies for PAI in Sudan are congenital adrenal hyperplasia (CAH; mostly CYP21A2) and Triple A syndrome (AAAS). Here we investigate other genetic aetiologies of PAI in a cohort of 43 Sudanese families ($n=46$; 29M). Inclusion criteria were clinical presentation of PAI paired with biochemical finding of low cortisol and high ACTH, and/or a negative response to synacthen stimulation. Exclusion criteria were clinical and/or genetic diagnosis of CAH or Triple A syndrome. Candidate gene sequencing (CGS) of commonly causative genes in our global cohort (mostly European ancestry), was followed by whole exome sequencing (WES), in mutation negative individuals, using QCI and IGV tools for sequence interpretation. The genetic aetiology was determined in half of the families (23/43), with only 2 mutations discovered by CGS and the rest after WES analysis. Mutations in ABCD1 (7/23), NNT (5/23), AIRE (3/23) and CYP11A1 (3/23) were most common in this population with mutations in HSD3B2, MC2R, NR0B1, STAR and a CYP11B1-B2 fusion event accounting for the others. 3 families had a splicing defect in NNT (p.T731=) and 2 families had a 5-exon deletion in AIRE, possibly representing founder mutations. PAI in Sudan has heterogeneous aetiology with a different spectrum of PAI genes than our global cohort, resulting in fewer solved cases (53% compared to 85%). CGS of founder mutations and region-specific, commonly mutated genes may be a cheaper alternative to WES for developing countries. However, WES and whole genome sequencing are likely to become the standard, with their ability to find single nucleotide variations and deletions respectively, as the cost continues to fall.

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P16

Acute adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia (CAH): Changes during the period 2019-2022 in I-CAH

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Background

In 2019, the International CAH Registry (I-CAH) performed a benchmarking exercise of acute adrenal insufficiency related adverse events including adrenal crises (AC) and sick day episodes (SDE).

Methods
In 2022, I-CAH data on children aged <18 years at first visit with 21-hydroxylase deficiency CAH from 35 centres in 19 countries were analysed to examine the current occurrence of SDE and AC and compared to the data that had been collected up to 2019 when 34 centres had participated in this exercise.
Results
In 2022, a total of 510 children with a median of 10 children (range 1, 58) per centre had 2,461 visits evaluated over a 3-yr period (2019-2022). The median patient age at the time of visits was 8.3yrs (range 0, 20.6). In 2022, of the 2,461 visits in 510 children, a total of 464 SDE were reported in 402 visits (16%) from 207 children (41%). The median SDE per patient per visit in 2019 and 2022 were 1 (0, 4) and 0 (0, 2), respectively. Infectious illness remained the most frequent precipitating event, reported in 69% in 2022 and 72% SDE in 2019. Comparing the 19 centres that participated in both 2019 and 2022, the median SDE per patient year per centre in 2019 and 2022 was 0.4 (0, 6) and 0 (0, 2.5), respectively in 2022 ($P=0.01$). Of these 19 centres, 11 (58%) showed a reduction in SDE per patient year in 2022 compared to 2019, in 3 centres (16%) the SDE rate had increased and in 5 (26%) it remained unchanged.
Conclusions
The current study shows that the rate of reported SDE has fallen in 2022 compared to 2019. There is a need to continue widening participation whilst exploring the underlying factors that have led to a change in the rate of reported SDE.

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P17

Weaning patients off long-term low dose (5mg) prednisolone: A national survey of current endocrine practice

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Background
Prolonged glucocorticoid use is associated with significant morbidity and mortality, including the development of glucocorticoid-induced adrenal insufficiency (GI-AI). There is no consensus regarding glucocorticoid weaning (<5mg prednisolone-equivalent dose) to alleviate withdrawal symptoms while promoting the quickest adrenal axis recovery. There is also limited research into understanding current practice and the barriers to weaning.
Aim
To establish how long-term glucocorticoid weaning is currently managed by UK endocrinologists.
Methods
An anonymous online survey was disseminated to all clinical members of the Society for Endocrinology between 15/05/2023 and 22/06/2023.
Results
163 responded to the survey (66.7% consultants, 14.7% specialty trainees, 11.5% endocrine specialist nurses, 7.1% other). Approaches to managing GI-AI were very heterogeneous. Respondents were asked how they would investigate and manage a patient, with a 9am cortisol of 98 nmol/l, no longer requiring long-term prednisolone for asthma. 54% of respondents opted for a short synacthen test whilst on 5mg prednisolone; 33% would not investigate whilst on this dose but would wean further first; 11% would not investigate further at all. When managing patients, 60.5% opt to switch to hydrocortisone (39.5% continue prednisolone) and 75% favoured weaning slowly. 17.9% continue life-long replacement glucocorticoid without further investigation, the majority favouring replacement hydrocortisone. 62.1% of respondents did not have a local steroid weaning protocol. Over half (53.4%) would not consider discharging the patient from endocrinology follow-up until weaned off prednisolone. Over half of those (52.5%) would follow-up six-monthly. The commonest perceived cause for weaning failure was relapse of the underlying condition (58.2%) while 20.3% felt that glucocorticoid withdrawal symptoms hindered weaning. 16.5% reported that biochemically confirmed adrenal axis suppression on prednisolone led to a clinical decision not to pursue further steroid weaning.
Discussion
There is huge variation in the management of long-term glucocorticoid weaning, with a clear need to develop evidence-based steroid weaning pathways.

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P18

Composite Pheochromocytoma with Adrenocortical Carcinoma - a rare coexistence

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A 65-year-old man presenting with urinary symptoms was incidentally discovered to have an adrenal mass. Abdominal computed tomography (CT) revealed a 9.5x8cm heterogenous solid right adrenal tumor with no evidence of metastatic disease. The initial differential lay between adrenocortical carcinoma (ACC) or a phaeochromocytoma. The elevated plasma fractionated normetanephrine at 14439 pmol/l (0-1180), metanephrine 15202 pmol/l (0-510), 3-MT 415 pmol/l (0-180) led to a presumed preoperative diagnosis of phaeochromocytoma. However, there was evidence of autonomous cortisol secretion with a positive overnight dexamethasone suppression test of 209 nmol/l, a suppressed ACTH and an elevated DHEAS of 14.9umol/l. The lesion demonstrated heterogenous I-123 metaiodobenzylguanidine (MIBG) avidity. Right adrenalectomy via an open right-subcostal approach was opted with a possible capsule breach. Histology demonstrated an 8cm, 222g phaeochromocytoma with a PASS of 11/20 with areas of atypical mitoses, tumour stain positive for synaptophysin and chromogranin-A, S100, melan-A and inhibin, however calretinin was negative. Ten weeks post operatively CT scan demonstrated significant disease recurrence in the tumor bed with a 9.4 x 5.2cm mass encasing the IVC, other vessels and invading a segment of the liver. Plasma metanephrines were normal and the lesions were not MIBG-avid with a significant elevation in DHEAS to > 27umol/l. A CT guided biopsy was consistent with ACC. Histology demonstrated pleomorphic cells with mitotic rate 12/10hpf. Immunohistochemistry was positive for adrenocortical markers and a Ki67 proliferation 80-90%. The appearance was morphologically similar to the previous resected specimen, although presence of medullary neoplasia made this a challenging histological diagnosis. He had negative genetic testing for the MEN1 gene, DP53, AIP MEN1, CDKN1B, RET and CDC73. He was diagnosed as metastatic adrenocortical carcinoma with malignant Cushing's, commenced on mitotane and received six cycles of Cisplatin/Etoposide/Doxorubucin. As serial imaging showed disease progression, Gemcitabine and Capecitabine was initiated with consideration of immunotherapy with Pembrolizumab.

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P19

A case of functioning adrenal tissue post-bilateral adrenalectomy for Hereditary pheochromocytoma-paraganglioma syndrome

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Introduction
Endogenous cortisol secretion should cease after bilateral adrenalectomy (BAL) and steroid hormone replacement is life sustaining at the regular physiologic dosage. However, there are reports of occurrence of functioning adrenal tissue in the setting of BAL treatment for ACTH dependent Cushing's syndrome and not the other known indications for BAL.
Case report
A 44-year-old lady with functioning adrenal tissue after BAL for Hereditary pheochromocytoma-paraganglioma (PGL/PCC) syndrome with germline SDHD mutation. She underwent right adrenalectomy in 1984 and left adrenalectomy 20 years later. She currently has bilateral jugular paraganglioma, right vagal paraganglioma and right carotid body tumor. Her other medical history includes familial X-linked hypophosphatemic vitamin D resistant ricket. She has always been on low dose of maintenance hydrocortisone (HC) 5/2.5/2.5 mg daily and fludrocortisone 25 mg every third day. Her surveillance whole body MRI and Gallium Doctatate scans confirmed paraganglioma but did not demonstrate

residual adrenal tissue or ectopic adrenal. Biochemistry confirmed residual cortical functions as shown below.

Cortisol after 24 h off HC(nmol/l)	169
HCDC in nmol/l on 5/2.5/2.5mg HC	288,528,289,104
SST (baseline,30 min,60 minutes)	185,415,488
ACTH ng/l	6.9
Renin nmol/l (NR 0.5-3.5)	0.6
Aldosterone in pmol/l (NR90-700)	180
DHEAs in umol/l (NR 0.96-6.95)	1.6
plasma normetanephrine pmol/l (NR 120-1180)	398
Plasma metanephrine (NR 80-510)	<100
Plasma 3-methoxytyramine (NR <180)	<180

Conclusion
Although, there are reports of increased catecholamines influencing adrenal steroidogenesis in pheochromocytoma but this is not reported in the absence of adrenal tissue. Cortisol production could be from microscopic adrenal remnant, residual or adrenal rest from an accessory adrenal gland which is yet unidentified in this patient. To our knowledge, this is the first case of functioning adrenal tissues after BAL in the setting of PGL/PCC syndrome and highlights the fact that other factors apart from ACTH could stimulate adrenal tissue formation after BAL.

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P20

Case of non-hodgkin lymphoma presenting as adrenal mass

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70-year-old male patient was referred by GP on account of low blood pressure and falling platelet levels. He reported persistent shortness of breath, lethargy and reduced exercise tolerance alongwith 2 stones weight loss with poor appetite in the last 4 months. He has a background history of corneal transplant and was on immunosuppressant therapy including mycophenolate mofetil which was tapered and then stopped few weeks ago when his GP first noticed the low platelet count. His baseline blood tests on admission showed Platelet 51 (109 a month ago), WBC 9.6, Hb 111, CRP 129, Na 131. Since admission, he had continuous temperature spikes thus blood cultures were sent and started on broad spectrum IV antibiotics for sepsis of unknown source. CT- TAP was done given the history of weight loss and it showed a large lobulated left suprarenal mass, probably a confluent lymph nodal in origin with likely involvement of the left adrenal gland and marked splenomegaly. No lymphadenopathy elsewhere. The main differential was between lymphoproliferative disorder and primary adrenal malignancy. His plasma metanephrines, ACTH, aldosterone: renin ratio, cortisol and dexamethasone suppression test tumor markers, hepatitis and myeloma screen were normal EBV PCR was 1420 IU/ml. Thus, US guided biopsy was done to establish a histological diagnosis which demonstrated CD45 positive non-Hodgkins lymphoma, likely high-grade. Patient was referred to lymphoma MDT, reviewed by hematology team and he is now awaiting his first cycle of chemotherapy. Conclusions This case highlights the importance of histology diagnosis in an atypical presentation of adrenal mass. Biopsy of adrenal mass is rarely taken due to high risks such as adrenal hemorrhage or hypertensive crisis. However, in this patient with a history of acute drop in platelet count and the presence of red flags with normal adrenal work up justified the biopsy.

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P21

Beware progressive unilateral adrenal haemorrhage

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Background
Unilateral adrenal haemorrhage is usually asymptomatic and picked up incidentally on CT imaging. However, adrenal haemorrhage can cause flank pain and when bilateral, adrenal insufficiency or adrenal crisis. Biochemical changes include electrolyte imbalances, low platelet count and anaemia. We report a case of unilateral adrenal haemorrhage with devastating outcome.
Case
A 45-year-old male smoker was incidentally found to have a rapidly growing left adrenal mass, reported as adrenal haemorrhage. Initial CT imaging for respiratory symptoms showed right upper lobe and hilar lymphadenopathy, but subsequent mediastinoscopy and biopsy revealed only reactive changes. At this stage he had normal sized adrenal glands with preserved tri-cornuate architecture. On interval scanning 4 months later, he was first noted to have a heterogeneous, spherical, 3cm enlargement of his left adrenal reported as adrenal haemorrhage, along with resolution of the hilar lymphadenopathy. However, further scanning over the next 8 weeks showed progressive enlargement of a heterogeneously enhancing left adrenal mass from 3cm to 5.5cm then 9cm. An MDT decision for open adrenalectomy was made. At operation, 10 days later, the lesion was 12cm and adherent to the left kidney and posterior peritoneum, with multiple neovascularisations. Histology showed a poorly differentiated oncocytic tumour, Ki-67 index 60% with epithelial staining (AE1-3) but no more specific features. Post-operatively, he continued to lose weight and re-presented 10 days later with right upper quadrant and back pain. Repeat imaging showed metastatic collapse of the L5 vertebral body and multiple liver, right adrenal, bone, skin, and lung metastases. He was commenced on carboplatin and etoposide chemotherapy but died a few weeks later.
Discussion
Around 20% of adrenal haemorrhages are due to adrenal tumours and serial imaging should be performed to ensure that there is not progressive enlargement before the radiological diagnosis can be accepted.

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P22

Pathological fractures: Atypical first symptom of adrenal cushing's in a young female

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Cushing's syndrome can lead to various complications, including pathological fracture. As an initial presenting symptom pathological fracture is not very common in Cushing's syndrome. This abstract aims to present a case study of a female patient with multiple pathological fractures at a young age and subsequently diagnosed with Cushing's syndrome. A 32-year-old female (at the time of referral) after a stress fracture of the right neck of the femur without any trauma history, was treated with DHS(dynamic hip screw) and then referred to the Rheumatology clinic for investigation of secondary causes of fracture. She had normal childhood and puberty with uncomplicated pregnancy four years ago. Her past medical history and medication history were unremarkable. Her clinic blood pressure was high and antihypertensives were initiated. The next year she suffered from another unprovoked right superior pubic rami fracture and that triggered hormone profile investigation with an endocrine referral. Vitamin D level was mildly low and supplemented aggressively. She also had menstruation irregularity and subsequent cessation. The overnight dexamethasone suppression test failed to suppress. MRI pituitary was normal but adrenal MRI showed lipid-poor Right adrenal 3.3cm nodule suggestive of adenoma. DEXA scan showed osteopenia, ACTH was undetectable, high dose dexamethasone test failed to suppress as well,24 hrs urine cortisol came high compatible with adrenal Cushing's. MDT discussion decided on adrenal surgery with initiation of Metyrapone and prophylactic VTE prophylaxis. After this management, she was doing well and started on corticosteroid which was weaned off subsequently when pituitary-adrenal axis partially improved. She is due for genetic testing as her parental aunt was found to be Cushing's as well. This case highlights the importance of recognizing and addressing the skeletal consequences of Cushing's syndrome. Collaborative efforts among endocrinologists, orthopedic surgeons, and other healthcare professionals are vital in managing these complex cases effectively.

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P23

A case of primary adrenal hydatid cyst

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Introduction
Hydatid disease (Cystic echinococcosis) is a zoonotic parasitic infection with the Echinococcus granulosus tapeworm resulting in cyst(s) within viscera. The predominant site for cyst formation is the live, with primary adrenal cyst accounting for less than 0.5% of presentation. We report a case of primary adrenal hydatid disease.

Case Report
A 62 year old female presented to the hospital with history of right upper quadrant pain and recurrent urinary tract infections. She underwent a CT scan of abdomen that demonstrated a large cystic lesion measuring 14.7cm (CC) x12.4cm (AP) x 11.6cm (W) in the right upper quadrant and contains fluid/fat at the anterior aspect with peripheral calcification. Her bloods showed evidence of hypereosinophilia (2.01 x109/l). She had extensive travel history in the past, including the countries endemic with hydatid cyst. Although Echinococcal IgG assay was negative, she was started on an extensive course of Albendazol on the basis of strong clinical suspicion. Given the primary location of the cyst, she had adrenal screening blood tests which were all within normal range. She underwent open exploration which confirmed right adrenal cyst and therefore had right adrenalectomy and pericystectomy. Histology report confirmed fibrous cavity wall compatible with a Hydatid cyst. She recovered well after the surgery. Interestingly her requirement of blood pressure medication decreased since the operation.
Discussion and learning point
Hydatid cyst of the adrenal gland is an uncommon pathology, which should be suspected in case of any cystic tumor of the adrenal gland. Echinococcal IgG assay is commonly negative in un-ruptured hydatid disease. Differentiation of large primary liver and adrenal peri-diaphragmatic cysts may prove difficult as adrenal function may be normal in adrenal cyst and imaging indeterminate therefore surgical exploration is deemed necessary to determine location. Association between an adrenal hydatid cyst with hypertension is still unclear.

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P24

Unusual presentation of two patients with spontaneous pheochromocytoma

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Here we present two interesting cases of pheochromocytoma with unusual presentation.
Case1
A 61-year-old gentleman presented with syncope after noticing small amount of haematuria. His initial working diagnosis was vasovagal syncope but on further exploration, he reported previous history of palpitations and atypical chest pain. He was non-smoker with longstanding hypertension. His CT(urogram) showed incidental left adrenal nodule after undergoing workup for haematuria. Urine metanephrines were elevated 4-times above upper limit of normal range with normal overnight dexamethasone suppression test (DST) excluding any iatrogenic cortisol excess. His MRI(adrenals) and MIBG scan confirmed 3.2cm left-sided phaeochromocytoma. His elective left adrenalectomy was performed uneventfully. Histology showed a composite phaeochromocytoma, PASS 3, with ganglioneuromatous elements, present at margin. At 3-month follow-up, he remained normotensive and repeat plasma metanephrines were normal. He was planned for repeat CT and genetic testing.
Case2
A 36-year-old gentleman was referred to endocrinology for incidental 3.5cm indeterminate adrenal nodule on CT (abdomen) after investigating abdominal symptoms. He denied constitutional symptoms, chest pains, palpitations, syncope, excessive weight gain, sweating or flushing. His initial CT and MRI (adrenals) could not differentiate between lipid-poor adrenal adenoma, phaeochromocytoma, adrenocortical carcinoma or adrenal metastasis. Given his age and tumour size, surgical intervention was suggested. However, as he was not keen on surgery initially, serial imagings were planned. On follow-ups, he started experiencing flushing and headaches. His blood/24-h-urine normetadrenaline were elevated with normal overnight DST. His serial MRIs later demonstrated avidly-enhancing 34-mm left-sided adrenal nodule and MIBG found avidly intense uptake, consistent with pheochromocytoma. Given the above findings, patient agreed to proceed with adrenalectomy.
Conclusion
Our 2 cases of pheochromocytoma highlight the importance to exercise high degree of suspicion in sporadic pheochromocytoma which can present with atypical features at diagnosis and during follow-up.

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P25

Abiraterone related hyponatremia

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Introduction
Abiraterone acetate, potent selective irreversible inhibitor of CYP17A1, is increasingly used with prednisone to treat prostate cancer resistant to androgen deprivation therapy.
Case presentation
64-year-old gentleman with BG of prostate cancer with widespread metastatic bone disease. He was on abiraterone since 2019. Admitted with generally unwell, aches/pains, headache, and dizziness. Euvolemic hyponatremia (123) with normal potassium and glucose. Blood pressure was 100/60mmHg. Morning cortisol 87 nmol/l, TSH 1.4 mu/l, serum osmolality 252 mmol/kg, urine osmolality 327 mosm/kg and urine sodium of 38 mmol/l. Short synacthen test - stimulated cortisol 296 nmol/l. On further enquiry, he was earlier taking prednisolone 5mg once daily with abiraterone. However, discontinued recently causing symptomatic adrenal insufficiency. The prednisolone restarted at 10mg with planned reduction to 5mg once feeling better. Unfortunately, he developed metastatic small cell carcinoma and had to start carboplatin/etoposide chemotherapy with discontinuation of Abiraterone and prednisolone. Later the year, he succumbed to disease.
Discussion
CYP17A1 has 2 roles: as 17-α hydroxylase and 17,20 lyase. 17-α hydroxylase catalyses conversion of pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone, which are precursors for cortisol. 17,20 lyase catalyses dehydroepiandrosterone and androstenedione production which are precursors of testosterone. Inhibition of 17-α hydroxylase and 17,20 lyase by abiraterone decreases cortisol and testosterone production. CYP17 inhibition by abiraterone: loss of negative feedback, high ACTH levels, and mineralocorticoid excess syndrome (MES) through uninhibited steroidogenesis pathway – hypokalemia, fluid retention, and hypertension. Addition of glucocorticoid to abiraterone attenuate development/severity of MES. Lowering excess ACTH also reduces ACTH-driven androgen formation via a backdoor pathway. Adrenal insufficiency in our case could be due to 17-α hydroxylase inhibition or to secondary adrenal insufficiency from long term steroid withdrawal. ACTH level should have helped in differentiation. In either case, patient needed prednisolone in double dose during this unwell period for symptomatic improvement.

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P26

Withdrawal of glucocorticoid replacement in patients following treatment for Cushing's: The importance of reassessing the need for long term replacement

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Generous glucocorticoid (GC) replacement following pituitary or adrenal surgery for Cushing's can result in persistent suppression of the pituitary corticotrophs, evidenced by poor short synacthen test (SST) responses. Dose reduction can result in increased fatigue so patients tend to prefer to remain on higher doses. Long-term GC therapy is associated with increased morbidity and mortality. We present two cases where GC therapy was successfully weaned through a gradual tapering approach.
Case 1
A 26-year-old woman with Cushing's syndrome underwent a left adrenalectomy for a 3.4cm left adrenal adenoma. She was discharged on once-daily Prednisolone 3mg. Subsequent SSTs showed a suboptimal response (Table 1). Given the intact right adrenal, a gradual tapering of GC dosage was initiated, allowing for recovery of the hypothalamic-pituitary-adrenal (HPA) axis and endogenous cortisol production.
Case 2
A 44-year-old woman underwent transsphenoidal hypophysectomy for Cushing's disease. She was discharged on once-daily Prednisolone 6mg. A year later, cortisol levels indicated HPA axis recovery (Table 1) and she was gradually weaned off GC therapy, considering the preserved adrenal function. Similar to Case 1, this tapering approach facilitated successful discontinuation of GC treatment.
Discussion
These cases emphasise the importance of postoperative HPA axis reassessment in patients with surgically treated Cushing's, as endogenous cortisol production may recover over time. Limited evidence exists regarding HPA axis recovery, and our cases contribute to the growing knowledge in this area. The proposed strategy of

gradually tapering GC dosage, accompanied by clinical assessment, appears effective in facilitating the weaning process.

Date and Prednisolone Dose	Baseline Cortisol (nmol/l)	30-minute Cortisol (nmol/l)	ACTH (ng/l)
Case 1: 27/07/22 (3mg)	59	78	78.5
Case 1: 03/02/23 (1mg)	187	189	130
Case 1: 03/02/23 (1mg)	236	352	78.5
Case 2: 20/10/20 (6mg)	<28	N/A	<5
Case 2: 12/07/21 (2mg)	236	N/A	28.9

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P27

Evaluation of the hounsfield unit approach for streamlining investigations for adrenal incidentalomas

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Background
Adrenal incidentalomas (AIs) detected on pre surgical scans often present a logistical challenge due to the pressing need for preoperative exclusion of a phaeochromocytoma. Our local guideline recommends endocrinology referral for all AIs for further investigations, including pre clinic 24-hr urine metadrenalines. This approach can be time-consuming, particularly for patients awaiting unrelated surgery.
Methods
Our review included all AIs identified within our centre over a 2-year period (from 1/1/2021 to 31/12/2022). All AIs underwent unselected screening for phaeochromocytoma, including urine metadrenaline (MN) & normetadrenaline (NMN) analysis, followed by measurements of plasma MN and NMN concentrations in those with raised 24-hr urine MN/NMN concentrations.
Results
Initial analysis revealed 13 patients with elevated 24-hr urine NMN or MN levels, with 5 patients confirming elevated levels on 2 separate occasions. Subsequently only 2/13 (15.4%) patients had confirmed raised plasma normetadrenaline and/or metadrenaline concentrations, suggesting possibility of a phaeochromocytoma. On retrospective review, both these patients also had an AI with raised HU (>10 HU; recommended diagnostic threshold for pheochromocytoma screening for AIs).
Conclusion
Our ongoing review aims to validate the guidance that early adoption of the HU approach as an initial screening tool for adrenal incidentalomas is cost-effective and clinically safe. However, practical application of this approach requires a standardised multidisciplinary assessment for all AIs including careful evaluation of all imaging, prior to undertaking endocrinology assessment, to optimise resource utilisation in clinical practice.

Patient number	Gender	Age (yr)	24-hr urine NMN (F ≤ 3.0 μmol/24hr; M ≤3.8 μmol/24hr)	24-hr MN (F ≤1.8 μmol/24hr; M ≤2.2 μmol/24hr)	Plasma NMN (<1180 pmol/l)	Plasma MN (<510 pmol/l)	HU
1	F	66	5.1	0.5	1201	99	40
2	M	72	6.9	6.7	1392	797	22.3

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P28

Refractive hypokalemia due to Ogilvie's syndrome

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Introduction
Acute Colonic Pseudo-Obstruction (Ogilvie's syndrome) is characterized by colonic distention in the absence of mechanical obstruction. Those without ischaemia/perforation is treated conservatively by withdrawing offending drugs, correcting electrolytes/underlying risk factors, neostigmine and colonic decompression.
Case presentation
90-year-old frail lady from care home with HTN, CVA, and dementia, admitted with recurrent falls and unwell. After 2 days, developed abdominal distention and vomiting. She was mostly constipated. Seen by surgical team. X-ray/CT abdomen showed colonic pseudo-obstruction. Electrolytes were normal on admission. Hypokalaemia - 2 days after vomiting. Not on any drugs to cause hypokalemia. Magnesium was normal. Correction of hypokalemia was virtually impossible. She was started on spironolactone and referred to endocrine. Aldosterone, renin, and urine potassium can't be done as on spironolactone. ODST ruled out Cushing. Sando-K and spironolactone (400mg/day) failed to maintain potassium. Distention continued despite this and flatus tube for 4 months. Age and comorbidities limited colonoscopic/surgical options. Decided for palliative discharge.
Discussion
Ogilvie's syndrome develops in hospitalised patients with serious underlying medical/surgical conditions, with risk factors being critical illness, surgery, metabolic imbalance and nonoperative trauma. Precise mechanism - unknown. Alterations in autonomic nervous system and colonic atony is proposed. Main clinical feature is abdominal distension. 80% have abdominal pain. Nausea and vomiting in 60%. Constipation and, paradoxically, diarrhoea in 50-60% and 40%, respectively. Two variants: classical variant (common) is associated with constipation. Secretory Diarrhoea variant (less common) is associated with secretory diarrhoea, profound hypokalemia, resistance to neostigmine and decompression, and increased mortality. The latter variant may have only minimal episodes of diarrhoea. However, they will have pooling of potassium rich secretions within the distended colon, causing volume repletion, secondary hyperaldosteronism, upregulation of BK channel in colonic mucosa and raised colonic potassium secretion. Spironolactone suppress BK channel and reduce colonic (and renal) potassium secretion.

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P29

An unusual case of hypercalcemia in a patient with chronic hypoparathyroidism and mineralocorticoid insufficiency

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Introduction
Hypercalcemia is a relatively common ionic imbalance, mostly due to primary hyperparathyroidism or neoplasia. Hypercalcemia rarely occurs in patients with acute adrenal insufficiency and establishing its etiology can be a challenge.
Clinical presentation:
We present the case of a 27-year-old patient, admitted in June 2023 with severe fatigue, recurrent diarrhea, vomiting and anorexia, symptoms that have progressively worsened in the last months. He was known to have chronic severe hypocalcemia since childhood, uninvestigated until 2019, when the diagnosis of congenital primary hypoparathyroidism and Fahr syndrome was established. Under treatment with 4.5 grams of calcium and 3 micrograms of alfacalcidol the serum calcium value was maintained at the lower limit of normal. He was also diagnosed with hyperreninemic hypoaldosteronism in 2020 and treated with fludrocortisone, with a normal ACTH-cortisol cycle at that time and subsequently. General examination revealed low blood pressure (90/70 mmHg) and tachycardia, hyperpigmentation of the skin with areas of depigmentation on anterior thorax and forearms (vitiligo). Blood tests showed mild normocytic normochromic anemia (Hgb=12.3 g/dl), moderate hypercalcemia (Ca=13.5 mg/dl) and an altered renal function with a creatinine of 1.58 mg/dl and an eGFR of 61 ml/min/1.73 m2. The hormonal profile revealed a very high ACTH (1706 pg/ml) and a low cortisol (0.11 micrograms/dl) level, with normal thyroid functions and negative thyroid antibodies. We started intravenous hydration plus iv glucocorticoid treatment, with rapid normalization of the renal function and of the serum calcium; alfacalcidol and calcium supplements were withdrawn for 2 days and than resumed. Patient was discharged after 5 days on 7.5 mg prednisone, 0.1 mg fludrocortisone and alfacalcidol and calcium supplements.
Conclusion
This is a case of type 1 autoimmune polyglandular syndrome, which started with hypoparathyroidism, followed by mineralocorticoid deficiency occurring 3 years before the development of cortisol insufficiency.

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P30

Trials of therapy are subject to a placebo effect and should not be used

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When patients with type 1 diabetes present with hyponatremia, Addison's is an important condition to exclude. It is however important to consider other causes, and a trial of hydrocortisone is not part of the diagnostic test for adrenal failure. A 43-year-old lady, with a background of Type 1 Diabetes and depression, presented unwell with hyponatremia. Her basal cortisol was low 162 nmol/l along with an ACTH 16.2 ng/l. A short synacthen test (SST) revealed a baseline cortisol of 229 nmol/l rising to 357 nmol/l at 30 minutes, and 462 nmol/l at 60 minutes, which was reported as a normal response. Her urine osmolarity was 597 mOsm/kg, consistent with SIADH, likely secondary to antidepressant use. The patient obtained a second opinion, and despite normal synacthen results, it was felt that "partial" adrenal insufficiency might be confirmed with a trial of hydrocortisone 5mg which was then increased to 10mg once a day, following which she subjectively felt better. So, the hydrocortisone was continued assuming she did have Addison's disease. Lockdown then occurred in March 2020, so she spent over a year on 10mg hydrocortisone without further investigations. When seen in the Endocrinology clinic a year later, she had become Cushingoid with a weight gain of almost 30kgs and slight worsening of her diabetes control. She was weaned off the hydrocortisone, and over a few months lost about 26kg. She was managed with fluid restriction, and later a change of antidepressant, which led to near normalisation of her sodium levels. Learning point: Trials of therapy lead to false diagnoses, as patients may benefit from the placebo effect.

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P156

Glucocorticoid receptor and PARP-1 genomic binding changes in response to corticosterone excess in mice

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Ligand binding of the glucocorticoid receptor (GR) initiates recruitment to GR Response Elements (GRREs). GR transcriptional activation of genes manifests many of the pleiotropic actions attributed to glucocorticoids. However, excessive exposure to GCs produces detrimental impacts, shifting GR behaviour and driving dysregulated metabolic states. Moreover, GR, its interacting partners, and influencing proteins remain ambiguous. Poly-(ADP-ribosyl) polymerase 1 (PARP1) is a chromatin-interacting protein, shown to influence a range of biological pathways. PARP1 is also described as co-operating with pioneer factors to direct transcription factor binding, through genome accessibility. Our existing data show GCs reduce PARP1 activity, and we hypothesise that PARP1 plays a role in the GR binding events triggered by GCs. To evaluate this, we gave C57BL/6J mice drinking water containing corticosterone (CORT) or vehicle control for 3 weeks. Liver tissue was subject to ChIPseq for GR and PARP1 binding. CORT significantly increased GR binding events within 2kb of transcriptional start sites (TSS) from 410 to 602 (+46.83%) (peaks called using MACS2 Pvalue 0.05). GR recruitment to the whole genome was also elevated (+9.29%). PARP1 binding events were reduced from 4975 to 1004 (-79.06%). CORT reduced overlap of PARP1 and GR binding sites from 248 to 115 (-53.63%). Together, findings indicate PARP1 is influenced by intracellular GC availability as its genomic interaction is greatest before steroid receptor-ligand binding. Pathway analysis indicates necroptosis (adjP 5.7x10-38) and RNA transport (adjP 3.6x10-22) are differentially regulated as a result. RNAseq will reveal the impacts of PARP1 genome. It will also show the influence of PARP1 over transcriptionally productive GR binding. These data explore PARP1 cooperation with pioneer factor proteins to improve accessibility of the chromatin prior to steroid hormone receptor binding. Together it reveals mechanisms of transcription factor-directed gene expression and provides new knowledge into how GC excess may impact fundamental biological programmes.

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P157

Identification of a novel constitutively active $G\alpha_s$ variant associated with cortisol-producing adrenocortical adenoma

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Adrenocortical adenomas are among the most commonly identified human neoplasias, with a prevalence of 2-3% in the population. In some cases they are associated with autonomous cortisol excess that leads to increased morbidity and mortality. Altered cAMP/protein kinase A (PKA) signalling is common in sporadic cortisol-producing adenomas (CPA), mostly caused by somatic mutations in the genes coding for the catalytic subunit α of PKA (*PRKACA*) or the stimulatory G-protein α subunit, Gαs (*GNAS*), CPA-associated mutations in GNAS commonly affect the Arg201 residue, located within the GTPase binding domain, and are associated with constitutive cAMP activity. In a previous study, we identified a private Lys58Gln *GNAS* somatic variant in a patient (female, 44 yrs) with a 5.3 cm adenoma and overt Cushing's syndrome (Ronchi *et al* 2016). This variant was predicted likely pathogenic, and structural modelling showed Lys58 is located near to the critical Arg201 residue, suggesting Lys58Gln may affect $G\alpha_s$ function. To clarify whether this Lys58Gln variant had a functional effect we assessed signalling by the melanocortin-2-receptor (MC2R), an adrenocorticotropic hormone (ACTH) receptor. We utilised HEK293 cells depleted of *GNAS* to establish *GNAS*-WT and *GNAS*-Lys58Gln stable cell-lines and investigated ACTH-induced MC2R receptor activity using cAMP Glosensor kinetic assays. This showed the Lys58Gln $G\alpha_s$ variant had a significantly higher basal cAMP concentration and a significantly greater response to ACTH between 0-10nM ($n=6$, $P<0.001$), when compared to wild-type $G\alpha_s$. The Lys58Gln Gαs variant diminished the receptor's maximal response to ACTH ($P<0.001$), although it did not affect the ligand's potency. In conclusion, we demonstrated that Lys58Gln is a likely pathogenic $G\alpha_s$ variant associated with constitutive MC2R signalling, similarly to the previously described Arg201 mutations. Our findings identify this variant as a new potential pathogenic mechanism that could be observed in a small subset of patients with adrenal Cushing syndrome.

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P158

Development of PP-UHPLC-MS/MS workflow for the high-throughput and sensitive targeted steroid analysis of mouse plasma samples

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Stress is increasingly pervasive in modern society and an unavoidable stimulus to the human organism. Stressors, whether of social or physical type, activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the upregulation of glucocorticoid levels and, in some cases, its de novo biosynthesis. Aside from HPA axis regulation, corticosteroids modulate the immune response to inflammation and affect whole-body metabolism. Despite numerous studies using traditional GC-MS and LC-MS methods, the accurate quantification of steroid levels in biological matrices continues to pose significant analytical challenges. High structural similarity between steroid isomers and their active and inactive forms in various abundance levels with variable ionizability can result in significant interferences and false positive or negative results. The present study aimed to develop a selective and sensitive high-throughput reversed phase ultra-high performance liquid chromatography-tandem mass spectrometry (RP-UHPLC-MS/MS) method for the simultaneous quantification of 40 endo- and exogenous steroids covering progestogens, corticosteroids, androgens, estrogens, and synthetic steroids in human, rat and mouse plasma. Overlapping of retention times and masses or fragmentation patterns of 31 of 40 steroids and difficult ionizability had to be overcome when developing the 20-minute long RP-UHPLC-MS/MS method. The sample preparation method of protein precipitation (PP) was developed to eliminate matrix effects. The optimized method was validated according to the EMA guideline on bioanalytical method validation, and the PP-UHPLC-MS/MS workflow has been applied so far to analyze 140 mouse plasma samples of mice exposed to different stress conditions (immune stress, acute stress response, food allergy). The study was supported by the GA UK project No. 348221, STARSS project (Reg. No. CZ.02.1.01/0.0/0.0/15_003/0000465) co-funded by ERDF, the project of specific research SVV 260548 and CSF project No. 21-10845S.

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P159

A pragmatic approach to monitoring for adrenal axis recovery after a failed Short Synacthen Test (SST)

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Background
The short Synacthen test (SST) is commonly used for assessing adrenal reserve. Depending on the cause, we often use serial SSTs in current practice, to assess whether people with adrenal insufficiency (AI) have adrenal axis recovery. We aimed to explore if baseline cortisol levels were a suitable screening test for recovery in people with AI rather than using serial SST in all cases.
Methods
We retrospectively reviewed all SSTs ($n=1{,}570$ tests; $n=952$ individuals) conducted in our hospital over a 10-year period (1st February 2013 to 30th January 2023) that had a baseline cortisol taken before 9:30 am. We measure both 30- and 60-minute cortisol values for all SSTs and currently use the Abbott Architect method. We used the follow-up SSTs ($n=115$ tests; $n=66$ individuals) for those who failed their first SST to see whether baseline cortisol could be used to predict a threshold below which there was a less than 5% chance of passing an SST. We used the full SST dataset to refine the construction of a quantile regression model to predict the 95% centile of peak cortisol response. This model was refitted to the SST data for those who failed the first SST.
Results
Individuals with a baseline cortisol of ≤ 126 nmol/l, had a 95% chance of failing an SST. Of all our follow-up SSTs, 60% (69 of 115) had a baseline cortisol of ≤ 126 nmol/l; none of these passed an SST.
Conclusions
A baseline 9 am cortisol ≤ 126 nmol/l is common in those followed for AI recovery and is an excellent indicator of non-recovery of adrenal axis. Baseline cortisol measurements are therefore a simple way of screening for adrenal axis recovery. Those with a cortisol of >126 nmol/l should go on to have an SST.

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P160

Defining the basal serum cortisol cut-off for weaning patients off glucocorticoids in suspected tertiary adrenal insufficiency

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Background
Cut-offs for basal cortisol (early morning) have been determined to predict the 30-minute cortisol level post-synacthen, but not for determining when patients with suspected tertiary adrenal insufficiency (AI) are weaned off glucocorticoids.
Aims
The aim of this study was to compare the predictive values of basal cortisol, basal ACTH and basal cortisol:ACTH ratio to determine appropriate thresholds to reduce the required number of Short Synacthen tests (SST).
Methods
This was a retrospective cohort study of all adult patients on long-term glucocorticoids who were referred to a tertiary endocrinology steroid clinic for suspected tertiary AI between 2015-2022 and underwent an SST (08:00-12:00). Basal cortisol, basal ACTH and cortisol:ACTH cut-offs with 95% and 99% specificity and sensitivity were determined via receiver operating characteristic (ROC) curve analysis. AI was defined as post-synacthen 30-minute cortisol of <430 nmol/l, analysed using Roche Elecsys II (Roche, Mannheim, Germany) assay.
Results
A total of 262 patients underwent 443 SSTs, of which 36.3% tests were normal. The ROC curve analysis showed that basal cortisol was the best-performing test with area under curve of 0.89 (95%CI 0.85-0.92) compared to 0.56 (95%CI 0.51-0.62) and 0.80 (95%CI 0.76-0.84) for basal ACTH and cortisol:ACTH, respectively. Basal cortisol cut-offs with 95% and 99% specificity to predict adrenal sufficiency were 285 and 349 nmol/l respectively. Analysis of patients with basal cortisol between these two cut-offs showed that none had an AI-related admissions in the following 12 months. These 57 patients consisted of 54 who were successfully weaned while observing standard steroids sick-day rules, two remained on glucocorticoids long-term, and one was weaned later.
Conclusion
Basal cortisol is superior to the basal ACTH and cortisol:ACTH in predicting SST outcome and the 95% specificity threshold of 285 nmol/l can be used to wean patients off glucocorticoids.

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P161

An international study of the association between local health care resources and acute adrenal insufficiency events in children with congenital adrenal hyperplasia

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Background
The reported occurrence and management of acute adrenal insufficiency–related adverse events in children vary widely between centres and may depend on available resources.
Methods
Real world data from the I-CAH Registry from 44 centres [32 from high income (HIC) and 12 from low/middle income (LMIC) countries] and a total number of 607 children were linked to the results of a health care survey of local resources and clinical management of CAH completed by healthcare professionals. Resources included written and steroid emergency plans with one point assigned for each resource.
Results
The median reported rate of sick day episodes per patient year per centre at HIC and LMIC centres was 0.69 (range 0, 6) and 0.49 (0,3) respectively ($P=0.603$). Although the availability of resources for management of adverse events was numerically greater at HIC centres vs LMIC with a median score of 4 (1,7) and 3 (2,6) respectively, this did not reach statistical significance ($P=0.109$). There was no significant association between the availability of resources and the (sick day episode) SDE rate in LMIC or HIC centres ($P=0.195$). The use of double dose hydrocortisone was reported more frequently in LMIC vs HIC centres (67% vs 22%, $P=0.005$). For management of adrenal crises, the most frequently reported medications included parenteral bolus hydrocortisone (100% in HIC vs 75% in LMIC, $P=0.003$) and saline solution (97% in HIC vs 83% in LMIC, $P=0.112$). Prednisolone was reported to be used more in LMIC (13% in HIC vs 42% in LMIC, $P=0.033$).
Conclusions
There is no clear association at centres between the level of resources available and the rate of SDE. However, there are differences in the management of adrenal crises and may reflect local availability of drugs.

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P162

Hormonal secretion pattern in patients with adrenal tumours referred to a UK tertiary care centre

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Introduction
Up to 3-7% of adults have an adrenal incidentaloma. These are most frequently non-functioning adenomas (NFA) but can be associated with adrenal hormone excess. According to the ESE-ENSAT guidelines on adrenal incidentalomas (2016), an accurate endocrine work-up is recommended.
Methods
We provide an extensive retrospective analysis of patients with adrenal tumours referred to a large UK tertiary centre between 1998 and 2022, with focus on non-aldosterone producing adrenocortical adenomas (NAPACA) and the relationship between hormonal secretion patterns and demographic characteristics.
Results
Our cohort consisted of 1398 patients (56% women, median age at diagnosis: 60 years [IQR 49-70]). Adrenocortical adenomas (ACA) accounted for majority of tumours (56%, $n=782$); of these, 90% ($n=706$) underwent full endocrine work-up including overnight dexamethasone suppression test. While most patients had NFA (51%), the others most frequently had mild autonomous cortisol secretion (MACS, 32%), followed by primary aldosteronism (10%) and Cushing's syndrome (CS, 4%). Most patients with NAPACA were women, with a higher proportion among those with CS (61% in NFA, 60% in MACS, 87% in CS, $P<0.05$). Moreover, patients with CS were younger (NFA median 60 years [IQR 51.5-68], MACS 67 years [IQR 58-74], CS 44 years [IQR 30.5-54.5], $P<0.05$). There was no significant difference in availability of endocrine work-up or proportion of diagnosed autonomous cortisol secretion between patients referred before (1998-2015) or after the publication of the ESE-ENSAT guidelines (2016-2022).
Conclusion
In our large cohort of patients referred for adrenal tumours, full endocrine work up was available in 90% of ACAs and showed presence of autonomous cortisol secretion in 36% of cases. Patients with CS were more frequently younger females. These figures did not change after the implementation of the 2016 guidelines.

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P163

Mild autonomous cortisol secretion in patients with adrenal incidentalomas – how common and what is the prevalence of co-morbidities?

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The widespread use of cross-sectional imaging has led to increased detection of adrenal masses in 2% of general population and over 7% of those above age 70. Although majority are benign, it is important to exclude hormonally active or malignant lesions. Mild autonomous cortisol secretion (MACS) is the most common and found in 30-50% of patients with adrenal mass. We reviewed our adrenal incidentaloma database for patients who attended the nurse-led pathway for biochemistry investigations followed by medical review. Patients were excluded if investigations were refused or incomplete. We reviewed 516 patients between April 2017 and December 2022. We primarily performed 1mg overnight dexamethasone suppression tests (ODST) and some underwent 24-h urine cortisol collections. A total of 139(27%) patients had abnormal biochemical corticosteroid status(either test abnormal). A total of 465 patients had ODST of which 315(67.7%) were normal, 118(25.4%) had cortisol level between 51-138 nmol/l (MACS-1), 22(4.7%) had cortisol >138 nmol/l (MACS-2) and 10(2.2%) were unassessable. Patients with MACS consist of 46(32.9%) males and 94(67.1%) females. The mean age was 66.9 years. Seventy-three(52%) have hypertension, 31(22%) type 2 diabetes, 7(5%) osteoporosis and 2(1.4%) vertebrae fracture. Seventy-six patients (54.3%) were screened for diabetes with normal results, 9(6.4%) abnormal glucose regulation and 24(17.1%) were not screened. Patients with MACS should be screened and treated for hypertension, type 2 diabetes and asymptomatic vertebrae fracture. Our audit identified the need to improve screening for osteoporosis. These comorbidities are more prevalent in the older age group. It remains a challenge to identify patients who would benefit from surgical intervention, particularly with growing evidence that MACS can adversely impact on these co-morbidities. Increased surgical intervention would have a significant impact on provision of healthcare services and a personalised approach should be advocated.

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P164

MHRA steroid card for patients prescribed high dose steroids

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Introduction
Steroids are used in an array of conditions, ranging from asthma through to haematological malignancies. When using steroids for prolonged periods patients are at risk of developing adrenal crisis with sudden withdrawal. To allow early recognition and support treatment of adrenal crisis patients prescribed high dose steroids should be issued with an MHRA steroid card. Our aim was to identify how many patients needed a steroid card, amongst those taking high dose steroid medication. Our data showed that 24% of those prescribed high dose steroids (oral, topical, subcutaneous and inhaled) had not been issued with an MHRA card. Therefore, we have implemented change by ensuring that these patients are issued with a steroid alert card to support early detection of a crisis.
Methods
We collected data through using the practice software, SystmOne, to identify patients prescribed steroids. 77 patients were identified as having been prescribed steroids at some point from their medical history.
Results
Out of our total sample (77 patients), 53 of these were actively still taking steroids and so had a repeat prescription for a chronic condition, and therefore were at risk of adrenal crisis. 25/53 patients (47%) had been prescribed a high dose and were identified as needing an MHRA steroid card. Further to this, 6/25 patients on high dose steroids (24%) did not have a steroid card, and so were detected as needing a card to achieve our overall aim.
Conclusion
We have implemented change by ensuring that patients prescribed high dose steroids for prolonged periods are issued with an MHRA steroid card. Utilisation of the MHRA card will enable early recognition and support emergency treatment in the event of adrenal crisis.
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P165

Assess and improve (AAIM) implementation of corticosteroid sick day rules in transplant and oncology services. A single-centre steroid safety project

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Objective
The project was designed to Assess And IMprove (AAIM) the practice of healthcare professionals (HCPs) around the corticosteroid sick-day rule, involved in caring for transplant and oncology patients requiring treatment with corticosteroids long-term.
Introduction
Corticosteroids are widely prescribed drugs in oncology and post-transplant patients. Long-term treatment with corticosteroids dose, which equals prednisolone 5mg/day for at least 4 weeks, suppresses the hypothalamic-pituitary-adrenal (HPA) axis, known as tertiary adrenal insufficiency. These patients are at risk of developing life-threatening adrenal crisis if corticosteroid dose is not increased during periods of stress, which is preventable with education on steroid sick-day rules.
Methodology
A survey including a set of questions was circulated among HCPs (clinicians and nurses) looking after Transplant (Liver and Kidney) and Oncology patients at Royal Free Hospital, to evaluate the educational practice of corticosteroid sick-day rules. These included internal medicine trainees (IMTs), speciality registrars, consultants and specialist nurses.
Results
Variability was observed in sick-day rule education; 40% confirmed counselling patients at the time of initiation of long-term corticosteroids, 27% counselled on subsequent contact after initiating treatment, 50% HCP counselled on illness with fever and 27% mentioned they do not offer advice on sick-day rules.
Discussion
Trust-wide corticosteroid sick day rules guidelines and patient information leaflet were formulated based on the recent evidence with specific mention of sick-day rules for patients on dexamethasone. Education is being arranged Trust-wide for HCPs on steroid safety. Education sessions are delivered to the foundation and IMTs, who deal with these patients at the front door. A steroid safety session was also arranged on local oncology day.
Conclusion
This is the first single-centre project that can be replicated Nationally to AAIM implementation of corticosteroid sick-day rule across non-endocrine specialities, hence improving the level of care of patients on long-term corticosteroids and reducing hospital admissions with adrenal crises.
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P166

Malignant pheochromocytoma and paraganglioma – clinical course and outcomes from a tertiary care centre in India

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Objectives
To study the clinical, biochemical, imaging profile and treatment outcomes of patients with malignant pheochromocytoma and paraganglioma(PPGL). Also, to compare their characteristics with non-malignant PPGL to identify the factors that may predict metastasis.
Methods
This retropsective cohort study included 212 patients with PPGL managed at our centre over a period of 10 years(2013-2022). Their clinical, biochemical, radiological profile, treatment data and response were retrieved from the electronic medical records.
Results
Thirty patients had malignant PPGL and the median age at diagnosis of metastasis was 38.5 years(range10-52). 16(53.3%) patients had synchronous metastases and 14(46.7%) developed metachronous metastases after a median duration of 7.8 years(range1.1-22.5) from the diagnosis of the primary tumour. 43%(13/30) underwent genetic testing and among them 38.5%(5/13) tested positive for gene mutation related to PPGL. Median follow-up after diagnosis of metastases was 20 months(range1-96). Metastases detection rate was 100% for both 18FDG(4/4) and DOTATATE(4/4) PET-CT, 97(28/29) for CT/MRI and 78%(18/23) for I131 MIBG scan. 14(46.7%) patients received MIBG therapy. Seven patients succumbed due to metastatic disease and among them five died within a year of diagnosis of metastases, the median survival was 41 months(range13 to 83). On comparing the clinical, biochemical and imaging parameters of malignant($n=30$) and non-malignant PPGL($n=182$), it was found that patients with malignant PPGL had larger tumors(8.5 ± 5vs6.2 ± 3.3,$P=0.012$), had less frequent adrenergic symptoms and more often were extra-adrenal in location. On logistic regression, tumor size was found to be an independent predictor of metastases.
Conclusion
Malignant PPGLs had variable clinical course and treatment response. Although, malignant PPGL were larger compared to benign tumors, a size cut-off predicting metastases could not be derived. Majority of the patients in our cohort received MIBG therapy for metastases.
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P167

Improving Steroid prescribing in patients at risk of Adrenal Insufficiency: A Quality Improvement Project to enhance recognition and communication to patients at risk

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Background
Patient Safety Noticed issued by Welsh Government in June 2021 set out multiple action plans to be implemented by Welsh health boards to improve recognition and management of adrenal crisis. Hospitals were advised to review policies to ensure all patients at risk of Adrenal Crisis [(primary/secondary/tertiary adrenal insufficiency (AI)] were identified.
Aim
In response, our hospital commenced a quality improvement project seeking to better equip doctors to identify patients at risk of AI and ensure optimal communication of sick-day steroid rules to patients.
Methods
Teaching series was initiated to provide updated information to steroid prescribing specialties, including medical meetings and targeted teaching to

Respiratory, Acute Medicine and Endocrinology departments, who frequently encounter patients at risk. Poster highlighting salient findings from patient safety alert was distributed throughout the hospital reinforcing teaching sessions. The poster included QR code enabling access to written sick-day steroid rules produced by the Society for Endocrinology, allowing patient distribution. Anonymised questionnaires provided to hospital doctors at 3 monthly intervals were analysed to review self-assessed clinical practice. Questions related to written and verbal communication of sick-day steroid rules, use of steroid cards and individual's self-judged confidence managing AI.
Results
Results demonstrated increase in questionnaire ratings of 'always'/'sometimes' for providing verbal and written communication of sick-day steroid rules of 55% and 48.87% respectively between initial and end results. Increase of 42.9% in ratings for 'always'/'sometimes' providing steroid cards was also observed at end point. Self-judged rating of confidence managing AI increased from 32.1% from beginning of project to 88.89% at final questionnaire.
Conclusion
Data analysis demonstrates improvement in communication of sick-day steroid rules, use of steroid cards and confidence managing AI in relation to the project. Limitations included the subjective nature of questionnaires and regular change of departmental junior workforce during the timeframe.

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P168

Developing a methodology to measure post-mortem hair hormone concentration to investigate causes of unexplained stillbirth – assessing cortisol, aldosterone, 17-hydoxyprogesterone and total bile acids

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Background
3.8 per 1000 UK babies are stillborn, a large proportion of which are "unexplained"; aberrations in adrenal hormones and bile acids are possible contributors. In this study, we aimed to develop methodologies for simple laboratory measurement of adrenal hormone and bile acid concentrations that can be applied to postnatal samples from stillborn babies, using hair as a relatively stable medium, reflective of retrospective fetal hormone levels.
Methods
Hormone concentrations were measured in 14 hair samples from 8 individuals, including serial samples and from different sites, and across a variety of ages. Following the optimisation of hair preparation, washing and hormone extraction; cortisol, aldosterone, 17-hydroxyprogesterone and bile acids were quantified using ELISA immunoassays. Linear regression was used to interrogate relationships between samples from different ages and between hormones. Spike recovery and linearity under dilution were used to assess the reliability of results.
Results
Cortisol, 17-hydroxyprogesterone, aldosterone and bile acids were measurable in many hair samples. No significant relationship could be demonstrated between different analyte concentrations, ages, years or between immunoassay plates. Analysis of spike and recovery has shown a variable retrieval of expected concentrations.

Assay plate	Median concentration	Interpolation range	% of samples in range
Cortisol	28.47 ng/ml	1-100 ng/ml	90%
Aldosterone 1	109.92 pg/ml	31.25-1000 pg/ml	100%
Aldosterone 2	87.92 pg/ml	62.5-1000 pg/ml	63.6%
17-hydroxyprogesterone	21.60 pg/ml	10-1000 pg/ml	81.8%
Total bile acids	2.10 μM	1.56-25 μM	60%

Discussion
This study has demonstrated an ability to quantify concentrations of cortisol, aldosterone, 17-hydroxyprogesterone and bile acids from human hair using ELISA kits. Further research aims to improve analyte retrieval and validate these findings using larger numbers of adult hair, adapting the methodology as required for use in neonatal hair.

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P169

A comparison of hydrocortisone and prednisolone for the treatment of adrenal insufficiency

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Background
Patients with adrenal insufficiency (AI) require glucocorticoid replacement therapy. Current Endocrine Society guidelines recommend thrice-daily hydrocortisone (15-25mg) or once-daily prednisolone (3-5mg). Concerns around prednisolone use have been based on evidence using higher doses. We have been using low-dose (2-4mg) once-daily prednisolone since 2014 for glucocorticoid replacement in adult patients with AI. This study aimed to compare the effects of each glucocorticoid on the risk of cardiovascular disease and adrenal crises.
Methodology
A cohort of adult patients with AI at Imperial College Healthcare NHS Trust ($n=100$), initially studied in a 2017 audit, were re-audited in 2021. Data on anthropometric and biochemical markers of cardiovascular risk, including body mass index (BMI), blood pressure, lipid profiles, and HbA1c, were obtained from the most recent electronic medical records since May 2019 (2-4 years from initial data collection). Adrenal crises occurring since May 2017 were also recorded.
Results
58 patients were taking hydrocortisone (mean total daily dose of 18.7 $\pm$ 5.0mg) and 42 were taking prednisolone (mean daily dose of 3.26 $\pm$ 1.16mg). There were no significant changes in markers of cardiovascular risk in patients who remained on prednisolone between 2017-2021 ($n=32$), nor in patients who switched from prednisolone to hydrocortisone ($n=5$). In patients who remained on hydrocortisone ($n=54$), HbA1c and random glucose were significantly higher in 2021 than 2017. In patients who switched from hydrocortisone to prednisolone between 2017-2021 ($n=9$), weight and BMI were significantly lower on prednisolone (mean weight difference -5.4 kg, $P=0.04$). One adrenal crisis occurred on hydrocortisone compared to none on prednisolone.
Conclusion
Once daily low-dose prednisolone is safe for the treatment of AI and may have a beneficial effect on weight in patients switched from hydrocortisone. Further clinical studies are actively recruiting to determine the optimal glucocorticoid replacement therapy for AI (The HYPER-AID Study (NCT03608943)).

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P170

Aldosterone variability in patients with primary aldosteronism undergoing adrenal vein sampling

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Adrenal vein sampling (AVS) is used to differentiate between unilateral and bilateral subtypes of primary aldosteronism (PA). However, AVS results may be misinterpreted due to a procedural artefact resulting in low aldosterone levels at the inferior vena cava (IVC), thus making an interpretation of aldosterone to renin ratios difficult. We investigated whether this artefact was due to patients' being supine before and during AVS, given aldosterone varies with posture, and/or due to conducting AVS at midday, given aldosterone's diurnal variation. We obtained peripheral samples of aldosterone and cortisol pre-AVS while patients were ambulatory, during AVS from the IVC while patients were supine, and post-AVS while patients were in an elevated bedrest position. We then analysed the variation of aldosterone with postural changes throughout the day and assessed the correlation between aldosterone and cortisol on the day of AVS. From 5 AVS procedures, the IVC aldosterone was low (<200 pmol/l) in three and below the limit of detection (≤ 60 pmol/l) in one. When examining aldosterone's variation with posture in patients with PA, peripheral aldosterone showed non-significant reductions from pre-AVS to AVS ($P=0.11$) and from pre-AVS to post-AVS ($P=0.19$) and a non-significant increase from AVS to post-AVS ($P=0.09$). Assessment of aldosterone and cortisol's relationship on the day of AVS revealed a mild positive correlation ($r2=0.59$; $P=0.02$). The decreases in aldosterone from pre-AVS to AVS suggests posture plays a major role. The correlation between aldosterone and cortisol on the day of AVS suggests diurnal variation likely also contributes to low IVC aldosterone during AVS. Overall, our preliminary findings indicate minimizing the time patients spend supine during AVS and shifting AVS timings from midday to morning may prevent suppression

of aldosterone during AVS. Further collection of prospective data is necessary to confirm the significance of these findings.

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P171

A clinical case demonstrating the challenges in diagnosing and managing Paraneoplastic Cushing's Syndrome

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We present a case of a 62-year-old lady with a grade 3 well-differentiated metastatic gastric-neuroendocrine tumour complicated by symptoms of CS (weight-gain, bruising, proximal weakness) which developed over 4 weeks. She had progressive disease after exhausting all conventional anti-neoplastic therapeutic options. Screening tests revealed raised 24-h urinary free cortisol (3460 nmol/24h[< 165]), post-overnight dexamethasone suppression serum cortisol (serF) 1200 nmol/l(< 50) (measured by immunoassay), mean (of 5) cortisol day curve (CDC) serF (CDC-serF) 1300 nmol/l but adrenocorticotropic hormone (ACTH) was in the normal range at 21 ng/l (0-46). Cross-sectional imaging of her pituitary and adrenal glands were unremarkable apart from bilaterally enlarged adrenals. ACTH precursors (pro-ACTH, proopiomelanocortin) were elevated: 3168 pmol/l (0-40). The patient commenced metyrapone, but intolerable nausea (at low doses with no evidence of hypocortisolaemia) precluded its use. Ketoconazole was contraindicated due to elevated transaminases therefore funding for the novel 11-β-hydroxylase inhibitor, osilodrostat, was obtained. Weekly CDC (serF measured by both immunoassay and liquid-chromatography tandem mass spectrometry [LC-MS/MS]) were undertaken for each dose escalation to assess the adequacy of treatment (target CDC-serF 120-240 nmol/l). Before starting osilodrostat, her CDC-serF was 1305 nmol/l. Following dose titration to 2 mg bd, her clinical symptoms of CS improved as did CDC-serF (to 115.8 nmol/l); replacement hydrocortisone was introduced. Bland-Altman revealed a 31% positive bias in serF measured by immunoassay compared to LC-MS/MS. This case highlights the utility of measuring ACTH precursors to prevent diagnostic delay. While ACTH precursors cross-react approximately 2% in most ACTH assays, if tumours primarily secrete POMC, the cross-reactivity can be lower and lead to ACTH concentrations in the normal range. We also demonstrate that LC-MS/MS should be used in osilodrostat-treated patients to measure serF due to the bias conferred by the build-up of cortisol precursors.

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P172

A case series of gastric diverticulum masquerading as adrenal adenoma

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Case 1
A 57-year-old lady referred to the Endocrinology department due to a CT Abdomen, performed for abdominal pain, reporting the presence of an incidental left adrenal adenoma. Imaging was reviewed in the Adrenal MDT meeting and further CT Abdomen arranged. Images were reviewed before and after oral contrast. Pre-contrast images revealed a small volume of high-density material within a rounded structure in the left upper quadrant, immediately superior to the left adrenal. The oral contrast then went on to fill the stomach and this structure – indicating this as a gastric diverticulum (neck measuring 1.4cm, with both food material and contrast present within the diverticulum). A normal appearance of the adrenal glands was noted.
Case 2
A 54-year-old male presenting with left sided pleuritic chest pain. CTPA was performed; with no evidence of pulmonary emboli but a 30mm lipid rich adenoma in the left adrenal gland was reported. On re-review of this scan in the Adrenal MDT meeting, normal adrenal glands were noted and this adrenal adenoma was reclassified to infact be a gastric diverticulum.
Case 3
A 60-year-old lady presenting with concerns relating to weight gain and skin changes, having requested referral to Endocrinology due to her own worry that an adrenal cancer was underlying these symptoms. Biochemical testing and CT Adrenals were arranged which excluded this, but did highlight the presence of a gastric diverticulum.
Conclusions
This case series highlights three patient cases in which an adrenal adenoma has been initially identified, but following re-review of imaging these have been reclassified as Gastric Diverticulum. This is an important differential to be excluded prior to extensive biochemical assessment of potential hormone excess, especially with the increasing number of scans being performed and incidental diagnoses identified.

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P173

A rare case of hydatid cyst disease in the adrenal gland

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Introduction
Hydatid cysts disease (HSD) is a parasitic disease caused by echinococcus granulosus. It is common in areas where the parasite is endemic; North Africa, the Middle East, Central and Far Asia, Central America and Australia. Liver (44-77%) and lungs (10-50%) are the preferred locations for HSD. Here we report a rare case of HSD affecting the adrenal gland.
Case Report
A 62-year-old female complained of right abdominal pain for a few weeks. CT scan showed a large right upper quadrant cyst measuring 14.7x12.4x11.6cm with calcified margins. It was inseparable from the right adrenal gland and contains fluid level with pressure effect on the liver and the right kidney. Further scans showed no evidence of other cysts in the chest. The patient denied contact with animals but had been travelling to South East Asia and South Africa many years ago. She received 3-month course of Albendazole followed by surgical removal of the intact cyst. Examination of the cyst material confirmed the diagnosis of HSD with no viable parasite. Albendazole was stopped two weeks after the surgery with no complications.
Conclusion
Hydatid cysts of the adrenals are extremely rare. So far, only 57 cases have been reported. This case represents the UK first known case HSD of the adrenal gland. Once suspected, biopsy must be avoided due to risk of spillage of cyst contents and septic shock. The treatment of choice is by removing the intact cyst via open laparotomy. Final diagnosis can only be confirmed after histological examination of the excised cyst.
Learning point
1. Consider HSD as a differential diagnosis when evaluating adrenal cyst especially following exposure to endemic areas.
2. Avoid biopsying cyst of suspected parasitic origin as it can cause serious complications.
3. Laparotomy as opposed to laparoscopic resection is recommended to remove intact cyst capsule.

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P174

Case series of catecholamine-induced Takotsubo cardiomyopathy secondary to pheochromocytoma and discussion of relevant literature

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Catecholamine-induced cardiomyopathy is a rare presentation of pheochromocytoma (PCC) with typical and atypical subtypes. These patients are associated with worse rates of morbidity and mortality compared to patients with PCC that were incidentally found. Frequently, these patients would present in the emergency setting with cardiac symptoms that may be difficult to distinguish from ischemic cardiomyopathy, and hence patients may be prescribed cardiac treatment in the form of angioplasty or coronary artery bypass grafting (CABG). In our case series, we discuss 4 cases in our tertiary centre since 2017, presenting with cardiac symptoms suggestive of takotsubo cardiomyopathy and were later

diagnosed with PCC as well. 2 patients presented with global hypokinesia of the heart on a background of a normal coronary angiogram, that resolved after excision of the PCC. 2 patients that presented diagnosed with concurrent triple vessel coronary disease and pheochromocytomas, underwent CABG and were found to have relatively normal coronary arteries, these patients were only able to wean off anti-hypertensives after excision of the PCC. On histology, 3 PCC were extra-adrenal and these tested positive for genetic mutations (2 had SDH-B expression). At the time of diagnosis, it is challenging to establish that cardiomyopathy is solely due to catecholamine-excess, which would dictate the best management approach of excision of the PCC. These patients are also at higher risk of peri-operative complications of cardiac arrest and respiratory failure. It is essential to achieve early appropriate diagnosis, stabilisation with alpha blockade before beta-blockade before PCC surgery.

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P175

Laparoscopic adrenalectomy for phaeochromocytoma in the context of acute coronary syndrome

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A 54-year-old man presented to the heart attack centre with cardiac chest pain, vomiting and collapse. Biochemistry (troponin incremented from 117 to 315ng/l) and electrocardiogram confirmed a diagnosis of non-ST elevation myocardial infarction (NSTEMI). Past medical history included type 2 diabetes mellitus and hypertension (diagnosed 8 years previously), hypercholesterolaemia and a 20 pack year smoking history. Secondary prevention for MI was commenced and coronary angiography revealed critical triple vessel disease with urgent coronary artery bypass graft (CABG) suggested. To investigate iron deficiency anaemia, he underwent a CT scan of the abdomen which demonstrated a left 7cm heterogeneous adrenal mass. Further questioning revealed he had a history of the classic triad of phaeochromocytoma symptoms: headache, palpitations and diaphoresis. Plasma metadrenaline was elevated at 3554 (0-510 pmol/l) as was normetadrenaline at 6021 (0-1180 pmol/l). Alpha-blockade (phenoxybenzamine (PBZ)), beta blockade (bisoprolol) and antihyperglycaemic agents were titrated and volume status was restored. Detailed discussion took place regarding options for coronary vessel management (stent vs bypass) and the order of management (adrenalectomy vs coronary intervention). After effective blockade was achieved (PBZ 30mg QDS and bisoprolol 15mg OD), he proceeded to laparoscopic adrenalectomy with good peri- and intra-operative haemodynamic stability and made a rapid post-operative recovery. He is now under discussion by cardiology regarding further management of his coronary artery disease. Secretory phaeochromocytomata, leading to catecholamine excess, can cause life-threatening cardiovascular complications and mimic acute coronary syndrome. A multidisciplinary team carefully managed this complex case and we discuss the different potential approaches to this clinical scenario to achieve the best patient outcome. We highlight the importance of adequate alpha-blockade in restoring normal circulating volume and improvement in cardiac function as assessed by echocardiography.

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P176

Current perceptions and practices by general practitioners (GPs) in the management of resistant hypertension

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Introduction
About 12% of patients present to the GPs with hypertension or related symptoms. The current practice of managing resistant hypertension in primary care is inconsistent and general practitioners (GP's) do not have a criteria for referral to tertiary care.

Methods
Quantitative anonymized online survey of 26 questions on the current prescribing practices and thresholds for referral of resistant hypertension cases amongst GPs in Singapore. Specialists and consultants from various clinical disciplines were excluded from the survey. The survey was conducted over 3 months and sent out twice to encourage maximum participation. The questionnaire included 26 questions and data was compiled and analyzed using SPSS v2022; chi-square test was used where appropriate.
Results
Of the 58 responses, 38/58 (66%) GPs had nearly 10 years of clinical practice and on the average managed up to 50 cases of hypertension per week. 34 of 58 (59%) respondents found it difficult to diagnose resistant HT and 14 of 34 (41%) felt there was no clear definition of resistant HT. The choice of antihypertensives was calcium channel blockers in 25/58 (43%), alpha blockers in 17/58 (29%) and the rest ACE inhibitors. Once resistant HT was suspected, most GPs referred the patients to endocrinology (29/58; 50%), and cardiology (26/58; 45%). Majority (53/58; 91%) referred when patients were on 3 or more antihypertensive agents, usually after a period of 3 months of refractoriness. 85 percent of respondents felt that there was a need for a separate guideline to manage resistant HT. Response rate of the survey was 97%.
Conclusion
Heterogeneity exists in primary care in the management of resistant HT and most felt the need for a separate guideline to help them manage and refer the patients for appropriate treatment.

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P177

Adrenal Insufficiency is rare among patients referred to cardiac autonomic dysfunction clinics

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Background
Syncope and pre-syncope are well recognised symptoms of primary adrenal insufficiency (AI). Some guidelines[(1)] recommend screening for AI in all patients who present with symptoms of orthostatic intolerance. However, the incidence of AI in these patients is unknown.
Aims
The aim of the study was to determine the incidence of AI in patients referred to a cardiac autonomic dysfunction clinic at a single tertiary care centre.
Methods
This was a retrospective cohort study of all new consecutive patients referred to cardiac autonomic dysfunction clinics between November- December 2022 at Sheffield Teaching Hospitals. Electronic case notes were reviewed to collect data on demographics, final underlying diagnosis (i.e., postural orthostatic tachycardia syndrome [POTS], postural hypotension, reflex syncope or others), and the incidence of AI.
Results
A total of 180 new patients were referred and reviewed in cardiac autonomic dysfunction clinic during the study period. Mean $\pm$ SD age of the study population was 45.2 $\pm$ 21.0 years with 61% ($n=109$) females. After investigations and review, 30% ($n=54$) were diagnosed with postural hypotension, while POTS was diagnosed in 3.9% ($n=7$) of patients. Diagnosis of reflex syncope was made in 17.8% ($n=32$) of the patients and 48.3% of patients ($n=87$) had a diagnosis other than above categories. Of all these patients 50% ($n=90$) were screened for AI, but only 1 patient who also had pre-syncopal symptoms was found to have AI secondary to opioid overuse and remains under endocrine review.
Conclusion
Despite the similarity in symptoms, the incidence of AI in patients referred to autonomic dysfunction clinics is very low. The need to screen for AI in this patient group is debatable.
Reference
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P178

Glucocorticoid receptor resistance unmasked by bilateral adrenal histoplasmosis

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Background
Generalized glucocorticoid-resistance (GCR) is a broad spectrum and heterogeneous syndrome that may be familial or sporadic caused by mutations in glucocorticoid receptor function and signalling. These patients present with hypercortisolism with enlarged adrenals but no Cushing features. Identification of GCR requires extensive investigations.
Case Report
An 81-year-old thin-built man of South-East Asian origin, presented with a 1-year history of reduced appetite, weight loss, postural symptoms and extreme fatigue. His family reported darkening skin creases, earlobes and scar tissues. His past medical history included Type 2 diabetes mellitus and hypertension. His CT-CAP excluded malignancy but found bilateral adrenal nodules suggestive of infiltrative process. This was confirmed by subsequent PET and biopsy which demonstrate adrenal histoplasmosis. Biochemistry revealed persistent hyponatremia at 125mmol/l, random cortisol 383 and 359 nmol/l (NR: 133-537) with ACTH 765 ng/l (NR:7.2-63.3), low renin and aldosterone, normal plasma metanephrines and adrenal androgens. His overnight-Dexamethasone-Suppression Test suppressed cortisol adequately to 41 nmol/l. His urine and serum free cortisol (using LCMS) was normal. Given non-concordance between clinical and biochemical findings, patient was commenced on hydrocortisone 10/5/5 mg daily. Within a month, he reported significant symptoms improvement. He regained weight with skin hyperpigmentation gradually resolved and normalisation of his serum sodium. His adrenal histoplasmosis was managed with Posaconazole 300 mg OD. This antifungal treatment is a cytochrome P450 inhibitor which should decrease steroid metabolites, but patient's clinical status declined, and ACTH day curve showed high ACTH levels at 164, 381 and 221 ng/l and so hydrocortisone dose was increased instead.
Conclusion
Cortisol receptor resistance is a rare cause of normal/high cortisol levels with no Cushing's features. This case is an unusual presentation of GCR. Cortisol replacement here improved patients' symptoms, hyperpigmentation and helped maintain weight. The underlying molecular basis of GCR needs further research.

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P179

Rare case of a giant Adrenal Schwannoma

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Introduction
Adrenal schwannomas are rare but important causes of adrenal tumours which can often only be diagnosed histologically. We present an interesting case of an incidentally detected adrenal schwannoma.
Case
A 67-year-old gentleman had an ultrasound imaging of the abdomen that incidentally revealed a large right adrenal mass prompting referral to the endocrinology service. His past medical history included myocardial infarction and hypertension. There were no clinical features suggestive of hormonal excess and his blood pressure was well controlled on medications. CT scan revealed a 15cm cystic lesion that was heterogenous in appearance not invading any adjacent structures, although the images suggested some pressure effects on the bowel and kidney. Endocrine tests confirmed non-functional status. FDG PET scan was undertaken in view of the lesion size and characteristics, and it confirmed the cystic swelling with foci of calcification. There was heterogenous moderate activity (SUV max up to 6.2) in the solid components, mimicking malignancy.
Management
Open right adrenalectomy was performed, and post-op recovery was uneventful. Histopathology revealed a smooth outer surface, with a calcified capsule. There were areas of Antoni A and B cells, which helped determine schwannoma and the type. Ancient degenerative cystic changes were present as well as cellular polymorphism and nuclear atypia, both of which made it hard to distinguish the tumour from malignancy. Immunohistochemical analysis revealed presence of several markers (S100, p16, SOX10) suggestive of a schwannoma tumour. The tumour also presented with a low proliferation index (ki-67), which also coincides with schwannoma in keeping with previous studies.
Discussion
Adrenal Schwannomas are rare and only around 80 cases have been documented in the literature. Furthermore, a diameter of 15cm makes this tumour one of the largest described. Diagnosis could only be determined after operation following immunohistochemical and histopathological analysis.

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P180

The golden ratio for cortisol replacement

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Current cortisol dosing regimes for patients with adrenal insufficiency are unable to accurately replicate the physiological profile of healthy patients. This work is part of an interdisciplinary study with the aim of using mathematical approaches to understand the treatment strategies for patients with adrenal insufficiency. We also aim to then tailor treatments specific to an individual or situation. We present a simplified model of hydrocortisone delivery via intravenous bolus (IV) and continuous intravenous infusion (CIV). The model is formulated in terms of linear kinetics and considers the dynamics of glucocorticoid-protein binding. We utilise the disparity of system rates to simplify our model. In the case of IV dosing, we can divide the model into 2 regions which includes finding a balance equation to describe behaviour for all time after the dose has been delivered. We aim to fit this simplified model to patient response data to estimate model parameters. This should allow us to optimise and personalise treatment strategies to work out what works best for specific patients. When a high dose of hydrocortisone is delivered, we find a famous mathematical quantity, The Golden Ratio, appears in the level of binding protein. The objective of this analysis is to fit our model parameters to recently published data on 50mg dosing every 6 h (or a 200mg continuous infusion) using Bayesian inference with the software Stan.

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P181

Ectopic ACTH secretion (EAS) presenting with hypokalemia and succumbing to Covid-19

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Introduction
EAS is an endocrine emergency requiring emergency diagnosis/treatment. Bronchial carcinoid is known to cause EAS and carcinoid syndrome (without liver involvement).
Clinical features
58-year-old lady with COPD and fibromyalgia referred as 2WW pathway with abdominal pain, diarrhoea, and weight loss. Investigated with CT-CAP: inflammatory looking 7mm lung nodule left upper lobe, enlarged left hilar, aorto-pulmonary, pre-tracheal and sub-carinal nodes without any intra-abdominal lesion. Lung MDT: rescan/discuss. Diarrhoea settled and she slowly gained weight. After 3 months admitted with fatigue and oedema legs with severe hypokalemia (not on any drugs causing hypokalaemia). Potassium - normal during earlier work-up - marginally normalised with oral and intravenous supplements. Endocrine review: Aldosterone <55 pmol/l, renin 0.5 nmol/l/h. Cortisol 1673 and 2199 nmol/l. 24-h urine free cortisol 38987 nmol/24hr. ACTH 101 ng/l. Patient had proximal myopathy, easy bruisability, and a new diagnosis of hypertension and diabetes without central obesity, purplish striae, or osteoporosis. Diagnosis - ACTH dependent Cushing. MRI pituitary – normal. Ectopic ACTH secretion (EAS) considered. With history of diarrhoea, weight loss, and lung nodules, possible bronchial carcinoid with carcinoid syndrome and EAS considered. Lung MDT planned for urgent FDG-PET. While awaiting, developed covid pneumonia and succumbed.
Discussion
EAS patients often have a shorter disease course, severe hypercortisolism, and life-threatening comorbidities including thromboembolism, hyperglycemia, hypertension, hypokalemia, infection, muscle wasting, osteoporosis, and steroid psychosis. Most have resistant hypertension and one-third have diabetes. Due to pronounced catabolism, weight gain and central obesity may not be present. EAS require simultaneous treatment of steroid induced comorbidities, cortisol

lowering drugs and specific etiological treatments with rapid and complete excision of ACTH-secreting tumor. If this is not feasible, pharmacological agents and bilateral adrenalectomy are advised. Covid-19 is a severe disease with high risk of progression to ARDS, high morbidity, and mortality in patients with active CS.

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P182

Clinical challenges in the biochemical evaluation of Pheochromocytoma: A case report of pseudo-pheochromocytoma in a patient with Obstructive Sleep Apnoea(OSA)

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The diagnosis of Pheochromocytomas often poses a great challenge. We report a case of pseudo-pheochromocytoma causing challenges in the clinical diagnosis. A 35-year old gentleman with high BMI, was admitted with worsening headache, visual field defects and accelerated hypertension. MRI pituitary and biochemical profiling revealed a non-functioning pituitary macroadenoma with optic chiasm compression, warranting urgent surgical intervention, vindicating an endocrinology referral and in parallel, investigating for secondary hypertension. Initial investigations were highly suggestive of Pheochromocytoma, including a significantly elevated 24-h urinary catecholamines and subsequent MIBG scan showing bilateral positive tracer uptake. CT adrenals however did not identify any lesions. Discordant results engendered further exploration to identify the presence of confounding factors including preanalytical drug interference. No medication interferents were identified. On the contrary, he was identified as high risk for obstructive sleep apnoea (OSA) and subsequently, he was started on home non-invasive ventilation. Two different plasma metanephrines samplings came back within normal limit, leading to confidence of proceeding to Trans-sphenoidal surgery safely. 24-h urinary catecholamines sampling was repeated to check on OSA as a confounding factor for the discrepant results. Guidelines recommend the measurement of plasma or 24 h urinary metanephrines as the initial biochemical test, positive tests to trigger further urgent investigations, as delay in treatment is often debilitating. The supraphysiologic effects of endogenous catecholamines in OSA is well-established, acknowledging it as an independent confounding factor in biochemical assessment of pheochromocytomas. Overlapping clinical features like headaches and hypertension are common, thereby making the diagnosis more challenging. Clinical symptoms, blood pressure and catecholamine levels tend to improve with treatment of the OSA. This case highlighted the importance of identifying confounding factors prior to organising expensive biochemical investigations and imaging studies, and hence endorsing the pitfalls involved in the diagnosis of this challenging condition deservedly known as' the great masquerader".

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P183

The management of adrenal incidentalomas referred to the adrenal radiology meeting at heartlands hospital in 2021

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Background
An adrenal incidentaloma (AI) is an adrenal lesion found on imaging performed for an indication other than adrenal disease. The current European Society of Endocrinology guidelines recommend that all AIs are discussed in a dedicated adrenal multidisciplinary meeting.
Method
We evaluated the outcomes of AI cases referred to the Adrenal Radiology Meeting (ARM) at Heartlands Hospital between January 2021 and December 2021 using a local database. Imaging reports, as well as clinical and laboratory data were reviewed.
Results
178 patients were referred from different specialities across the Trust for discussion in the ARM. The mean age of patients in this cohort was 64 years, of which 56% were female. 75% of patients (134/178) had benign, non-functional adrenocortical adenomas or other benign lesions, such as myelolipoma (6 patients). Three patients were diagnosed with unilateral adrenal haemorrhage. Hormonal evaluation was carried out for 98/178 (56%) patients, of which 52 patients had an indeterminate lesion by imaging. 23 of these patients had raised normetadrenaline results, of which 2 had confirmed phaeochromocytoma by MIBG scan and post-operative histology. 29/98 (30%) patients failed the overnight dexamethasone suppression test (ONDST); 2 had ACTH-independent Cushing's syndrome, 6 had definitive and 21 had possible mild autonomous cortisol secretion. 22/29 patients that failed the ONDST had relevant, associated co-morbidities including diabetes mellitus, hyperlipidaemia, hypertension and obesity. Two patients had non-classic congenital adrenal hyperplasia (CAH) and one had adrenocortical carcinoma. There was no biochemical diagnosis of Conn's syndrome.
Conclusion
Each patient with an AI should be discussed in an adrenal meeting/MDT and undergo a clinical and biochemical assessment. Although, the majority of patients with AIs have benign non-functional lesions, a small percentage of patients have functional lesions that often require surgical treatment and should not be missed.

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P184

Prednisolone replacement therapy is associated with significant weight loss in patients who switch from hydrocortisone with adrenal insufficiency

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Background
Adrenal Insufficiency (AI) is a life-threatening disorder caused by dysfunction of the adrenal axis (primary AI) or of the hypothalamic-pituitary-adrenal axis (secondary AI). Both result in glucocorticoid deficiency, requiring life-long replacement, with additional mineralocorticoid replacement required in primary AI. However, accurately reproducing the endogenous circadian and ultradian rhythm of cortisol secretion is challenging. Current Endocrine Society guidelines recommend either hydrocortisone (thrice-daily) or once-daily prednisolone (3-5mg). Concerns around adverse metabolic outcomes associated with prednisolone have been based on evidence using higher prednisolone doses. We have used low-dose (2-4mg) prednisolone once-daily since 2014 for glucocorticoid replacement in adults with AI. Since 2018 we have prospectively audited patients switched from hydrocortisone to prednisolone, and from prednisolone to hydrocortisone (HYPER-AID study (NCT03608943)).
Methods
Patients were clinically followed up at for least 4 months following the switch prior to repeat measurements being taken. Data was analysed using Microsoft Excel and GraphPad Prism version 9.3.1 (GraphPad, San Diego, CA,). Significance was assessed using paired t-tests, with significance defined at $P<0.05$.
Results
Of the 23 patients who have completed both visits, 12 switched from hydrocortisone to prednisolone, and 11 from prednisolone to hydrocortisone. The mean weights of patients on hydrocortisone and prednisolone were 80.2kg and 77.7kg respectively, with a difference of 2.6kg ($P<0.01$). In those who switched from prednisolone to hydrocortisone, there was a significant weight gain of 3.2kg ($P<0.004$).
Discussion
The mechanism of the weight loss found with prednisolone may be due to overall less glucocorticoid exposure or because it mimics a more physiological circadian profile, avoiding supraphysiological cortisol levels later in the day. Once-daily low-dose prednisolone in the treatment of adrenal insufficiency is safe. Preliminary results of the HYPER-AID study suggest that prednisolone may have a beneficial effect on weight in those who are switched from hydrocortisone.

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P303

The hidden duo: phaeochromocytoma and primary peritoneal metastatic carcinoma unmasked

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A 71-year-old woman was referred to the urology department with macroscopic haematuria. An ultrasound scan revealed a suspicious solid mass measuring 6.6cm arising from the left kidney. Subsequent CT scan confirmed the presence of a left adrenal mass along with omental and peritoneal disease and small-volume ascites. The patient was referred to the adrenal surgeons for consideration of left adrenalectomy in view of suspected adrenal cancer. At the surgical outpatient department, the patient reported experiencing palpitations and occasional headaches. She had a history of hypertension and was taking verapamil and perindopril. Her blood pressure was 185/105mm Hg, raising suspicion of phaeochromocytoma. Hormonal testing revealed elevated levels of 24-h urine normetanephrine (17.9 µmol/24h; reference range: 0.6-3.5) and urine metanephrine (72.8 µmol/24h; reference range: 0.2-1.5), confirming the diagnosis. The patient was referred to the adrenal and upper gastrointestinal multidisciplinary teams (MDT). The adrenal MDT concluded that the imaging findings were consistent with adrenal involvement and peritoneal disease, likely malignant. An ultrasound-guided biopsy of the peritoneal lesion was recommended. Meanwhile, the patient was seen in the endocrinology clinic and started on doxazosin while continuing verapamil. No significant omental thickening suitable for biopsy was identified. Instead, a biopsy was taken from the left adrenal lesion, confirming the morphological features and immunohistochemical profile of phaeochromocytoma. The differential diagnosis included primary peritoneal malignancy with adrenal metastases, malignant phaeochromocytoma, or dual pathology. A MIBG scan was performed, showing increased uptake in the left adrenal mass consistent with phaeochromocytoma. Omental and peritoneal disease was not observed PET CT scan revealing hypermetabolic phaeochromocytoma, FDG-avid peritoneal and omental disease, and multiple bony metastases. The biopsy of omental lesion confirmed serous adenocarcinoma of primary peritoneal or ovarian origin. The patient was referred to the oncology department for chemotherapy, but unfortunately developed bowel obstruction and passed away at home.

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P304

Assessment of adrenal incidentalomas: Benefits of a nurse-led clinic

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Background
Adrenal incidentalomas (AI), the finding of asymptomatic adrenal lesion on unrelated imaging, represent an increasing number of endocrine referrals. In 2022, we introduced a nurse-led pathway to manage AI.
Aim
To assess the cost savings and patient experience of a telephone nurse-led AI service at Musgrove Park Hospital.
Methods
Records for patients seen in the AI clinic from 1/4/22 to 1/4/23 were assessed. The clinical outcome, number receiving consultant follow up and resultant cost saving were calculated. Subsequently, 10 of these patients were randomly selected and asked for feedback via telephone consultation. They were asked to score out of 5 questions relating to their satisfaction with the service, understanding of why they were contacted, ease of the biochemical tests and knowledge of who to contact with further questions.
Results
104 patients were referred through the AI pathway during the 12 months. 54 required a further characterisation scan. 58 patients were discharged with telephone specialist nurse appointments only. 28 patients have not attended or are awaiting biochemical test results. 18 patients were referred on to be seen by a consultant or registrar in clinic. This resulted in a provisional cost saving of 20%, which is likely to be closer to 25% when outstanding patients results are reviewed. Of the 10 patients interviewed, there was a high degree of satisfaction ($n=4.2$, where n is the average score out of 5 for the question), and patients generally understood why they were being contacted ($n=4.1$). The biochemical tests were also broadly thought to be easy to undertake ($n=4.3$). Fewer patients were certain who to contact with further questions ($n=3.0$).
Conclusion
A nurse led clinic is a method for managing AI referrals that is both cost-effective and convenient for patients. Increased information on who to contact if there are questions can be provided.

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P305

Abstract withdrawn

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P306

The heterogeneous spectrum of adrenal ganglioneuromas: two interesting cases

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Introduction
Ganglioneuromas (GNs) are rare, benign tumors, arising from neural crest cells. Their incidence amongst adrenal masses is 0.3%-6%. The majority are incidentalomas and hormonally inactive but a subset may cause compressive effects. Presentation in the context of genetic syndromes (NF1/NF2, RET, MAX, Von Hippel Lindau disease) has been reported. We present two cases of adrenal GNs: Case 1. A 31-year-old female patient who presented with a history of early pregnancy loss at 9 ½ weeks. During a therapeutic dilatation and curettage, she developed persistently high blood pressure. Further work-up showed a large heterogeneous tumor with microcalcifications in the left adrenal gland. It compressed the left renal veins and the inferior vena cava. Endocrine evaluation was negative for hormonal hypersecretion. The patient underwent an open left adrenalectomy and nephrectomy. Histology revealed a left adrenal mature ganglioneuroma with dominant schwannian stroma. Her postoperative course was uneventful and she remains asymptomatic and normotensive during a 50-month follow-up. Case 2. A 37-year-old male patient was admitted to the hospital because of left abdominal pain and haematuria. Computer tomography demonstrated a 4 cm right adrenal lesion. Despite that urine catecholamines were elevated the patient did not present arterial hypertension or flushing. After appropriate alpha and beta blockade he underwent laparoscopically a right adrenalectomy. Histology revealed a 4.5-cm mass with components of phaeochromocytoma and ganglioneuroma, thus a composite phaeochromocytoma. His post-operative course was excellent and he remains asymptomatic 60 months later.
Conclusion
We describe two challenging cases of a) a giant adrenal GN that compressed the left renal vein and presented with hypertension and b) a composite phaeochromocytoma-ganglioneuroma that presented with abdominal pain and haematuria. The extension of ganglioneuroma in the first case and the concurrence with a clinically silent phaeochromocytoma in the second case, highlight the fact that adrenal GNs can be diagnostic chameleons.

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P307

Unique case of pembrolizumab induced adrenal suppression

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We present a unique case of Pembrolizumab induced adrenal insufficiency. A 65 year old lady was admitted with septic shock secondary to chest infection. She was 3 weeks post neo adjuvant chemotherapy plus immunotherapy for triple receptor negative solitary Right sided breast cancer. She has Type II Diabetes mellitus, hypercholesterolemia and varicose veins. She takes Metformin and Atorvastatin. She is single, with no significant family history. On intravenous antibiotics her biochemical parameters improved, however she remained very unwell with persistent nausea, dizziness. Her 9 am Cortisol was noted to be low at 52 nmol/l. She was immediately started on steroids and her clinical condition improved over the next 24 h. A full pituitary profile has been requested, ACTH report awaited. A short Synacthen test confirmed adrenal insufficiency, 9am Cortisol 76 nmol/l with Cortisol values of 133 nmol/l and 138 nmol/l at 30 and 60 minute intervals post Synacthen respectively. She was advised about long term steroid use and precautions. Pembrolizumab is an immune checkpoint inhibitor used in the treatment of various cancers. Pembrolizumab induced adrenal insufficiency is autoimmune mediated affecting the pituitary gland. The incidence of adrenal insufficiency is reported after the Pembrolizumab is used for various

months. This is a unique presentation in our case, as the patient received a single doses of Pembrolizumab and developed adrenal insufficiency.

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P308

Exploring the impact of unilateral adrenalectomy on health-related quality of life: a retrospective audit

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Introduction
Laparoscopic unilateral adrenalectomy (UA) is a frequent approach in managing patients with structural and functional adrenal disorders. Suboptimal assessment post-operatively can result in multiple adverse consequences, including adrenal insufficiency. However, the optimal post-operative assessment and long-term effects on physical and mental health have not been sufficiently documented. This study aims to investigate the long-term effects of UA on the health-related quality of life (HRQoL) of patients with adrenal pathologies.
Methodology
For this retrospective audit, we identified patients who had undergone the procedure for endocrine and non-endocrine indications over the last seven years. All eligible candidates were contacted by telephone and invited to participate in this HRQoL survey. We used the 12-Item Survey (SF-12) to evaluate the scores of the physical- (PC) and mental-health components (MC). Moreover, participants were asked for information regarding the intake of steroids after the surgery.
Results
We audited 163 patients, 18 were reported as deceased and 75 agreed to participate. The most common PC-complaints were limitations in what they accomplished (42.7%) and their physical activities (38.7%). Regarding MC, only 36% felt they accomplished less than desired, with 48% reporting variable feelings of depression. The HRQoL scores differed according to the indication for surgery (phaeochromocytoma vs incidentaloma vs adrenal-related malignancy, MC: 49.2 ± 13.0 vs 48.5 ± 13.6 vs 43.6 ± 17.8, P-value $= 0.679$ and PC: 47.3 ± 9.6 vs 38.5 ± 12.9 vs 44.2 ± 7.6, P-value $= 0.089$). Patients operated for phaeochromocytoma had better PC scores than those operated for adrenal incidentaloma (P-value $= 0.031$). We also found a difference in steroid requirements post-operatively, comparing phaeochromocytoma vs adrenal incidentaloma patients (post-op steroid use, permanent 0% vs 36.8%, never 100% vs 63.2%, p value $= 0.017$).
Conclusion
In order to better improve health outcomes for UA patients, adopting a multidisciplinary approach is required not only for optimal HRQoL post-surgery, but also to ensure optimal steroid use when needed.

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P309

The diagnostic dilemma of discordance between cross-sectional imaging of an adrenal mass and adrenal vein sampling: a case report

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Introduction
We present a case of primary aldosteronism (PA) with adrenal mass, where lateralization of aldosterone production by adrenal-vein sampling (AVS) was discordant with cross-sectional imaging. We highlight an approach to investigation of PA using functional nuclear imaging, and show that subclinical cortisol excess may impact the reliability of AVS.
Case
70 year old female with 2.6 cm left-sided adrenal mass, with previously normal biochemical work-up. She subsequently developed hypertension, and was re-investigated. She had an elevated ARR of > 327 (< 60 pmol/mIU), 24-h urine cortisol of 64.3 (< 229.9 nmol/day), and ACTH of 7.5 (2.0-11.5 pmol/l) with undetectable DHEAS (0.3-6.0 umol/l). AVS was pursued, which lateralized to the right. Lateralization by AVS is the ratio of adrenal vein aldosterone concentrations normalized by respective cortisol concentrations. Thus, cortisol co-secretion from an adrenal mass could make AVS point to the wrong adrenal. On the basis of the interpretation rule previously suggested to detect subtle tumoural cortisol production[1], cortisol co-secretion was suspected to explain the unexpected lateralization results. Dexamethasone-suppressed NP59-iodocholesterol adrenal scintigraphy showed uptake into the left adrenal, with no activity within the right adrenal. The patient consequently underwent left adrenalectomy. Pathology showed an adrenal cortical adenoma with zona glomerulosa hyperplasia. Post-operatively, the patient had a complete clinical and biochemical response by PASO criteria and her ACTH increased compared to pre-operative levels at 14.6 pmol/l.
Conclusions
Though currently the 'gold-standard' for detecting unilateral PA, and critical in the work-up for possible adrenalectomy, lateralization of aldosterone excess by AVS is susceptible to pathologic cortisol production asymmetry. We hypothesize that subtle cortisol excess may explain a proportion of cases with AVS-imaging discordance, and propose that functional imaging can help localize autonomous adrenal hormone production, and guide surgical decision making.
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P310

Unilateral nonhemorrhagic adrenal infarction presenting as acute abdomen in a pregnant woman

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Introduction
Diagnosing acute abdominal presentations in pregnant women poses challenges due to the physiological and anatomical changes during pregnancy. The differential diagnosis is broad, encompassing both obstetric and non-obstetric causes. Among the rare occurrences, nonhemorrhagic adrenal infarction presents a particularly unusual scenario, lacking established guidelines for management and follow-up. We discuss a case of nonhemorrhagic adrenal infarction manifesting as acute abdomen during pregnancy, accompanied by a comprehensive review of existing literature.
Case
A 24-year-old woman ($34 + 5$ weeks, primigravida) presented with sudden and severe upper abdominal pain, radiating to back. Initial blood tests showed normal results. The patient had no prior medical history and no family record of thrombotic disorders. A CT angiogram of aorta revealed findings consistent with nonhemorrhagic right adrenal gland infarction. Her thrombophilia screen (including Protein C & S (a low protein S is a normal physiologic phenomenon in pregnancy), Factor V, anti-thrombin, Lupus anticoagulant, anticardiolipin IgM & IgG) and autoimmune screen was negative. A 0900 am cortisol level was 514 nmol/l. Anticoagulation therapy was initiated for a duration of 3 months. At 37 weeks gestation, the patient underwent an elective Caesarean section and delivered a healthy baby. A 6 months follow up is planned, involving repeat CT adrenals and assessment of adrenal function.
Conclusion
Pregnancy is a hypercoagulable state, and women are at a 4- to 5-fold increased risk of thromboembolism during pregnancy. Instances of adrenal infarction during pregnancy are scarcely documented in medical literature. A heightened degree of suspicion is essential for accurate diagnosis. Given the rarity of this condition, comprehensive guidelines for subsequent management remain lacking. It is crucial to acknowledge that, due to inherent risks associated with anticoagulation, it is advisable to adopt a personalized, multidisciplinary approach for management of such patients.

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P311

Autoimmune adrenal cortex insuffiency induced cardiomyopathy - A case report and literature Review

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We are reporting a 33 years old female, known case of primary adrenal failure who presented to our emergency department feeling generally unwell, lethargic

and short of breath, She found to be hypothermic, hypotensive and hypoglycaemic. ECG showed low voltage QRS complex with prolonged QT intervals and ECHO confirmed moderate to severe left ventricular dysfunction with features of 'broken heart' and ballooning suggestive of Takusobo cardiomyopathy. In our case report, glucocorticoid replacement therapy led to near full recovery and restoration of normal cardiac function. Primary adrenal failure associated cardiomyopathy is a rare manifestation, challenging clinical dilemma and a life threatening condition, high clinical index and proper management could result in complete recovery. we are discussing the case and reviewing the literature of this rare cardiac manifestation of adrenal crisis.

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P312

The investigation and management of adrenal incidentalomas at guy's and St Thomas's NHS foundation trust

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Background
Rapid improvements in imaging have led to a 10-fold increase in the incidence of adrenal incidentalomas (AIs) over the past two decades. Delays in the diagnostic evaluation of AIs are associated with patient anxiety and significant burden on medical resources. We retrospectively audited the investigation and management of AIs at Guy's and St Thomas's NHS Foundation Trust (GSTT).
Methods
Patients with newly identified adrenal incidentalomas, discussed at the weekly adrenal multidisciplinary team meeting (MDM) at GSTT between 1st January to 31st March 2022, were reviewed. Data was collected by using Electronic Patient Record and e-Noting.
Results
Of the 139 patients discussed, 100 patients were excluded (non-adrenal pathology, referral due to abnormal investigations, re-referrals); therefore 39 patients were included in data analysis. 82% of patients were referred to the MDM by endocrinology; the remaining referrals were from non-endocrine specialties including urology and gastroenterology. 48.7% of patients had a non-functioning adenoma, 30.8% of patients had a functioning adenoma. The table shows the proportion of functional tests sent before the MDM discussion by endocrinology and non-endocrine specialties:

	Percentage of tests sent by endocrinology (%)	Percentage of tests sent by non-endocrine specialty (%)
Plasma/Urinary Metanephrines	56.3	14.3
Aldosterone-Renin Ratio	71.9	14.3
Urinary Steroid Profile	3.1	14.3
Overnight Dexamethasone Suppression test	71.9	0

Conclusion
Our results highlight a significant disparity in the proportion of functional tests sent off by non-endocrine specialties before the MDM in comparison to endocrinologists. This has subsequently led to delays in decision-making about the management of AIs. We intend to implement a Trust-wide A4 guideline aiming to educate non-endocrine teams on how to initially investigate AIs. This would therefore increase the proportion of functional tests performed before MDM referral, and improve the efficiency of the AI pathway at GSTT.

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P313

An unusual cause of secondary HTN

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We present the case of a 32-year-old gentleman who was reviewed in the endocrinology clinic for hypogonadotropic hypogonadism and he was investigated for persistent HTN. His only symptoms were anxiety and palpitations. We have controlled his blood pressure with doxazosin 10 mg BD and bisoprolol 1.25 mg OD. Investigations: bloods (Jan 23) normetanephrine:3,460 picomole/l, metanephrine:120 picomole/l, aldo/renin ratio: 92, TSH 2.3, prolactin 307, IGF-1: 26,6, testosterone: 5,9 nmol/l. CT Adrenal was normal. NET MDT recommended a MIBG scan and it showed possible mass near the bladder. MRI pelvis prostate showed a partially cystic lobulated lesion measuring 3.9 x 4.2 x 3.2 cm which is closely related to the left superior bladder, but is extra mucosal/perivesical. This has some malignant features and in the context of MIBI uptake is entirely consistent with a pheochromocytoma. Genetic testing has revealed that our patient was heterozygous for a pathogenic FH variant which causes hereditary paragangliomas/pheochromocytomas (HPP). In his case it's important to test his relatives for HPP. He underwent surgical resection in July 23 and his histology report is still awaited.
Conclusion
Primary paraganglioma of the urinary bladder is very rare, making up less than 0.05% of all bladder malignancy [1]. It is thought to arise from embryonic rests of chromaffin cells within the bladder wall, and it can present with various complications like paroxysmal hypertension, hematuria, therefore many are misdiagnosed due to lack of specificity. [2] A lesson learnt, to be open to look for other conditions while presenting with another diagnosis, hypoandrogenism in this case.
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P314

Case of insulinoma – non surgical therapy

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Background
The gold-standard therapeutic approach for benign insulinoma is surgery. If surgery is not feasible, minimally invasive ablative procedures by interventional radiology can lead to partial or complete remission of hormone hypersecretion and tumour control.
Summary
72-year-old woman, admitted with recurrent hypoglycaemia with whipple triad symptoms and presyncopal attacks for 5 weeks, relieved by eating carbohydrates. Investigations showed high insulin and c-peptide levels at low glucose level of 1.9mmol/l. MEN-1 screen showed normal calciumand prolactin levels. CT abdomen showed focal arterial enhancement in the head of pancreas (13 mm). Hypoglycaemia improved with Diazoxide, but patient developed lower limb oedema (side effect of diazoxide). So Bendroflumethiazide was prescribed to reduce oedema. Surgical treatment was discussed in NET MDT and Pancreaticoduodenectomy was offered as enucleation of insulinoma was not an option as the lesion was deep-seated. However the patient was high risk of mortality rate (10%), for the surgery because of high BMI (>50) and short neck. Therefore Trans-arterial embolization of Gastroduodenal artery for pancreatic head neoplasm was offered. Diazoxide stopped a day prior to procedure and procedure remained uneventful. She didn't have further hypoglycaemia during 6 month follow up. Libre2 CGM, Ambulatory glucose profile (self-funded) showed normal blood sugars. From literature there is a small risk of recurrence ~16% after chemoembolization and hence further surveillance was considered. Her follow up image after 3 months showed complete resolution of the lesion. A planned yearly follow up with imaging surveillance was considered. She was advised to check capillary blood sugars if she develops any hypoglycaemia symptoms.
Conclusion
It is important to involve Multidisciplinary team (endocrinologist, physicians, surgeon, dietician and radiologist) to decide best treatment options for insulinoma. Minimally invasive ablative procedure can lead to complete remission of hormone hypersecretion and tumour control in patients with a high risk for surgery.
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P315

New onset adrenal insufficiency post-astrazeneca vaccine

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The COVID-19 vaccine plays an important role in managing the pandemic. Unfortunately, there are endocrine side effects also noted. The 36-year-old lady felt unwell 2 weeks post-AstraZeneca COVID-19 vaccine. She got admitted to the hospital after 6weeks with persistent vomiting and significant hyponatremia. She has a past history of well-controlled asthma and hypothyroidism. Random cortisol on admission was 31 nmol/l, and a short synacthen test(SST) confirmed adrenal insufficiency. She was on steroid inhaler at this stage. Repeat SST, after withholding steroid inhaler, was consistent with adrenal insufficiency. She was treated with IV hydrocortisone during admission and discharged on oral prednisolone. On further workup, adrenal auto-antibodies were negative. MRI(adrenals) showed normal adrenal glands. There was no evidence of pituitary adenoma on the MRI(pituitary) with the normal pituitary biochemical profile. Previously, cases were reported with Covid vaccine-induced immune thrombocytopenia and thrombosis, leading to adrenal haemorrhage and infarction. Notably, the AstraZeneca vaccine has been recognized as a cause of adrenal crisis in known adrenal insufficiency. Furthermore, a case report of new-onset adrenal insufficiency in patients with COVID-19 has been reported. Regarding the pathophysiology of COVID-19, S glycoprotein binds to ACE2 receptors in many tissues, including lungs, heart and blood vessels, adrenal glands, etc. On the other hand, AstraZeneca Vaccine comprises chimpanzee adenovirus(ChAdOx1) vector encoding S glycoprotein of SARS-CoV-2. In our case, the pathophysiology is unclear, but arguably, there might be the likelihood of S glycoprotein from AstraZeneca Vaccine binding to our patient's adrenal gland and attributing to adrenalitis.

Conclusion

In this interesting case, we can conclude that it was due to possible adrenalitis associated with the COVID-19 vaccine.

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P316

Deciphering atherosclerosis: unravelling spatial lipid heterogeneity through advanced MALDI-MSI profiling in rabbit aortic and human carotid artery plaques

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Atherosclerosis, a multifaceted cardiovascular disease characterised by fatty plaque buildup in large and medium-sized arteries, is a leading cause of heart attacks, strokes and peripheral arterial disease. Its global impact on morbidity and mortality rates poses a significant health challenge. This study aimed to comprehensively understand its complex pathogenesis using histologically aided Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI-MSI) to elucidate the spatial lipid profiles in rabbit atherosclerotic aortas and human carotid artery plaques. Rabbit aortas were harvested from male New Zealand White rabbits (aged 6-9 months, $n=6$) following double-balloon injury to the abdominal aorta and maintenance on a high-cholesterol diet (0.2%) to induce atherosclerosis. Human carotid artery plaques were collected ethically from NHS patients (men aged 50-80y $n=5$) undergoing Carotid Endarterectomy. MS images were co-registered with histopathological images to define important plaque features. Orthogonal Partial Least Squares for Discriminant Analysis (OPLS-DA) and variable importance in the projection (VIP) scores (>1.0 considered significant) were used to highlight potential markers and differences between plaque features. These include neointima and media in rabbit aortas, fibrous cap, and necrotic core in human plaques. The lesions were characterised by a high abundance of sphingomyelins, cholesterol esters and phosphatidylcholines, among other lipid classes. In both rabbit and human plaques, the most abundant lipid was sphingomyelin (34:1), observed in macrophage-rich regions, supporting their role in promoting lesion inflammation. Phosphatidylinositol (38:4) (VIP score = 1.47) and phosphatidylcholine (34:2) (VIP score = 1.91) distinctly differentiated rabbit aortas (media and neointima, respectively), whilst, in human plaques, phosphatidylcholine (34:2) (VIP score = 1.45) and lysophosphatidylcholine (16:0) (VIP score = 2.14) enriched the fibrous cap and necrotic core, respectively. This comparative study of an early-stage rabbit model and human pathology highlighted the translational relevance of animal models in atherosclerosis research while showcasing MALDI-MSI as a tool for spatial lipidomic profiling.

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P317

Predictors of morbidity in autoimmune adrenal insufficiency

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Adrenal crisis (AC) is an acute life-threatening emergency contributing to excess mortality in patients with autoimmune adrenal insufficiency (AAI). Clinical, demographic and educational factors associated with high rates of AC admission remain unclear. We therefore examined the long-term clinical course of 91 patients with AAI.

Methods

A retrospective observational study of 91 patients with AAI was performed. Electronic health records (Trakcare systems US), laboratory data and national death and deprivation repositories were linked. Patient questionnaire was performed examining emergency injectable glucocorticoid availability, Sick Day Rule (SDR) delivery and understanding. Poisson regression modelling (R version 4.22) was performed to examine explanatory variables against admission rate for infection, collapse and AC.

Results

Median follow-up was 13.5 years (IQR 9.6–15.2). Increasing deprivation, lower clinic sodium (IRR 0.93; 0.88–0.98/mmol) and fludrocortisone dose (IRR 1.46; 1.25–1.70/50mg) were strongly, independently associated with rate of hospital admission ($P<0.05$). 88 patients completed a questionnaire. 67(76%) had access to emergency intramuscular hydrocortisone, this was only within use-by date in 57(64%) and only carried regularly by 21(24%). Knowledge of SDRs was variable; 69/88(78%) correctly treated minor illness and only 36/82(43%) correctly treated severe illness. Patients who recalled SDRs from their endocrine appointment had a significantly lower incidence of admission (IRR 0.72; 0.54-0.95 $P<0.05$).

Conclusion

Chronic hyponatraemia and higher adrenal replacement therapy doses at clinic review are associated with a higher risk of hospital admission risk while SDR delivery was associated with a reduced risk. Expanding delivery and understanding of SDRs as well as encouraging treatment concordance may reduce risk of hospital admission.

Predictors	Incidence rate ratios	CI	p
Most deprive 2 quintiles	1.37	1.03–1.81	0.03
Mean hydrocortisone dose (per 5mg)	1.06	0.94-1.19	0.309
Mean sodium level (1mmol/l)	0.93	0.88-0.98	0.009
Fludrocortisone dose (per 50 mg)	1.46	1.25-1.70	<0.001
SDRs covered	0.72	0.54-0.95	0.019

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P318

LH-dependent female testosterone excess persisting after bilateral oophorectomy

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A 55-year-old post-menopausal female presented with hirsutism and increased libido. Testosterone was elevated at 9.7 (RR <1.8 nmol/l). LH/FSH were appropriate post-menopause (LH 28.8; FSH 54.1U/l). DHEAS, androstenedione and 17-hydroxyprogesterone were unremarkable. GnRH analogue suppression testing (GnST) appropriately suppressed LH/FSH and testosterone (testosterone 0.2 nmol/l), suggesting an LH-dependent source of testosterone. Pelvic MRI suggested a left ovarian tumour. This was felt by gynaecology to require urgent resection and, also noting a presumed likely ovarian source for her excess testosterone production, bilateral salpingo-oophorectomy was performed. Histology demonstrated bilateral stromal hyperplasia without hyperthecosis and hilar Leydig cells but no tumour. At the time of oophorectomy, LH and FSH remained suppressed post-GnRH analogue. As this suppression wore off, LH/FSH increased. Unexpectedly, testosterone also rose, to 5.3 nmol/l, with a return of hyperandrogenic symptoms. Repeat GnST again demonstrated suppression of testosterone, continuing to suggest LH-driven production. Low-dose-dexamethasone-suppression testing did not affect testosterone

(while appropriately suppressing cortisol). The pelvic MRI had suggested a left adrenal mass. Dedicated adrenal CT demonstrated a 14mm nodule. No other radiological abnormality was seen to suggest ectopic ovarian tissue. 11C-metomidate PET/CT demonstrated tracer avidity within the adrenal lesion, suggesting adrenocortical tissue. Suppression testing excluded autonomous production of cortisol or aldosterone. Urine steroid profiling was unremarkable. Adrenal vein sampling demonstrated markedly higher testosterone levels from the left adrenal vein than either IVC or the right adrenal vein, raising the possibility of a left adrenal source for the testosterone. Interestingly, the size of the adrenal nodule changed on serial CT (14mm – 10mm – 12mm), with the size reduction occurring after the two GnSTs (12 and 6 months prior to scan). The subsequent re-enlargement was seen 9 months later. This is an intriguing case of LH-dependent female testosterone production, persisting after bilateral oophorectomy, suggesting a rare LH-responsive adrenal source.

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P319

Selective non-lipogenic ABCA1 inducer, CL2-57, affects cholesterol efflux pathways and adrenocortical cancer cell migration in 2D and 3D spheroid models

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Adrenocortical carcinoma (ACC) is a rare tumour with a poor prognosis. There are a lack of successful targeted therapies and an urgent need to explore novel therapeutic avenues for ACC [1]. In other cancer types, there has been some success in exploiting lipid metabolism. One example is manipulating intracellular cholesterol levels to starve cancer cells. [2] Another possibility is targeting the ligand-dependent nuclear receptors Liver-X receptors (LXRab), which act as master regulators of lipid metabolism.[3] Despite the potential for beneficial effects of LXR therapies, the complexity of LXR signalling (e.g. LXRb-regulates cholesterol efflux via ABCA1 and APOE and LXRa regulates lipogenesis via SREBP1, FAS), this has in part hindered systemic LXR therapies due to potential adverse effects due to hepatic lipogenesis. The recent development of non-lipogenic selective ABCA1 inducers, which target cholesterol efflux pathways, poses an attractive alternative approach.[4] In this study, we used the ACC cell line H295R, in 2D and 3D culture models, to test the effects of the ABCA1 inducer CL2-57 on adrenal ABCA1 gene expression, cancer cell viability and migration. Treatment with 1uM CL2-57 led to 5.7-fold induction of ABCA1 expression ($P<0.001$) with markedly less induction of lipogenic genes (SREBP1, FAS) when compared to pan-LXR agonist, GW3965 (1uM). These effects were retained in the H295R 3D spheroid model. CL2-57 did not affect ACC cell viability, but there was significant reduction in ACC cell migration using wound scratch assays with CL2-57 ($P<0.01$). This study provides valuable insight into the effects targeting cholesterol efflux pathways in ACC cells using CL2-57 and this is associated with reduced cancer cell migration, supporting use in ACC therapy. Understanding the impact of LXR pathways in ACC may help in developing new treatment approaches to address the challenge of ACC cancer progression.

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P320

An audit of the use of plasma renin measurements to guide mineralocorticoid therapy in primary aldosteronism

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Introduction
Primary aldosteronism (PA) accounts for 5-10% of patients with hypertension. Approximately 40-50% of cases are bilateral, usually managed using mineralocorticoid receptor antagonists (MRAs). Recent literature suggests a higher risk of renovascular disease and cardiovascular events in PA patients treated medically, compared to those with essential hypertension. This excess risk is mitigated in individuals with unilateral disease managed surgically with adrenalectomy, and in patients on MRA therapy where renin de-suppression (>1 mg/l per h) is achieved (1,2). These findings suggest titration of MRA therapy to raise renin should be adopted into clinical practice.
Aims and Methods
To identify those patients with PA in whom a decision was made for medical therapy, and to establish how many have had an attempt to titrate MRA therapy against renin. We report outcomes in consecutive patients under the care of a clinician with an academic interest in PA at a single Endocrinology centre between January 2019 to June 2023. Patients participating in other clinical research studies were excluded.
Results
20/43 (47%) patients with PA managed medically had renin monitoring during follow-up. In 16/20 patients, monitoring of renin resulted in an improvement in their renin levels, which required multiple dose changes in 10 individuals. Renin remained suppressed in 4/20 patients despite attempts to uptitrate MRAs.
Conclusion
Renin monitoring was not conducted in more than half the study population. The most likely reason is lack of awareness of the importance of renin de-suppression in improving long-term cardio and renovascular outcomes. Other factors such as the COVID-19 pandemic and patients' reluctance to attend for face-to-face follow-up appointments may have also contributed to this shortfall. Our intention is to disseminate these findings and recommendations to our peers using this platform, to ensure patients receive evidence based clinical care.
References
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P321

The dexamethasone assay as a useful tool to identify false positive dexamethasone screening test results

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The dexamethasone suppression test (DST) is a common screening test in Cushing's syndrome but associated with false positive result in 10-20%. One cause of false positivity is inadequate dexamethasone absorption. An assay to measure serum dexamethasone concentration can be used to validate the accuracy of the DST result.
Aims
To audit 1) Use of the dexamethasone assay in DSTs 2) How frequently dexamethasone levels are inadequate 3) Causes of inadequate dexamethasone levels
Methods
The records of 178 patients in our centre who underwent ONDST/LDDST including dexamethasone level results between August 2021 and June 2023 were retrospectively analysed. Dexamethasone levels were included as part of the screening test rather than for a specific indication in patients.
Results
21 patients (11.8%) had low dexamethasone level (<3.0 nmol/l) as defined by the Wythenshawe Lab and based on liquid chromatography and tandem mass spectrometry. Of these 21 patients, 2 patients (9.5%) were on an interfering medication (carbamazepine); 2 (9.5%) had gastric absorption issues; 6 patients (28.5%) had repeat DST which was subsequently negative and it was deemed that compliance was the most likely cause of the initial false positive result (and low dexamethasone level). BMI was not associated with dexamethasone assay level result ($P=0.16$).
Conclusion
We find 11.8% DST results to be false positive due to inadequate dexamethasone absorption as per dexamethasone assay results. Of these, 28.5% are subsequently negative on repeat testing (with adequate dexamethasone level) and initial false positive was likely due to compliance issue. To our knowledge this is the first study to demonstrate use of the dexamethasone level assay to identify absorption or compliance issues as cause of false positive dexamethasone screening test results. It emphasises the importance of considering possibility of false positive results and secondly, need for clear instructions to patients to ensure compliance.

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Bone and Calcium

P31

A single infusion of Zoledronic acid suppressed bone turnover markers for up to seven years: Results from the Zoledronate in the Prevention of Paget's disease (ZiPP) study

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Zoledronate in the Prevention of Paget's disease (ZiPP) trial (ClinicalTrials.gov ID:NCT03859895) is a multi-centre, double-blind, placebo-controlled, randomised trial of Zoledronic acid (ZA) in sequestosome1 (SQSTM1) mutation carriers. SQSTM1 mutation has high penetrance and is associated with the early onset of Paget's disease of bone. Participants with the SQSTM1 genotype received either a single dose of IV 5mg ZA (Aclasta, Novartis); intervention group $n=111$, age mean (range) 49.8 (32-74)yrs, or placebo $n=111$, 50.5 (32-75)yrs. Serum samples collected were rapidly centrifuged/stored frozen for bone markers CTX (resorption), PINP (formation) and BSALP (osteoblasts activity) every 12 months from baseline for five years and at end-of-study(EoS) 2-yr follow-up. Urine bone resorption marker uNTX and radionuclide bone scans were performed at baseline/EoS. In the Intervention group, CTX and PINP showed respective decreases in serum concentrations of average -44.8% and -29.2% across all time points; greatest reductions were observed at 12mths (CTX -57.6%, PINP -46.7%), and remained below baseline concentrations to EoS (CTX -15.2%, PINP -20%). Serum BSALP showed a -20.9% decrease at 12mths then returned to baseline concentration at 36mths. uNTX showed a -36% decrease at EoS. Treatment effect (zoledronate vs placebo) was highly significant for CTX and PINP (ANCOVA $P<0.0001$) and significant for BSALP ($P=0.0005$). Bone scans revealed ZA treatment effect was associated with lower risks of developing new bone lesions (odds ratio, 95%CI: 0.406, 0.0-3.425,$P=0.246$), and further activities of existing lesions in patients (0.083, 0.0-0.424,$P=0.003$). We showed in SQSTM1 mutation carriers, a single treatment of 5mg ZA can achieve long-term suppression of bone resorption and formation markers for up to 7 years. ZA treatment is beneficial against the formation of bone lesions and improves outcome in patients with existing lesions. The different rates of decrease in bone markers offer insights into the bone remodelling process post ZA administration.

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P32

Review of current guidelines on fracture risk recommendations in patients on hormonal therapies for Breast Cancer

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Introduction
Women prescribed hormonal therapies for breast cancer (eg Aromatase Inhibitors (AI) and ovarian suppression therapy (OST)) are at increased risk of fracture and monitoring of Bone Mineral Density (BMD) is needed. Recommendations for BMD monitoring and treatment interval thresholds differ between guidelines which has implications for management. We compared the outcomes from the application of 3 commonly used guidelines for bone health in women with breast cancer (UK2008^1 and IOF^2 which are based on T-scores and NOGG^3 which is based on FRAX scores)
Methods
Data from 67 women (mean age 53yrs (range 24-82)) with breast cancer that were referred to the Christie for a DXA scan following initiation of hormonal therapy were collected (Treatments: 37 AI, 17 OST, 7 AI+OST and 6 tamoxifen). Each DXA scan was analysed using the 3 different guideline recommendations and the outcomes compared.
Results
Overall in the 67 patients, mean(+/-SD) 10 yr probability for hip fracture was 1.3(2.3)% and 6.1(6.1)% for major osteoporotic fracture. 54/67 patients were > 40 yrs; mean(SD) T-score at total hip was -0.45(1.11) and -1.08(1.37) at the lumbar spine. The recommendations from the NOGG guidance, using FRAX based intervention thresholds, differed significantly with regards to recommendations for intervention with bisphosphonate (BP) therapy compared to UK2008 and IOF guidance where intervention is based mainly on T-scores. NOGG2021 recommended BP therapy in only 10% of patients compared to 34% in UK2008 and 40% with IOF.
Conclusion
The results obtained show a discrepancy in recommendations for bone management in women with breast cancer between a FRAX based tool (NOGG2021) and T-score based interventions (UK2008/IOF) which has implications for clinical practice and DXA reporting and may influence fracture prevention in this high risk group.
References
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P33

Service evaluation of the metabolic bone centre primary hyperparathyroidism registry

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Background
At the Metabolic Bone Centre in Sheffield, UK, patients with asymptomatic primary hyperparathyroidism (PHPT) are followed up annually through a register, with annual blood tests, questionnaires inquiring about symptoms or renal stones within the past year, and biennial DXA scans, which doctors then evaluate. Patients are recalled to the clinic if their reported symptoms and/or biochemical results suggest abnormalities associated with PHPT requiring further assessment and intervention.
Objectives
This evaluation aims to describe the characteristics of the patients in the register and determine the effectiveness of the register in appropriately recalling its patients.
Methodology
A retrospective evaluation of all patients in the PHPT register since 2015 was conducted. The effectiveness was determined by identifying how many patients with indications for parathyroidectomy (according to international guidelines from 2015) were recalled to clinic.
Results
Ninety-two patients (mean age 73 $\pm$ 11 years, 87% female) were included in the evaluation. Their average duration in the register was 45 $\pm$ 20 months. Seventeen (18.7%) were recalled to clinic.

Table 1 Biochemistry and renal stones indications

Indication assessed	Total No. of patients	No. of patients recalled
Serum calcium >2.86 mmol/L	2	1
New onset eGFR<60 ml/min1.73 m2	6	1
Sustained decrease in eGFR >25%	2	0
New renal stone	1	1

Table 2 Skeletal Indications

Indication assessed	Total No. of patients	No. of patients recalled
New onset osteoporosis	4	4
BMD decrease >4.5%	22	21
New fragility fracture	2	2

Conclusion
Patients with skeletal indications were identified well. The lack of patient recalls for biochemical indications may be attributed to a selective review of blood tests only done as part of the register rather than all prior investigations. However, if the doctors are trained to review all past investigations, a PHPT register offers an efficient and resource-conserving approach to managing patients with stable PHPT.

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P34

Abstract withdrawn

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P35

Bones, physician's moans, and causes unknown: a challenging case of multifactorial hypocalcaemia

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Sclerotic bone lesions are a rare cause of hypocalcaemia. Calcium and vitamin D malabsorption are recognised complications of gastric bypass surgery. We describe the case of a 45 year-old woman with severe persistent symptomatic hypocalcaemia secondary to metastatic breast cancer, complicated by a previous Roux-en-Y gastric bypass, and the development of hypoparathyroidism. Her corrected calcium levels fell repeatedly and precipitously despite treatment with up to 8g/day oral calcium carbonate, and 6 mg/day alfacalcidol given orally and then intravenously. During her prolonged hospital admission, she required maintenance calcium gluconate infusions of up to 40g/day. Her initial chemotherapy regime of gemcitabine and carboplatin was changed due to concerns of carboplatin exacerbating hypocalcaemia. After weeks of maintenance calcium infusions, she continued on capecitabine. Radium-223, an alpha-particle emitting radionuclide and calcium mimetic, was considered but deemed unsuitable due to concurrent visceral metastases and pre-existing pancytopaenia. We believe that chemotherapy was the definitive management of her hypocalcaemia, controlling the sclerotic lesions and eventually allowing us to maintain normocalcaemia with oral agents. Takeaway points from this unusual case are the complexity of hypocalcaemia drivers and the difficulty in management. The likely causative factors were sclerotic metastases, malabsorption due to her gastric bypass, and hypoparathyroidism. Breast cancer bone metastases are mostly lytic or mixed lytic-sclerotic, with sclerosis often resulting from treatment. Even in cancers with predominantly sclerotic metastases, hypocalcaemia is rarely encountered. It is unlikely that hypoparathyroidism was unrelated to her coincident medical problems, but we were unable to determine its aetiology. Hypoparathyroidism presenting after bariatric surgery can be extremely challenging to manage. Our attempts to improve calcium absorption with calcium carbonate/calcium lactate were unsuccessful. Similarly, oral and intravenous activated vitamin D were insufficient to overcome the draw on serum calcium from bone metastases.

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P36

Unraveling the enigma: Calcifications and complications in PHP

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Introduction
Pseudo-hypoparathyroidism (PHP) is a rare endocrine disorder characterized by resistance to parathyroid hormone (PTH). We present a case of a 33-year-old, focusing on the clinical presentation, diagnostic, and management strategies, with particular attention to skeletal manifestations and tissue calcifications.
Case Description
The patient presented to the hospital with severe symptomatic hypocalcaemia. Initial assessment revealed low corrected calcium levels and slightly low magnesium levels, along with Vitamin D insufficiency. Treatment involved intravenous calcium followed by oral calcium and activated vitamin D.
Clinical Findings
She reported intermittent palpitations and expressed concerns about skeletal deformity, specifically genu valgum and subluxation of the patella. Physical examination showed normal blood pressure, height, and weight, with no physical signs of Albright hereditary osteodystrophy. The patient had a history of delayed menarche, regular menstrual cycles, and two successful pregnancies, as well as one miscarriage. She moved to Uk from Eastern Europe. She has no previous or family history of Endocrinopathies.
Diagnostic Workup
CT head imaging revealed extensive calcifications in various regions, including the corpus striatum, basal ganglia, sub-cortical white matter, cerebellum, and kidneys. CT KUB did not reveal renal stones. Genetic testing targeting the GNAS cluster supported diagnosing pseudo-hypoparathyroidism type 1b.
Management and Follow-up
She received alfacalcidol and calcium supplementation to maintain calcium levels slightly below the normal range. However, delayed presentation and lack of treatment during crucial periods resulted in skeletal deformities. A referral to orthopaedics was made for further management.
Conclusion
This case underscores the diagnostic challenges encountered in suspected pseudo-hypoparathyroidism. The patient's clinical presentation, imaging findings, and biochemical profile strongly supported the diagnosis of this rare metabolic disorder. Delayed treatment and lack of intervention during critical periods likely have contributed to the observed skeletal deformities. Early diagnosis, prompt treatment, and meticulous management are essential for achieving favourable outcomes in patients with pseudo-hypoparathyroidism.

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P37

Cinacalcet in primary hyperparathyroidism: The birmingham experience

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Background
In the UK, 1 to 4 per 1000 people have primary hyperparathyroidism (PHPT) and are at risk of hypercalcaemia and its complications. Whilst surgery is the only curative option in the management of PHPT, several patients are managed conservatively or medically. Cinacalcet (a calcimimetic) has a role in PHPT management, in those who have declined or are unable to progress to surgery. It is important that the use of Cinacalcet in these cases adheres to the guidelines for optimal patient management i.e. when adjusted calcium levels (aCa) are $>$ 3.00mmol/l or between 2.85-3.00mmol/l with hypercalcemia related symptoms.
Aims
To compare the QEH Birmingham practice to the NICE guideline [NG132] for prescribing cinacalcet and to also compare aCa before and after cinacalcet treatment.
Method
In this retrospective study, we collected demographic, biochemistry, clinical and prescribing data, using a structured proforma, from patients who were prescribed cinacalcet from the QEH Birmingham for PHPT.
Results
Of the 46 patients included, 27 were prescribed cinacalcet after [NG132] was published. 19 of these patients (70%), were prescribed cinacalcet in accordance with the guideline. The post-treatment aCa target for patients started on cinacalcet is 2.60mmol/l and only 20 out of 46 patients (43%) met this, over the study follow-up time. Overall, there was a reduction in aCa(mmol/l) when comparing before (Mean 3.01, 95%CI 2.95-3.07) and after treatment (Mean 2.66, 95%CI 2.57-2.75).
Conclusion
We showed that the cinacalcet was prescribed in accordance with the NG132 guideline in the majority of cases. Prescribing within the trust is structured and limited to patients seen by a specialist team. Structured prescribing checklists are completed to ensure that prescribing is rationalised. Reasons for prescribing outside of the guidelines may be due to hypercalcaemia following multiple failed surgeries, or to use cinacalcet as bridging therapy before elective surgery.

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P38

Familial hypocalciuric hypercalcaemia - benign diagnosis not to be missed!

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Background
Familial hypocalciuric hypercalcaemia (FHH) is a rare benign autosomal dominant condition which causes life-long mild to moderate hypercalcaemia. It is usually underdiagnosed due to lack of symptoms in majority of patients and low rate of screening even among endocrinologists. Recent NHS England National Genomic Directory testing criteria for FHH recommend testing patients presenting with hypercalcaemia and calcium creatinine clearance ratio (CCCR) <0.02.
Methods
We report 10 patients diagnosed with FHH in Birmingham Heartlands Hospital metabolic bone clinic from 2017 to 2023. Data was collected using local patients database.
Results
In our cohort, mean age at the genetic diagnosis of FHH was 50 years, 8 patients were females, most were asymptomatic and all but one had hypercalcaemia

discovered on routine blood test. One woman presented with recurrent renal stones. The mean calcium level at the diagnosis was 2.84mmol/l, mean PTH 7.95 and mean Vitamin D level was 55.7 nmol/l. The calculated mean urine CCCR was 0.0055. There was an average delay of 4.5 years from the referral to time of genetic diagnosis. Therefore, 70% of the patients were initially presumed to have primary hyperparathyroidism. Seven out of 10 patients had parathyroid ultrasound and CT of the neck performed. 3 patients has also Sestamibi scan. All of them had renal ultrasound and bone density scan, and one had renal stone and another osteoporosis. Two cases were diagnosed after having parathyroid surgery and persistent hypercalcaemia triggered genetic testing.
Conclusion
FHH remains largely underdiagnosed. Normal PTH in context of hypercalcaemia should prompt FHH screening. An early diagnosis reduces patient's anxiety, cost of unnecessary imaging and surgery.

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P39

PTH Independent hypercalcaemia in a pregnant patient

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We report an interesting case of a rare presentation of hypercalcemia in a 27-year-old pregnant woman with history of Uterine fibroids. The patient arrived at the emergency department with two weeks history of worsening lower abdominal pain. She had resorted to sleeping in a sitting position due to the intensity of pain. There was no vaginal bleeding and bowels were not opened for four days. Physical examination revealed dehydration, tenderness in the lower abdomen with an abdomen larger than expected for her gestational age of 14 weeks. Investigations revealed a calcium level of 3.01 mmom/l with normal kidney function. PTH was suppressed, and vitamin D was low. A subsequent renal ultrasound exhibited no significant abnormalities. Unfortunately assays for PTHrP and 1,25 (OH) Vitamin D were not available for testing. Treatment continued with intravenous hydration. Initial low radiation imaging studies with a chest x-ray and a neck ultrasound demonstrated no remarkable findings prompting the decision for to proceed with an abdominal and pelvic MRI. The MRI revealed a large necrotic uterine mass, likely to represent a fibroid with moderate volume ascites. Following discussion in the MDT, she underwent laparotomy, open myomectomy and partial subcolic omentectomy at 15 weeks of gestation. A 30 cm pedunculated fibroid was successfully, excised and sent for histopathology. Cytology of peritoneal fluid revealed no malignant cells but a full histopathology report is awaited. Calcium levels rapidly normalized post-surgery accompanied by a rise in PTH. Sadly, three days after surgery, the patient had a miscarriage despite calcium remaining within the normal range. Plans are in place to review the patient in clinic with repeat calcium, PTH and cross-sectional imaging. We suspect this is a case of PTHrP mediated hypercalcaemia from uterine fibroid. While such occurrences are extremely rare, they are documented in the literature.

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P40

Importance of Evidence-based management of Primary Hyperparathyroidism

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Background
Primary Hyperparathyroidism (PHPT) is the leading cause of hypercalcaemia. Early diagnosis and management is important to prevent long term complications. National institute of clinical excellence (NICE) published guidelines on diagnosis and management of Primary Hyperparathyroidism and we sought to compare our practice with the NICE guideline (NG 132).
Methods
This was a retrospective observational study of patients diagnosed with PHPT between January 2017 and December 2021. Data collected included patients' symptoms, calcium and parathormone (PTH) levels, diagnostic test results, management, and treatment outcomes.
Results
Twenty-four patients {mean age (range) 69 (34-87 years)} with a diagnosis of primary hyperparathyroidism were identified during the study period. Only 12/24 (50%) patients had symptoms consistent with hypercalcaemia. 9/24 (37.5%) patients had 24-h urinary calcium levels measured. Ten (41.7%) had renal tract ultrasound performed. Dual-energy x-ray absorptiometry (DEXA) was done in 23/24 (96%) patients and this revealed osteoporosis in 13/23 (56.5%) and osteopenia in 7/23 (30.4%). Nine (37.5%) patients were managed surgically, 10 (41.7%) medically. Majority (88.9%) of the surgically managed patients had normalisation of calcium levels compared to 30% patients managed medically (treatment with either bisphosphonate, cinacalcet or both). 29% patients' management was fully compliant with NICE guidelines.
Conclusion
The compliance with NICE recommendations was variable. Measurement of 24-h urinary calcium excretion levels and renal tract ultrasound should be incorporated into routine practice. Parathyroidectomy seems to be associated with the best outcomes and should be considered, if possible, in all patients.

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P41

Tumour-to-tumour metastasis to the parathyroid causing dual pathology hypercalcaemia

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An 85-year-old woman attended the endocrine clinic with hypercalcaemia and raised PTH levels. Her background included breast cancer treated with bilateral mastectomy and hormone therapy 3 years previously, with no evidence of disease on imaging 2 years previously. On attendance, her clinical examination was unremarkable, with no palpable neck mass. Biochemical investigations showed: Adj Ca 3.12 mmol/l, PTH 45.0 pmol/l, PO4 0.94 mmol/l, ALP 119U/l, Alb 45g/l, 25-OH Vit D 15.7 nmol/l, eGFR 47, calcium excretion index 0.097 mmol/l. A Sestamibi scan was consistent with a left-sided parathyroid adenoma. She was initially treated with 60mg cinacalcet, however became intolerant to this, with refractory symptomatic hypercalcaemia (Adj Ca 3.27 mmo/l) and acute kidney injury (eGFR 20). She subsequently underwent emergency parathyroid surgery, with resection of a 4cm left-sided adenoma and left hemi-thyroidectomy en bloc, due to intraoperative suspicion of parathyroid carcinoma. Interestingly, the histology was consistent with metastatic breast cancer within a parathyroid adenoma. Following initial normalisation of calcium levels, she was readmitted with hypercalcaemia (Adj Ca 3.08 mmo/l) and suppressed PTH (1.0 pmol/l). A CT thorax, abdomen, and pelvis identified lung and liver metastasis, however skeletal metastases were absent on bone scintigraphy, suggesting a diagnosis of humoral hypercalcaemia of malignancy. MDT discussion confirmed a diagnosis of metastatic breast cancer and recommended palliative management. Metastases to the parathyroid are present in 12% of patients with disseminated cancer on autopsy, with breast the commonest site of origin. Tumour-to-tumour metastasis within the parathyroid is much rarer and its incidence is unclear. Interestingly, endocrine tumours including parathyroid adenomas, account for 45% of recipient tumour-to-tumour spread, possibly due high vascularity. This rare case of tumour-to-tumour metastasis of breast primary within a parathyroid adenoma, illustrates the importance of considering dual pathology, in patients with hypercalcaemia and a background of malignancy.

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P42

Neonatal hypocalcaemia and association with maternal magnesium sulphate (MgSO4) administration in a single center, at the neonatal unit in walsall manor hospital

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Introduction
Hypocalcaemia is a biochemical abnormality noted in neonates and considered a possible side-effect of maternal MgSO4 administration. Suggested mechanism is

maternal hypermagnesemia inhibits secretion of maternal parathyroid hormone, causing maternal and foetal/neonatal hypocalcaemia.
Objectives
This study is aimed to identify common risk factors, presentation, biochemical abnormalities, severity, and any correlation between maternal MgSO4 therapy and hypocalcaemia in neonates.
Methodology
Retrospective cohort study for neonates admitted to Neonatal /Transitional Care Unit in Walsall Manor Hospital over 6-month, from 01/01/2022 to 30/06/2022.
Inclusion criteria
Term/preterm weighing >1500 g: total calcium <2 mmol/l or ionized calcium <1.1mmol/l Very low birth weight weighing <1500 g: total calcium <1.75 mmol/l or ionized calcium <1mmol/l.
Results
Total live births (TLB) were 1762, 195 admitted to NNU; 78 had biochemical evidence of hypocalcaemia, 18 were <34+6 gestation, 6 were <30 weeks and 12 were 30+0 - 33+6 weeks.

<33+6 gestation	Received maternal MgSO4	Not received maternal MgSO4
Number of patients	10	8
Number of hypocalcaemic patients	7	7
Number of normocalcaemic patients	3	1
Mean ionized calcium	1.03 mmol/L	0.98 mmol/L
Mean total calcium	2.29 mmol/L	2.53 mmol/L
P value (ionized)	0.256	
P value (total)	0.351	

Discussion and recommendation
Mean ionized calcium for neonates whose mothers received MgSO4 (1.03mmol/l) was higher than that of neonates whose mother's did not receive MgSO4 (0.98mmol/l). Mean total calcium for neonates whose mothers received MgSO4 (2.29 mmol/l) was lower than that of neonates whose mother's did not receive MgSO4 (2.53 mmol/l). P value is above 0.05, hence we reject the alternative hypothesis that maternal MgSO4 is correlated with neonatal hypocalcaemia and accept the null hypothesis that MgSO4 has no effect on neonatal calcium levels. The limitation is the small sample size, hence multi-center study is recommended.

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P43

Paradoxical severe hypercalcemia in a male bodybuilder with rhabdomyolysis: A case report

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Paradoxical severe hypercalcemia is a rare phenomenon observed in some patients in delayed phase following rhabdomyolysis. We present a case of 33-year-old male who developed severe hypercalcemia following successful treatment of rhabdomyolysis. Patient was admitted with agitation and disinhibition, was intubated in A&E due to metabolic acidosis (pH 6.7), hyperkalemia (K+ 7.3 mmol/l), lactic acidosis (23 mmol/l), and pyrexia (40°C). Toxicology screening shown presence of cocaine, levamisole (cocaine adulterant), and cotinine. Acute liver injury, sympathetomimetic cardiac overdrive, acute kidney injury (AKI) with reduced consciousness were also noted. Filtration was initiated for AKI, and the initial biochemistry indicated severe rhabdomyolysis (creatinine kinase [CK] 76,122 U/l) with adjusted calcium (Ca) levels of 2.06 mmol/l. Following filtration and aggressive intravenous fluid administration, CK level normalized to 108 U/l. However, the patient unexpectedly developed severe hypercalcemia (Ca 4.03 mmol/l) with low levels of vitamin D (<8 nmol/l), 1,25-dihydroxyvitamin D3 (14 pmol/l), and PTH-independent hypercalcemia (PTH <0.7).
Management
Initial consideration of hypercalcemia-of-immobilization led to bisphosphonate treatment; however, after renal team's advice for improved RANKL inhibition, the patient was switched to denosumab. Subsequent management included rehydration, avoidance of calcium supplementation, and continuing calcium free filtration for AKI. With denosumab, the patient's hypercalcemia gradually resolved, and vitamin D supplementation was initiated to correct the deficiency. Once stable, he was discharged from ITU with plan of local endocrine and renal team follow up.
Conclusion
This case highlights the rare occurrence of paradoxical hypercalcemia, in delayed phase of rhabdomyolysis, due to release of excessive calcium from sarcoplasmic reticulum. Awareness of this phenomenon is crucial for clinicians managing similar cases to ensure appropriate diagnosis and consideration of denosumab for RANKL inhibition in PTH-independent hypercalcemia associated with rhabdomyolysis. Further research is warranted to elucidate the underlying mechanisms for such complex cases.

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P44

Viral hypercalcemia

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A 64-year-old woman presented acutely with dry cough, difficulty in eating, diarrhoea and weight loss. Her past medical history included cervical carcinoma *in situ* treated with laser therapy. She was found to be hypercalcaemic, with a corrected calcium of 2.84 mmol/l. During admission, the calcium ranged between 2.8-3.87 mmol/l. The PTH ranged between 0.2-0.4 pmol/l (1.3-9.3 pmol/l). She had raised inflammatory markers and deranged liver function tests. On review, she was mildly hypercalcaemic for 6 months prior to admission. Of note, she had a maculopapular rash on limbs and torso, which faded with time. An ulcerated lesion on her labia majora was diagnosed as lichen sclerosis secondary to urinary and faecal incontinence. During admission, her general health deteriorated rapidly. She became bedbound and doubly incontinent. Her myeloma screen was negative, and CT chest abdomen and pelvis only revealed patchy ground glass changes in lungs. A differential offered by the radiologist was COVID, which she tested negative. There was no evidence of solid tumours or lymphadenopathy. Her ACE levels were 111 (8-52) and 25(OH)2 Vitamin D levels were 63.4 nmol/l. The hypercalcaemia was refractory to bisphosphonates and calcitonin. Given the constellation of clinical features, an HIV test was performed, which was positive. Reports of non-parathyroid hypercalcaemia with HIV have been reported in the context of either antiretroviral therapy (immune reconstitution syndrome), tuberculosis or solid tumours. The finding of hypercalcaemia outside the above context in HIV is extremely rare. It is indeed possible that there may have been a solid tumour that was not detected on imaging or indeed sarcoidosis. However, her calcium was improving after commencing anti-retroviral therapy. Unfortunately, despite antiretroviral therapy and non-invasive ventilation, the patient died. It is likely that she was HIV positive for an extended period prior to this presentation.

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P185

A retrospective audit of patients with fragility hip or vertebral fracture - assessing suitability for romosozumab

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Introduction
The current UK guidelines (NICE TA791) recommend the use of romosozumab, a monoclonal sclerostin inhibitor, for patients at high imminent risk of fragility fractures. However, elderly patients with a very high risk of fractures often exhibit frailty and other comorbidities. This retrospective survey was conducted in a major trauma centre in northern England to evaluate the potential utilisation of romosozumab in a real-world setting.
Methods
The study included patients admitted with femoral (neck, intertrochanteric, subtrochanteric, subcapital) and vertebral fragility fractures over six months from January 2022. The patients were identified from coding by the BI analytics team. DXA scans, electronic records and linked GP records were reviewed. Male and paediatric patients, atypical and high-impact trauma fractures, patients outside the local geographical area, death before discharge, or with insufficient clinical details were excluded.
Results
After exclusions, a total of 244 subjects (avg. age 84) were identified. Among them, 81 (33.19%) met the romosozumab criteria as outlined in the NOGG consensus advisory statement. The reasons for ineligibility are provided in the table below. 58 (72%) of the individuals meeting the criteria had not received DXA scans at the time of the survey.

Exclusion	Number of patients (N = 163)
Cardiovascular disease (CVD)	35 (21.5%)
Frailty (Frailty (CFS ≥6)	34 (20.9%)
Prior bisphosphonate use*	24 (14.7%)
Other	27 (16.6%)
Multiple	43 (26.4%)

Discussion
No age cut-off exists for romosozumab use but frailty and CVD were key factors influencing suitability. Given DXA is necessary to identify suitable patients, it is crucial to invest in staff to effectively identify and prioritise eligible patients. Prior bisphosphonate use does not exclude romosozumab use but initiating alternative treatments may be considered for treatment-naïve patients with delayed DXA and clinic review. Many fragility fracture patients could benefit from romosozumab, but significant changes in pathways and services are needed.

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P186

Teriparatide efficacy in the real world: a single UK centre experience

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Introduction
Teriparatide is an osteoanabolic agent approved for the treatment of osteoporosis in postmenopausal women, in men with increased fracture risk, and in glucocorticoid-induced osteoporosis. The aim of this study was to evaluate the real-world use and efficacy of teriparatide.
Patients and Methods
We retrospectively assessed all patients with available data, who received teriparatide at Leeds Teaching Hospitals over 2004-2022. Patients who did not complete the 2-year treatment course were excluded. Data on bone turnover markers (P1NP/CTX), bone mineral density (BMD), treatment adherence and sequential therapy was analysed.
Results
87 patients were identified. Three patients discontinued teriparatide early. Eight deaths were recorded. 76 patients (88% female; age at diagnosis 65.8 ± 11.3 years) were included in the final analysis. 65 patients (86%) met NICE criteria for teriparatide treatment. Eight patients (11%) were treatment-naïve. Prior to teriparatide, 49% received oral bisphosphonates, 32% IV bisphosphonates, 8% denosumab and 1% HRT. There was no significant difference in the baseline BMD between the treatment-naïve and pre-treated patients. Post-teriparatide, mean BMD gain was 12% (0.085 ± 0.15 g/cm^2) at the spine and 4% (0.027 ± 0.1 g/cm^2) at the hip respectively. There was no significant difference between the pre-treatment and treatment-naïve groups. Amongst the pre-treated patients, a significant gain in BMD was observed at the spine, but not at hip. There were 13 non-responders, based on BMD and/or bone turnover markers. 9 patients sustained a fragility fracture during the treatment course. Sites being vertebral (5/9), hip (1/9) or other sites (3/9) There was no significant difference in the fracture rate between the responders and non-responders. 58 patients (76%) switched to antiresorptive therapy in the form of oral bisphosphonates (5%); zoledronate (26%); denosumab (46%).
Conclusions
Initiating Teriparatide was in line with NICE guidance. Our data demonstrated the positive BMD response at the lumbar spine in keeping with findings from the EUROFORS study

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P187

Hyperparathyroidism in the young: A case and investigation pathway

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Introduction
Primary hyperparathyroidism may be sporadic or occur as part of a genetic predisposition. Inactivation of CDC73 tumour suppressor gene can cause hyperparathyroidism-jaw tumour (HPT-IJ) syndrome, parathyroid carcinoma or familial isolated hyperparathyroidism (FIHP).
Case details
We report a 26 year old gentleman, previously fit and well who was found to have hypercalcemia on a routine testing. Renal ultrasound demonstrated nephrocalcinosis. He was referred to hospital with adjusted calcium 3.60 mmol/l (2.20-2.60), PTH 31.3 pmol/l (1.6-6.9), phosphate 0.64 mmol/l (0.80-1.50) which were keeping with primary hyperparathyroidism. He was given IV bisphosphonate by the acute team for persistent hypercalcemia. He described non-specific symptoms of lethargy but had no jaw pain or clinical history to suggest a syndromic cause. His maternal grandfather had kidney stones and mother had a hysterectomy. Genetic tests were sent but pending results, samples were sent for calcitonin and plasma metanephrines as these may alter the treatment course. Both results were normal. The USS parathyroid scan and 99m Tc-MIBI scan demonstrated a parathyroid adenoma inferior to the left thyroid lobe. He started cinacalcet pending operative treatment. Genetic testing identified a pathogenic variant in CDC73. Family have been advised about cascade screening.
Discussion
This case highlights the importance of genetic testing in young patients with hyperparathyroidism. It also demonstrates a pathway for necessary pre-operative testing in those needing more urgent parathyroid surgery, where genetic results may be delayed. Concurrent phaeochromocytoma or medullary thyroid carcinoma as part of MEN2 could alter operative treatment approach. Increased identification may allow for more detailed screening recommendations in family members with CDC73 mutations. Current recommendations suggest annual parathyroid biochemistry alongside dental check-up and periodic pelvic ultrasound to evaluate for uterine tumours in women of reproductive age.

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P188

A clinical audit on pre-operative work up and post-operative follow up in patients undergoing surgical management for primary hyperparathyroidism in a large tertiary Centre in the United Kingdom

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Background
Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Aim of this audit was to assess clinical, biochemical parameters, localisation modalities and outcome in patients undergoing parathyroidectomy at University College London Hospital (UCLH).
Methods
We audited all patients aged 15-years or above, undergoing parathyroidectomy, from 01-02-2018 to 31-12-2021 at UCLH via retrospective data collection. The audit standards were as per the National-Institute-for-Health-and Care-Excellence (NICE) guidance, May 2019 and Journal-of Clinical-Endocrinology-and-Metabolism (JCEM) guideline 2018 (Table-1).
Results
There were 182 patients included. Majority 95 (52.2%) presented with incidental finding of asymptomatic hypercalcemia. Table-1 summarizes our performance against the audit standards.
Majority 100 (59.4%) had a hospital stay of 1-2 days, with 34 (18.7%) having a stay of <1 day. Three-month cure rate out of available data was 99.4% (175/176).

Section	Audit standard - 100%	Our performance n (%)
Diagnostic work-up	25(OH) Vitamin D level	166(91.2%)
	Urine calcium excretion	146(80.2%)
Screening for end organ involvement	Dexa scan - lumbar spine, hip, distal 1/3 radius	Only 114 (62.6%) had a dexa scan Only 34 (18.6%) had distal radius assessment
	Ultrasound kidneys	97 (53%)
Pre-operative localisation	Ultrasound neck	181 (99.5%)
	CT parathyroid	166 (91.2%)
	Sestamibi	91 (50%)
IOPTH monitoring	Only in re-operation	182 (100%)
Post-operative follow-up	Calcium before discharge	175 (96%)
	3-6 months	3 months data available in 176 (96.7%)

Conclusion
This data confirmed pre-diagnostic work up, and post-operative follow up are up-to the audit standards. Combination of ultrasound and CT neck with IOPTH monitoring used at our centre lead to high cure rates. The areas to improve were, urine calcium assays, dexa scans including distal forearm and ultrasound kidneys for all aiding the surgery decision. We have already taken steps to improve

through staff education, developing PHPT care pathways, and updating electronic order system to reflect specific dexa scan sites for PHPT.

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P189

Resistant hypocalcaemia in a patient with prostatic adenocarcinoma with extensive osteoblastic metastasis

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Introduction
Hypocalcaemia is rare in patients with malignancy, occurring in $<2\%$ of patients with malignancy. Osteoblastic bone metastases as an aetiology of hypocalcaemia are further rare.
Case description
A 75-year-old male presented to emergency with back pain, and immobility. He was diagnosed to have prostate cancer in 2019. A bone scan in April 2022 showed extensive sclerotic metastases involving axial and proximal appendicular skeleton. His treatment included antiandrogens, goserelin, palliative chemotherapy, and diethylstilboestrol. He had received a session of palliative radiotherapy to spine two months prior. CT and MRI scans of spine revealed progressive sclerotic metastases. His biochemistry revealed presence of new-onset hypocalcaemia (corrected calcium 1.75 mmol/l, and ionised calcium 0.94 mmol/l), and hypophosphatemia (0.85 mmol/l). Serum levels of vitamin D (51 nmol/l) and magnesium (0.75 mmol/l) were normal. His parathyroid hormone was elevated (16.4 pmol/l). 24-h urinary calcium was inappropriately low (3.0 mmol). He was treated with intravenous calcium infusion, along with oral calcium, vitamin D, and alfacalcidol supplements. During the hospital stay, he needed intravenous magnesium infusion and oral phosphorous supplements. Despite prolonged intravenous calcium replacement and higher doses of oral alfacalcidol (up to 8 mg/day) and elemental calcium (up to 4800 mg/day) replacement, he had persistent hypocalcaemia with calcium levels ranging from 1.70 to 1.87 mmol/l. Considering his debilitating condition and lack of any systemic therapy to treat the underlying condition, a plan for palliation was considered.
Discussion
Hypocalcaemia secondary to osteoblastic metastases is most commonly seen in background of prostate cancer. It can be life threatening and challenging to manage. Increased influx of calcium and phosphate into the sclerotic bone has been hypothesised to cause hypocalcaemia. Care should be taken to monitor serum calcium in patients with malignancy and rule out other aetiologies of hypocalcaemia when present.

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P190

Parenteral bisphosphonate therapy is effective and safe when given prior to parathyroid surgery in severe primary hyperparathyroidism

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Background
Primary hyperparathyroidism may severely manifest with an adjusted calcium $>$ 3.5mmol/l and increased risk of prolonged postoperative hypocalcaemia. Formal consensus on preoperative optimisation appears lacking, especially around the utility of parenteral bisphosphonate treatment. Bisphosphonate therapy has been demonstrated to cause prolonged hypocalcaemia when given to patients with a history of parathyroidectomy.
Methods
We retrospectively evaluated records of 21 patients, over a four-and-a-half-year period. All presented with severe primary hyperparathyroidism (adjusted calcium $\geq$ 3.5mmol/l). Anaesthetic risk at such high levels of adjusted calcium is markedly increased with many anaesthetists reluctant to give a general anaesthetic. Thus far, there are few data exploring the preoperative use of bisphosphonates to bring calcium levels to a safe range for administration of anaesthesia. We report the outcomes of preoperative interventions and evaluate the outcomes, namely risk of postoperative hypocalcaemia.
Results
Seventeen patients received at least one standard dose of intravenous pamidronate preoperatively as therapy for hypercalcaemia (8 patients were given this within 10 days of parathyroidectomy). Pamidronate disodium was effective in lowering calcium and appeared safe when administered preoperatively. No patient developed severe or prolonged postoperative hypocalcaemia. Furthermore preoperative 25-(OH)D insufficiency/deficiency was highly prevalent. No patient that had undergone adequate vitamin D repletion developed severe postoperative hypocalcaemia ($<$1.9mmol/l).
Conclusion
Pamidronate disodium appears safe when given to correct hypercalcaemia in severe disease (adjusted calcium $\geq$ 3.5mmo/l) preoperatively to reduce anaesthetic risk. Therefore, parenteral bisphosphonate therapy should be considered to facilitate surgery. Preoperative vitamin D replacement is standard practice in patients undergoing parathyroidectomy. We have demonstrated that it can be given to patients safely despite baseline adjusted calcium levels $\geq$ 3.5mmol/l. Indeed, ensuring vitamin D is replete preoperatively may have an impact on preventing postoperative hypocalcaemia in our cohort of patients.

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P191

Spontaneous remission of hypercalcaemia in PHPT due to necrosis of parathyroid adenoma

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Primary hyperparathyroidism (PHPT) affects approximately 0.3% of the UK population. The most frequent cause is solitary parathyroid adenoma, less commonly parathyroid hyperplasia, multiple adenomas, and parathyroid carcinoma. Cinacalcet is a calcimimetic which may be used in treatment of PHPT in certain circumstances. We report here a case of PHPT, treated by Cinacalcet, wherein apparently spontaneous necrosis of a parathyroid adenoma and resolution of hypercalcaemia occurred. A 58-year-old male with hypertension, alcohol misuse disorder and CKD (eGFR 50 ml/min/1.73m2) was referred for lethargy and abdominal pain. His usual medications included Enalapril, Lansoprazole and Atorvastatin. He was hypercalcaemic with an albumin adjusted serum calcium of 3.23 mmol/l (2.2 – 2.6) and Parathyroid Hormone (PTH) was 25.2 pmol/l (1.6 – 6.9). 25-OH-Vitamin D was 66 nmol/l ($>$ 50), urine Calcium: Creatinine Clearance Ratio 0.0229. Overall this was consistent with PHPT. Parathyroid Single Photon Emission Computed Tomography (SPECT CT) scan showed a 3.8 cm lesion posterior to the lower pole of the right thyroid lobe with focal tracer uptake on its inferior margin suggestive of parathyroid adenoma. He was admitted, treated with IV fluids and discharged on Cinacalcet 30mg BD. Upon subsequent preoperative review, he was found to be hypocalcaemic, he reported a two-week history of change in voice. A palpable mass in the right neck anterior triangle was noted. Flexible nasendoscopy showed right vocal cord palsy. Cinacalcet therapy was suspended. Parathyroidectomy was performed and a 4 cm, partly necrotic lesion was removed from behind the right thyroid lobe. He was discharged on CALVIVE 1 g Effervescent Tablets. Histology confirmed an adenoma showing partial necrosis. We hypothesise that resolution of hypercalcaemia could have been due to Cinacalcet induced necrosis. We have identified two other similar case reports of remission of hypercalcaemia associated with parathyroid necrosis following Cinacalcet treatment in the literature.

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P192

Aetiological complexity of Hypercalcaemia – A case report

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Background
Hypercalcaemia in endocrine patients often poses diagnostic challenge, with hyperparathyroidism and familial hypocalciuric-hypercalcaemia(FHH) being common differentials. This case-report presents unique and complex aetiology, underscoring need for comprehensive evaluation.
Case-Description
We present case of 57-year-old Caucasian-woman referred to our clinic with persistently elevated calcium and parathyroid hormone(PTH) levels over several months. Her medical history included bipolar disorder treated with Lithium (800mg) for 17 years. Family history was unremarkable, and patient was asymptomatic upon presentation. Laboratory evaluation revealed elevated PTH(79ng/l; reference-range:11-64ng/l), corrected-serum-calcium levels of 2.72 & 2.92mmol/l (ReferenceRange: 2.20-2.60mmol/l),24-h urinary calcium

excretion of 5.1mmol/24hr (reference range: 2.5-7.5mmol/l), VitaminD deficiency (4.2ug/l;ReferenceRange: > 20ug/l), normal electrolytes and renal functions, and subclinical hypothyroidism. Vitamin D was replenished, but persistent hyperparathyroidism with hypercalcaemia was observed during follow-up. Imaging studies, including Sestamibi-scan, DEXA-scan, and ultrasound of kidneys, thyroid, and parathyroid, failed to identify any abnormality. Considering possibility of Lithium-induced-hyperparathyroidism, consultation with psychiatrist was recommended to discuss discontinuing Lithium but declined by patient. Regular follow-ups and adequate hydration were advised. Serial calcium measurements demonstrated fluctuations between peak of 3.09 and nadir of 2.45mmol/l, associated with intermittent nocturia and increased thirst. Four years after initial presentation, patient became grandmother, and her granddaughter was found to have mild hypercalcaemia. Further investigations confirmed mild hypercalcaemia in patient's daughter as well. Familial cause of hypercalcaemia was suspected, leading to genetic testing of three generations. Results revealed Familial Hypocalciuric Hypercalcaemia. This diagnosis, coupled with persistent nocturia and thirst, prompted initiation of Cinacalcet 30mg twice daily. Gradual but sustained response was observed, culminating in normalization of hypercalcaemia, with last corrected calcium level measuring 2.61mmol/l.

Discussion

This case report highlights intricate aetiological complexity underlying what initially appeared to be straightforward case of primary hyperparathyroidism-induced hypercalcaemia. It underscores significance of considering detailed family history and need for persistent follow-up to unravel complex diagnostic scenarios.

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P193

Genetic Testing in Endocrinology: a clinical audit assessing the appropriate use, documentation, and communication of results

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Background

Confirming a genetic diagnosis earlier in patient pathways has multiple benefits: it informs and directs clinical management, enables patients to access support organisations, and helps patients adjust to their lifelong condition. This audit assessed the appropriate usage of genetic testing within Endocrinology at Birmingham Heartlands Hospital (BHH). The key three outcomes investigated were whether genetic testing was being appropriately ordered; whether test consent was being documented and whether the results were being appropriately communicated to patients.

Methods

An audit of all patients who had a genetic test requested by an Endocrinologist at BHH, between January 2021 and March 2022 (to allow time for receipt and communication of results) was conducted. Patients were identified from a laboratory database of DNA extraction. Data was extracted retrospectively using a piloted tool by two reviewers, including consent documentation, test indications, genetic test results, and results communication. The National Test Genomic Directory criteria was used to determine appropriate test usage.

Results

32 patients had a test requested in the audit period. 15.6% of tests yielded a positive result. 91% referred for genetic testing met the test criteria3. However, only 62.5% of patients had a consent form uploaded to their electronic records. 87.5% of patients had evidence that their results had been communicated to them. In the four cases where there was no documentation that the result had been communicated the requesting Endocrinologist was contacted by the audit team.

Conclusions

This audit identified appropriate ordering of genetic testing by the Endocrinology department of BHH but also a lack of documentation of test consent and incomplete evidence of result communication to patients. With increased availability and awareness of genetic testing, all centers will require robust processes to ensure accurate consent documentation and result communication. Following dissemination of our results within the department a re-audit is planned.

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P194

Management of primary hyperparathyroidism- A retrospective audit on use of cinacalcet vs surgical intervention

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Objective

To evaluate the efficacy of medical management of hyperparathyroidism and evaluate the financial and healthcare impact of delay in surgical intervention within a district general hospital. To assess the duration of use of cinacalcet prescriptions, compare wait times for surgery and assess the service needs.

Method

We retrospectively evaluated all patients with primary hyperparathyroidism who received cinacalcet prescriptions from January 2021 to December 2022. We measured the duration and appropriateness of cinacalcet use, evaluated the patients' eligibility for parathyroid surgery, compared and contrasted the current wait time for surgery against national standards, and reported the complications of hypercalcaemia alongside additional cost related to potentially avoidable inpatient admission due to hypercalcaemia.

Results

We evaluated 62 patients who received cinacalcet prescriptions. 32 (52%) patients were offered surgery (age 65 $\pm$ 12.5 years), out of which only 13 patients underwent parathyroidectomy. The average waiting time for parathyroid surgery was 22 months (range 8 to 43 months) from the point of the initial contact in surgical outpatient clinic. The mean duration of use of cinacalcet was 20 $\pm$ 6 months for those awaiting surgery and 15 $\pm$ 9 months for those not suitable for surgical intervention. Reduction in bone mineral density was observed in 55% of patients, renal stones in 17% and fragility fractures in 14.5%. 22 of the 62 patients (35%) required inpatient admission due to hypercalcaemia totalling 146 inpatient hospital days.

Conclusion

Prolonged delay and longer waiting times for definitive surgical intervention has resulted in higher cost and potential adverse outcomes in patients. Based on current data, we created a need for an MDT service to improve care for patients with the longest wait times in order to improve patient outcomes, reduce risk and improve the efficacy of the service.

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P195

A case of Severe hypercalcemia secondary to Milk-Alkali syndrome:

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Milk – alkali syndrome is a rare and distinctive disorder caused by ingestion of large amounts of calcium and absorbable alkali resulting in hypercalcemia. It is characterized by a triad of hypercalcemia, metabolic alkalosis and renal failure. Here we present a 59 years old female patient, who presented to Emergency department for a fall and Syncopal episode. She had a few days history of increasing thirst, polyuria and diffuse abdominal discomfort. This prior to her syncopal episode, which lasted for few minutes with quick recovery. She had a past medical history of Endometriosis, Type 2 diabetes mellitus, epilepsy and ex-IVDU user with hep B in remission. She was suffering with frequent episodes of heart burns and self-treated this with over counter Rennie tablets. She had been taking almost 100 Rennie tablets per day. On admission she was found to be confused and dehydrated. Her adjusted calcium level of 4.55, Phosphate levels of 0.85, Suppressed PTH levels with acute kidney injury. Her Vitamin D levels on admission was 34 with urea of 16.9 and creatinine of 334. She had ECG changes related to the severe hypercalcemia. CT head performed for her syncopal episode did not report any abnormalities. Bence jones proteins, electrophoresis and ACE levels were within normal range. A CT Thorax, Abdomen and Pelvis was reported a 25 mm exophytic low density lesion over the upper pole of the right kidney. Ultrasound performed following this was reported as simple cyst in the kidney. Her Calcium levels responded well to aggressive Intravenous fluid resuscitations. Her latest calcium levels and renal function are within normal range and she was also imitated on vitamin D therapy.

Conclusion

We would like to emphasise the importance of considering over counter antacids treatment as iatrogenic cause of hypercalcemia, especially in severe hypercalcemia like our patients.

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P196

An unexplained case of phosphaturic hypophosphataemia

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Introduction
We present an unusual case of hypophosphataemia with diagnostic dilemma.
Case
43-year-old female presented with 4-year history of muscle weakness, fatigue, bony pains, and limb paraesthesia. There was no background of fractures or iron deficiency. Her medications included amitriptyline and probiotics. She was a non-smoker and teetotaller; mother was short stature, father normal height. There was no family history of fractures or rickets. On assessment, height-169cm, weight-91.8 kg, BMI 32 kg/m2, normal physical examination, no features suggestive of Fanconi's syndrome. Phosphate (PO4) was low 0.37mmol/l (0.8-1.5), vitamin D 28.3 nmol/l (>50) with normal calcium, magnesium, parathyroid hormone, renal function and TSH. 24hr urinary PO4 102.8mmol (15-50), fractional excretion of filtered PO4 60.4% (5-20), high fibroblast growth factor-23 (FGF-23) 115RU/ml (<100), 1,25-dihydroxy vitamin D 179 pmol/l (20-120), normal short synacthen test; genetic analysis negative. FDG-CT PET suggested metabolically inactive left ovarian cyst, transvaginal ultrasound revealed simple cyst which disappeared on repeat ultrasound. Tumour markers (AFP, CEA, CA-125, beta-HCG, LDH), gastrointestinal malabsorption tests were negative. Oral phosphate replacement with cholecalciferol commenced, despite which the phosphate levels were low, later changed to alfacalcidol. Phosphate remained low (0.3-0.9mmol/l), limited by hypercalcemia on increasing dose of alfacalcidol.
Discussion
Chronic hypophosphatemia results in childhood rickets, osteomalacia, and skeletal muscle myopathy. Severe hypophosphatemia (<0.32mmol/l) causes arrhythmias, rhabdomyolysis, acute haemolytic anaemia. FGF-23, produced by osteocytes/osteoblasts reduces intestinal absorption of serum phosphate by decreasing 1,25-dihydroxy vitamin D and restricting proximal tubular phosphate reabsorption. FGF-23 mediates hypophosphataemic disorders, both hereditary (X-linked hypophosphatemia-XLH) and acquired (tumour induced osteomalacia). Treatment is oral phosphate and active vitamin D with aim to achieve low-normal phosphate levels. Burosumab, a recombinant human IgG1 monoclonal antibody targeting FGF-23 is licenced for use in XLH.
Conclusion
Extensive investigations may fail to identify a cause for symptomatic phosphaturic hypophosphataemia and drug therapy may be suboptimal due to drug induced hypercalcemia.

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P197

Hypokalemia associated with Meropenem administration: a case report

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Introduction
Hypokalemia is one of the commonly encountered electrolyte derangements in clinical practice. Numerous conditions and certain medications can trigger hypokalemia such as Piperacillin/Tazobactam, Flucloxacillin, Cephalexin and Vancomycin.
Case report
A 72-year-old lady was admitted following a fall sustaining a right neck of femur fracture. Prior to this admission, she was on chemotherapy for non-small cell lung cancer and during this admission, she developed neutropenic sepsis. She was initially treated with Teicoplanin and Ciprofloxacin. However, her neutrophil count dropped further and she continued to have fever, hence the treatment was switched to Meropenem. Administration of Meropenem was associated with persistent and difficult to correct hypokalemia despite the absence of other possible aetiologies. The hypokalemia resolved, and potassium returned to normal after completing the course of Meropenem therapy.
Conclusions
Meropenem can cause refractory hypokalemia that could result in ileus, muscle weakness, rhabdomyolysis or respiratory failure. Hence, it is important to be aware of this side effect that can be life threatening. Meropenem-associated hypokalemia is believed to be due to the increased urinary potassium excretion, but it is not confirmed yet whether this is aldosterone-mediated or not.

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P322

Osteoporosis in a young male patient

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A 58 year-old man presented with backache and was found to have T10-T12 vertebral fractures on spinal-MRI. He was diagnosed with osteoporosis on a DEXA-scan (lumbar-spine T-score-2.6) and was treated with Alendronate and Cholecalciferol at a neighboring hospital. He was referred to the endocrine bone-clinic for a second opinion regarding his osteoporosis. He had a history of multiple small bone fractures and Brucellosis that required a 2-month bed-rest. His family history included early-onset osteoporosis in his father and brother. He didn't consume excessive alcohol nor smoke and had no hypogonadal symptoms/signs. Investigations excluded secondary causes of osteoporosis; he had a mildly elevated PTH (8 pmol/l) [ref.1.6-7.2] and low-normal adjusted-calcium (2.34 mmol/l) [ref. 2.2-2.6]. Endocrinopathy and haematological screens were unremarkable; (Hb 154 g/l [ref. 130-168], phosphate 1.01 mmol/l [ref. 0.80-1.50], ALP 65 U/l [ref. 30-130], normal renal/thyroid function, 25(OH)Vitamin-D 50 nmol/l [ref. 50-150], LH 4.3 U/l [ref. 2-12], testosterone 16 nmol/l [ref. 10-30]. He had an elevated 24-h urinary-calcium (10.1 mmol/24h [ref. 2.5-7.5]), which in the absence of other hypercalciuria causes, suggested Idiopathic Hypercalciuria as the main cause of osteoporosis. Other risk factors included the prolonged bed-rest during Brucellosis and family history of osteoporosis. A renal-ultrasound did not show nephrolithiasis or nephrocalcinosis. The patient was started on Indapamide MR (1.5mg once-daily) and was advised to maintain a low-salt diet and high fluid intake (≥2L/day). A repeat DEXA scan 3-years after Alendronate and 1-year of Indapamide treatment showed improvement in the bone mineral density (osteopenia in the lumbar spine;T score -1.9). This case demonstrates the importance of investigating for secondary causes of osteoporosis, especially in young men. It highlights the relevance of family history, as Idiopathic Hypercalciuria is associated with a higher polygenic risk of osteoporosis in first-degree relatives.

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P323

Analysis of the variables related to osteoporosis in chronic kidney disease patients from a latin american cohort

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Introduction
Chronic kidney disease is a pathology that has a great global impact on public health and its association with osteoporosis in this group of patients, however there are few regional descriptions.
Methods
retrospective, descriptive and longitudinal study. Documentary data collection applying validated densitometric criteria as well as the epidemiological characteristics of the population. Tabulation and analysis with SPSS2022.
Results
383 patients were included. In the sociodemographic characteristics, it was obtained that 87.4% of patients with CKD are older than 41 years. No significant difference was found in the comparison by gender (43% F, 57% M). No relationship was found with smoking, alcohol and CKD. The main causes of CKD are DM 36%, HTA 24.5%, mixed 8.6%. Osteoporosis was found in 232 patients, mainly in the male gender (135). The main risk factors associated with osteoporosis were consumption of corticosteroids 178-(65.86%), Obesity 69-(25.46%), and others 37-(11.8%) other than smoking.
Conclusions
The prevalence of kidney disease in South America is similar to other latitudes, the frequency of osteoporosis in our region is unknown due to the scarcity of studies in this regard, which is why it is essential to develop studies of this nature.

Keywords
osteoporosis, epidemiology, chronic kidney disease.
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P324

Age-specific reference intervals of Abbott intact parathyroid hormone (PTH) in adults

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Background
Assays for parathyroid hormone (PTH) are not standardized and therefore method-specific reference intervals are necessary for interpretation of results. PTH increases with age in adults but age-specific reference intervals for the Abbott intact PTH (iPTH) assay are not available. It is challenging and resource intensive to derive age-specific reference intervals by direct method because, depending on number of age partitions, samples from a large number of healthy individuals are required.
Methods
Age-specific reference intervals for Abbott iPTH were derived by an indirect method by means of refineR algorithm using deidentified serum PTH results between September 2015 to November 2022 retrieved from the laboratory information system of a laboratory serving a cosmopolitan population in the West Midlands region of England. The PTH results were retrieved for individuals aged 18 years and older if serum albumin-adjusted calcium and serum phosphate were within reference intervals, serum 25-hydroxyvitamin D was $>$ 50 nmol/l and estimated glomerular filtration rate (eGFR) was $\geq$ 60 mL/min. The refineR algorithm identifies non-pathological results from Box-Cox transformed normal distribution which is then used to derive reference intervals with bootstrap iterations.
Results
PTH increased with age and correlated with age when controlled for 25-hydroxyvitamin D, eGFR and adjusted calcium ($r = 0.093$, $P < 0.001$). The iPTH reference intervals for 18 to 45 years, 46 to 60 years, 61 to 80 years, and 81 to 95 years were 1.6–8.6 pmol/l, 1.8–9.5 pmol/l, 2.0–11.3 pmol/l and 2.3–12.3 pmol/l, respectively. PTH was higher in women compared to men ($P < 0.001$). Age and sex-specific reference intervals could not be derived because of sample size limitation.
Conclusions
Application of the derived age-specific reference intervals will impact the diagnosis and management of normocalcemic hyperparathyroidism, based on current definitions, and secondary hyperparathyroidism.

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P325

Case Report: Ectopic hyperparathyroidism with transient hyperthyroidism

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Ectopic parathyroid glands arise from aberrant migration during early stage of development. Lack of successful identification leads to failed parathyroid surgery and persistent hyperparathyroidism.
Case History
A 57-year-old lady presented with abdominal discomfort and diffuse bone pain. Her corrected serum calcium was raised at 2.81mmol/l, reduced serum phosphate with an inappropriate intact PTH concentration of 10.5 pmol/l. Initial, vitamin D level was low at 16 nmol/l and after treatment, levels rose to 40 nmol/l with persistent hypercalcaemia and elevated PTH. Neck ultrasound and 4DCT Parathyroid were consistent with a right inferior parathyroid adenoma.
Treatment
She underwent neck exploration which proved difficult. All four parathyroid glands appeared normal. An additional gland was found on the right inferiorly in the thyrothymic ligament, which was removed. Histology revealed partially regressed thymus tissue and ectopic parathyroid tissue. Following surgery, she developed palpitations and anxiety, and was hyperthyroid with raised free T4 and free T3 with suppressed TSH. She was offered symptomatic treatment with propranolol as needed. Her thyroid function normalised 4 weeks after surgery. Her corrected calcium rapidly returned to normal and the PTH level was recorded at 1.9 pmol/l. She is currently well, not requiring calcium supplements.
Conclusion
Parathyroidectomy has a success rate of $>$95 % for cure. In about 6-16 % of cases, hyperfunctioning parathyroid gland(s) are found in an ectopic location. Ectopic parathyroid are most frequently found in the anterior mediastinum, the thymus, or the thyroid gland. In our case, ectopic parathyroid tissue seen in the thymus which shares an origin with the parathyroid glands during development. Manipulation of the thyroid at surgery causes transient hyperthyroidism. Intraoperative handling impairs the physical integrity of the cells, with consequent inflammatory response and histologically results in a multifocal granulomatous folliculitis. Usually causes self-limiting hyperthyroidism and clinically significant thyrotoxicosis occurs in a minority. Awareness of this disorder is important to avoid inappropriate treatment.

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P326

Two cases of familial hypocalciuric hypercalcaemia (FHH) due to a homozygous CaSR gene mutation (c.-10C$>$T)

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Familial hypocalciuric hypercalcaemia (FHH) is a rare autosomal dominant condition due to a mutation in the calcium-sensing receptor gene (CaSR). The CaSR is located on chromosome 3 and mutations are commonly heterozygote mutations causing loss of function. Heterozygote mutations demonstrate benign disease with mild, asymptomatic hypercalcaemia. Homozygous mutations in the CaSR usually present with neonatal severe hyperparathyroidism (NSHPT) in the first few weeks of life and is characterised by failure to thrive, dehydration and can be fatal. This report discusses two siblings who present in adulthood with homozygous mutations in the CaSR. Mr A was found incidentally to have hypercalcaemia (adjusted calcium 3.1mmol/l) aged 39 years. PTH was raised at 29.8 pmol/l and urine calcium creatinine clearance ratio (CCCR) was low (0.0085). Genetic testing revealed a homozygous variant in the CaSR gene (c.-10C$>$T) causing an inactivating mutation. There were no end organ complications including nephrocalcinosis or osteoporosis, but he has CKD3 of unclear aetiology. Mr A's sister, Mrs B was diagnosed with presumed PHPT in 1995, aged 16 years, and she underwent a subtotal parathyroidectomy with 3.5 glands removed resulting in iatrogenic hypoparathyroidism. Following the genetic testing in Mr A, testing in Mrs B confirms the same homozygous mutation in the CaSR. The parents of Mr A and Mrs B are consanguineous (first cousins). Their mother has a heterozygous mutation and is normocalcaemic, and the father is deceased. Further cascade analysis is in progress. This is an unusual case of siblings presenting with homozygous CaSR mutations in adulthood and an FHH phenotype, despite this genotype usually associated with NSHPT. Mr A requires cinacalcet to manage his hypercalcaemia which is unusual when compared to heterozygote mutations, and this is partly due CKD3. Further work is required to identify the result of these gene mutations on CaSR function and the corresponding phenotype.

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P327

Hypercalcaemia due to hypervitaminosis D

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Background
Vitamin D supplements are readily available without prescription. Although vitamin D toxicity is infrequent, rising use may lead to an increase in reported cases. We present a case of hypercalcemia and acute kidney injury due to excess vitamin D intake
Case
A 46-year-old woman was admitted with three-month history of lethargy, reduced oral intake, and constipation. She also experienced intermittent nausea and vomiting, but did not report any abdominal pain or significant weight loss. Her medical history included bronchiectasis and reactive arthritis. She had a COVID-

19 infection six months ago, and since then, her symptoms had progressively worsened. Blood tests revealed elevated calcium 3.44mmol/l (normal: 2.20-2.60mmol/l), and low phosphate at 0.66mmol/l, along with acute kidney injury. Further investigations revealed suppressed parathyroid hormone (0.8 pmol/l; normal range: 1.6-7.2) and an increased 24-h urine calcium/creatinine ratio of 2.14mmol/mmolcreat (normal range: 0-0.70). Her thyroid function tests, B12, folate, ferritin, magnesium, albumin, and angiotensin-converting enzyme levels were all normal. No urinary Bence Jones protein was detected, and serum immunoglobulin levels were normal. A CT scan of the thorax, abdomen, and pelvis did not reveal any abnormalities. Upon further questioning, patient disclosed that she had been taking over-the-counter vitamin D drops and calcium supplements since her COVID-19 infection, as she believed they were beneficial and continued to take them. Her vitamin D3 levels were significantly elevated at 614 nmol/l, with a low vitamin D2 level ($<$ 8 nmol/l). With intravenous fluids and discontinuation of vitamin D, her kidney function and calcium improved, and at six-month follow-up, remained normal.

Conclusion

Hypervitaminosis D is an infrequently reported condition that typically arises from an excessive intake of vitamin D. It is crucial to acknowledge that, though rare, hypervitaminosis D can cause hypercalcemia. Patients should receive proper education about benefits and potential risks of vitamin D supplementation.

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P328

A rare case of Intrathyroidal parathyroid adenoma causing refractory hypercalcaemia. A challenging diagnostic and therapeutic journey

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Introduction

Hypercalcemia is a common clinical abnormality seen in clinical practice. One of the leading causes of hypercalcemia is Primary hyperthyroidism from a parathyroid adenoma. While the ectopic parathyroid tissue is typically found in the thymus and anterior mediastinum, Intrathyroidal parathyroid adenoma is a challenging cause of primary hyperparathyroidism leading to persistent hypercalcemia even post-surgery.

Case History

We present a case of 75-year-old female who presented with symptomatic, refractory hypercalcemia who initially underwent two parathyroidectomies.

Initial investigations

Adj Ca 2.9 and PTH 23.7. Sestimibi scan and US parathyroid detected no parathyroid adenoma. She had a neck exploration and biospy suggested right superior parathyroid adenoma.

Progress

She presented after her first parathyroidectomy with symptomatic hypercalcemia with an Adjusted Ca 3.05 and PTH 53. Subsequent Ultrasound parathyroid detected no parathyroid lesions however a 1cm thyroid nodule on the posterior aspect of the right thyroid gland was found.A CT CAP was performed to exclude malignancy which was unremarkable She had a re-do bilateral parathyroidectomy and biopsy samples confirmed left superior and inferior parathyroid hyperplasia Repeat Sestamibi scan showed that appearances were suggestive of a right parathyroid adenoma probably intrathyroidal. She continued to have frequent hospital admissions with severe symptomatic hypercalcemia and a PET CT was requested to ascertain the cause of her hypercalcemia. Her PET CT showed large 2cm parathyroid adenoma in the Right thyroid gland. She had a right thyroid lobectomy which showed a large 2cm intrathyroidal parathyroid and her PTH dropped from 112 to 1.7. Histology confirmed atypical intrathyroidal parathyroid. She remained well and normocalcemic after that.

Discussion

Incidence of IPAs range from 0.7% to 6%. IPAs can be challenging to manage due to complexity of the location. They are often difficult to localize preoperatively and intraoperatively. Studies have shown that MIBI-based techniques are useful in detecting IPA. They have a sensitivity of 60%–83% in detecting IPAs.

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P329

Persistent Hypophosphatemia and recurrent seizures after Ferric Carboxymaltose (FCM)

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Intravenous iron formulations allow administration of high doses of elemental iron enabling correction of total iron deficit in one or two infusions. An underappreciated complication is hypophosphatemia from increased fibroblast growth factor 23 (FGF-23) secretion. An 85-year-old male presented with a second episode of generalized tonic-clonic seizures. The first episode was a month ago, and serum phosphate was 0.2 mmol/l (0.8-1.4). He was treated with phosphate replacement alone. On this admission serum phosphate was 0.3 mmol/l, adjusted calcium 2.02 mmol/l (2.15-2.6), magnesium 0.86 mmol/l (0.7-1.0), vitamin-D 68 nmol/l and parathyroid hormone (PTH) 85 ng/l (15-65), with an eGFR of 62 ml/min. More than a year ago, he was admitted with melaena and iron deficiency anemia while on dual anti-platelet therapy. CT-Chest-abdomen-pelvis, upper gastrointestinal scopy and capsule endoscopy did not reveal any abnormalities and at that time he received two infusions of Ferric Carboxymaltose (FCM, Ferrinject) to replenish iron stores. He was treated with intravenous phosphate polyfusor and the plan was to use alfacalcidol if the calcium levels fell further, expedite the diagnosis of the cause of gastrointestinal bleeding and to use other intravenous preparations like Ferric Derisomaltose (FDI), that have a lower incidence and severity of hypophosphatemia. To reach the correct diagnosis, clinicians must recognize the typical clinical manifestations of intravenous iron-induced hypophosphatemia and identify a specific pattern of biochemical changes (hyperphosphaturic hypophosphatemia caused by FGF-23, resulting in low 1,25 DHCC, hypocalcemia and secondary hyperparathyroidism). Fractional excretion of phosphate if calculated would be high. Prolonged hypophosphatemia can occur and result in myopathy, osteomalacia and fractures. Physicians should monitor serum phosphate levels in patients receiving repeated doses of specific iron formulations. Identifying people who are at risk, such as those with vitamin D deficiency, might decrease the risk of developing such complications.

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P330

Retrospective audit on biochemical, radiological investigations done prior to Parathyroidectomy for Primary Hyperparathyroidism

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As per NICE guideline, referral for parathyroidectomy need to be according the below,

- symptoms of hypercalcaemia or
- End-organ disease (renal stones, fragility fractures or osteoporosis) or
- An albumin-adjusted serum calcium level of 2.85 mmol/litre or above.

Demographics:	Gender	number, %	
	Female	*n*= 126, 72%	
	male	*n*= 48, 28%	
Biochemical analysis:			
Calcium (mmol/l)	>=2.5	<2.5	not done
	n=163, 93%	*n*=10, 5%	*n*=2, 1%
PTH (pmol/l)	>=6.9	<6.9	not done
	n=144, 82%	*n*=2.9, 16%	*n*=2, 1%
Vitamin D (nmol/l)	>50	<50	not done
	n=94, 53%	*n*=58, 33%	*n*=14, 8%
Phosphate (mmol/l)	done		not done
	n=94, 53%		*n*= 81, 46%
Random urine calcium:	done		not done
creatinine clearance ratio	*n*=77, 44%		*n*=98, 56%
24h urine calcium	done		not done
	n= 76, 43%		*n*=99, 56%
Imaging:			
Ultrasound parathyroid	done		not done
	n= 159, 90%		*n*= 16, 10%
MIBI	done		not done
	n=151, 86%		*n*=24, 24%
4D CT	done		not done
	n=29, 16%		*n*=149, 83%
Renal tract USS	done		not done
	n=89, 50%		*n*=86, 49.9%
DEXA	DONE		not done
	n=137,78%		*n*=38, 21%
	normal *n*=29,		
	abnormal *n*= 108		

Methods
We conducted a retrospective analysis of investigations done as per recommendation of NICE guidelines for patients who underwent Parathyroidectomy under the care of 2 parathyroid surgeons at UHCW between 2017 to 2022. Data was collected from the hospital database. Data analysed using Microsoft excel.
Results
13 patients had recurrence following the parathyroidectomy (some of these patients were refereed from different hospitals).
Discussion
In this retrospective audit more than half of the cohort had not been screened for urine calcium excretion to exclude familial hypocalciuric hypercalcemia and 50% didn't had ultrasound of the renal tract. Although 98.3% patients had confirmed histology, all investigations should be performed as per NICE guidelines before undergoing a parathyroidectomy.

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P331

An interesting case of a complex parathyroid adenoma, mimicking the biochemistry of Parathyroid Carcinoma

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A 75-year-old lady was referred to our centre from a local DGH, where she presented with constipation, reduced consciousness and acute confusion. She was found to have severe hypercalcaemia (Adjusted Calcium 5.21mmol/l), with PTH of 1473ng/l, and urine calcium of 13.8mg/24 h. Based on available biochemistry, a presumptive diagnosis of Parathyroid Carcinoma was made, and Hypercalcemia management was started. She was given about 3 litres of fluid and 60mg of pamidronate. Subsequently, Cinacalcet was created at 30mg BD dose and quickly up-titrated to 90mg QDS due to resistance in decline of calcium levels. There was a worsening of renal function. She was commenced on Renal Replacement therapy to reduce her calcium in preparation for Parathyroid Surgery. She had an NM parathyroid SPECT CT and MIBI, which showed tracer retention in soft tissue in the right paratracheal and retrosternal region, suggesting a parathyroid lesion. The histopathology of the lesion showed a Right inferior parathyroid gland nodule that was finely encapsulated. The lesion was reminiscent of a paraganglioma with abundant finely granular pale staining cytoplasm and no evidence of invasion or necrosis. Despite the paraganglioma-like appearance, the tumour cells were strongly positive for cytokeratin AE1AE3, MNF116 and PTH stains, while the CD56, S100, TTF1 and synaptophysin stains were negative. The Chromogranin stain was weakly positive, and M1B1 stain showed a very low proliferative index. The overall gland architecture was preserved, with surrounding normal parathyroid and adipose tissue. The specimen was labelled as a Parathyroid adenoma, with paraganglioma-like architecture but negative stains. Her post-operative stay was complicated by severe hypocalcaemia, Hospital Acquired Pneumonia and need for ITU stay. She was managed with Intravenous Calcium and Alfacalcidol replacement till her Calcium levels stabilised. This case highlights the treatment challenges of a complex parathyroid adenoma, mimicking a Parathyroid Carcinoma, and the challenging peri-operative Calcium management.

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P332

A Rare presentation of a common Endocrine Disorder: Grave's Thyrotoxicosis induced severe symptomatic Hypercalcemia

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Introduction
Hypercalcemia has wide spectrum of diagnosis. Hyperthyroidism is known cause of parathyroid hormone independent cause of hypercalcemia. Increased osteoclast activity with excess bone resorption is underlying cause. Thyrotoxicosis associated hypercalcemia is usually asymptomatic, mild to moderate hypercalcemia is seen in 20% of patients, but severe hypercalcemia is rare. We report a case of young male who presented with abdominal pain, vomiting secondary to Grave's disease induced symptomatic severe hypercalcemia.
Clinical Case
33 year male known case of macroprolactinoma, presented with five days history of abdominal pain, vomiting with on and off palpitations, dizziness but no history of weight loss, kidney stones. He was on cabergoline 500 mg twice weekly. Family history was unremarkable. Examination revealed tachycardia, dry mucous membranes, bilateral gynecomastia and generalized abdominal tenderness. Neck and Testicular examination was normal. Initial investigations showed elevated adjusted calcium of 3.22mmol/l (normal range:2.08–2.80 mmol/l) with suppressed Parathyroid hormone and low Vitamin D, other investigations were normal. Further Investigations ruled out multiple myeloma, granulomatous disease, malignancy. Treatment was initiated with Intravenous hydration followed by intravenous Pamidronate 60mg in accordance with national guidelines for management of hypercalcemia. Due to persistent symptoms of palpitations, abdominal pain, tachycardia, thyroid function tests were performed for suspicion of Thyrotoxicosis. This showed significantly elevated free T4 level, free T3 levels with suppressed thyroid stimulation hormone. TSH receptor antibodies(TRAb) were elevated confirming Grave's disease. Carbimazole 40mg once a day was initiated. In this case, the main cause of this severe hypercalcemia was considered to be Grave's disease, other etiolgies were ruled out. His symptoms improved after starting Carbimazole and he was discharged with outpatient follow up with endocrinology department.
Conclusion
This is an atypical presentation of hyperthyroidism-induced symptomatic severe hypercalcemia. Clinicians should be aware of this unusual association, so that a prompt initial evaluation and proper intervention can be administered

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P333

An unusual case of refractory hypocalcaemia

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Introduction
Although skeletal metastatic diseases have commonly been associated with hypercalcemia; we present a case of severe hypercalcemia secondary to extensive skeletal sclerotic metastatic disease.
Case
A 92 year-old female was admitted from nursing home following a fall... She is known to have Alzheimer's disease, Type 2 diabetes and chronic kidney disease.
Lab results
Corrected Calcium: 1.6 mmol/l with normal C. Ca, 1 year ago (normal range 2.20 to 2.60). ALP $>$4555 IU/L(30-130), PO4: 1.29 mmol/l (0.8-1.5), Hb: 87 g/l (115-145), MCV 101 fL(81-102), eGFR 57 (baseline), Bilirubin, INR and liver enzymes were normal. Further tests shewed Vitamin D of 65.1 nmol/l ($>$49.9) and PTH of 41.5 pmol/l (2.7-11.1) Her severe cognitive impairment meant symptoms of hypocalcaemia were not elicitable.
Management
She was started on IV Calcium gluconate with oral alfacalcidol. Her Corrected Ca continued to be low despite of repeated Calcium infusions and alfacalcidol. Given the above abnormal blood tests (unexplained severe Hypocalcaemia with a very high ALP) a CT Thorax, Abdomen and Pelvis with contrast was done which showed evidence of extensive skeletal sclerotic metastatic disease with unclear primary although some suspicious areas were evident in left breast.
Discussion
Hypocalcaemia is uncommon in the context of malignancy. It is believed that osteoblastic bone metastasis can lead to increase influx of calcium and phosphate into the bone leading to hypocalcaemia. Common cancers associated with this are Breast and Prostate cancers.
Treatment
The treatment of Hypocalcaemia secondary to osteoblastic metastatic disease includes high dose of calcium and vitamin D-especially the active form Calcitriol-Treatment of underlying cancer may help. Rarely, patients may require prolonged calcium infusion.

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P334

Primary Hyperparathyroidism in Pregnancy

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Introduction
Hypercalcaemia in pregnancy is an uncommon event that can cause major maternal morbidity and/or foetal morbidity and mortality. We present a case report and discuss management.
Case
A 34-year-old woman was seen initially in endocrinology clinic with primary hyperparathyroidism. A neck ultrasound scan did not identify a parathyroid adenoma, but parathyroid MIBI scan suggested a left inferior parathyroid adenoma. Plasma metanephrines were normal, and a genetic testing ruled out multiple endocrine neoplasia-1. She got pregnant and then reviewed in antenatal clinic with calcium check every 4 weeks. Her case was discussed in a meeting between endocrinologist, obstetrician, and surgeon who agreed on going ahead with parathyroid surgery, which took place at 26 weeks gestation. Postoperative calcium was normal (2.36 mmol/l), PTH was low but normalised a few weeks later. The histology showed parathyroid adenoma, however one of the lymph nodes revealed a 1 mm focus of metastatic papillary thyroid cancer. Thyroid multidisciplinary meeting recommended surveillance. At 39 weeks, she had induction of labour due to reduced foetal movement, and gave birth to a healthy 2415 gram female baby.
Conclusion
Primary Hyperparathyroidism in pregnancy is a threat to mother and child. Medical management may be appropriate in mild disease, but in moderate to severe disease, parathyroidectomy under general anaesthesia in the second trimester is safe.

P334 tbl-7	Adjusted calcium (2.26-2.60 mmol/l)	Parathyroid hormone (19.0-67.0 pg/ml)
Prenatal	2.83	47.1
16 weeks gestation	2.9 >> Intravenous fluids >> 2.74	
20 weeks gestation	2.9	

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P335

Iatrogenic hypercalcaemia in a patient with duchenne muscular dystrophy: a case report highlighting multifactorial aetiology and therapeutic considerations

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Background
Duchenne muscular dystrophy (DMD) is a progressive muscle disorder characterised by muscle wasting and weakness. It is often associated with intracellular hypercalcaemia in dystrophin deficient muscle leading to disease progression. We present a comprehensive case report of extracellular hypercalcaemia in a DMD patient, a rare complication, emphasising the interplay of iatrogenic factors, immobilisation, and therapeutic approaches.
Case Presentation
A 28-year-old male with DMD, wheelchair-bound, on continuous CPAP with a background of severe cardiomyopathy, presented with fatigue, anorexia, and constipation. Laboratory assessment revealed markedly elevated serum calcium levels (3.78 mmol/l), normal vitamin D levels and suppressed parathyroid hormone (PTH) levels. A malignancy screening was done including CT of thorax and abdomen which showed no lesions, and a myeloma screening was negative. Thyroid function tests and cortisol were normal, ALP was within range ruling out primary bone disease. An in-depth examination of the patient's medical history uncovered that he was on multiple doses of daily nutritional supplement milkshakes that provided excessive amounts of calcium- 338% of reference nutrient intake (RNI). This was combined with prolonged immobilisation due to respiratory insufficiency.
Management and Outcome
The patient was diagnosed with iatrogenic hypercalcaemia induced by a combination of inappropriate supplementation and immobilisation-related factors. Intravenous fluids and furosemide were administered to lower calcium levels under close monitoring to avoid fluid overload. A dietician was consulted, and his nutritional supplements were optimised to lower calcium intake whilst still meeting energy and protein requirements. Meticulous monitoring of electrolytes, renal function, and bone health was initiated. Gradual normalisation of calcium levels and clinical improvement occurred over several weeks.
Discussion
This case underscores the need for tailored management in DMD patients, recognising the intricate relationship between iatrogenic factors, immobilisation, and hypercalcaemia. Awareness of the potential risks posed by unsupervised supplementation and prolonged inactivity is vital. Monitoring of calcium, vitamin D, and PTH levels is pivotal in preventing hypercalcaemia-related complications, which could exacerbate muscular weakness and impact overall health.
Conclusion
Iatrogenic hypercalcaemia demands consideration when evaluating DMD patients with unexplained symptoms, especially in the presence of inappropriate supplementation and immobilisation. A comprehensive approach encompassing thorough history-taking, judicious prescribing practices, and vigilant monitoring is indispensable to prevent and manage hypercalcaemia. Healthcare practitioners must be attuned to the complex interplay between these factors, ensuring optimal care for DMD patients while minimising potential adverse outcomes.

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Endocrine Cancer and Late Effects

P302

Thyroid function in patients receiving immune checkpoint inhibitors: a large real-world cohort study

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Objective
This study aimed to characterise the relationship between immune checkpoint inhibitors (ICIs), which are commonly used to treat cancer, and thyroid dysfunction in terms of the proportions affected, timing of onset, sequalae and risk factors.
Design
Retrospective cohort study
Methods
Patients with normal baseline thyroid function who received an ICI were included. Proportions of incident hyperthyroidism or hypothyroidism (subclinical, overt or isolated hyperthyroxinemia/hypothyroxinemia) were determined along with median times to onset and subsequent thyroid function statuses. Hazard ratios (HRs) and 95% confidence intervals for associations between baseline factors and abnormal T4 were estimated using Fine and Grey regression.
Results
1364 patients were included. Lung cancer and pembrolizumab, respectively, were the most common diagnosis and ICI. Hyperthyroidism was observed in 43.1% of patients, including in 73.5% receiving ipilimumab with nivolumab. In melanoma, hyperthyroidism was more common with adjuvant compared to palliative ICIs (45.2% vs. 26.9%). Hypothyroidism was observed in 36.9% of patients. Around half with subclinical thyroid dysfunction returned to normal, while 44.2% of overt hyperthyroidism led to overt hypothyroidism in a median time of 1.6 months. Raised T4 was associated with reduced estimated glomerular filtration rate (eGFR) (HR = 1.73, 1.26-2.38), body mass index (BMI) $\geq$40kg/m2 (HR = 2.96, 1.66-5.29) and, inversely, with raised aspartate aminotransferase (HR = 0.62, 0.41-0.96).
Conclusion
Thyroid dysfunction affects up to three quarters of patients receiving ICIs. Clinical courses vary from temporary dysfunction to rapid progression from hyperthyroidism to hypothyroidism. Further investigation is merited given increasing ICI use and the effect of thyroid dysfunction on mortality and quality of life.

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P46

Utility of recumbent, age-adjusted plasma normetadrenaline thresholds to guide identification of small SDHB-deficient paragangliomas in clinical practice

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Background
Plasma normetanephrine levels are an annual screening tool for detecting paragangliomas in SDHB mutation carriers. Sensitivity is increased when patients are fasting and recumbent prior to phlebotomy, to allow use of age-adjusted reference ranges rather than the 1180 pmol/l upper limit for ambulatory patients of any age. We present our clinic's results of samples taken after 30 minutes of recumbency to determine if applying age-adjusted ranges guides radiologists in identifying small paragangliomas.
Methods
Plasma normetadrenaline and reports of magnetic resonance with diffusion-weighted imaging from neck to pelvis were assessed for 170 adults with a pathogenic SDHB mutation. After excluding those without local plasma results and imaging in the past 3 years and those with known secretory paraganglioma, the results of 122 patients were separated into five age categories from the literature. Patients with levels above the age-related limit and below 1180 pmol/l were highlighted for radiology re-review.
Results
Ten individuals had levels above their respective age-adjusted thresholds: three patients, each over 70 years, had plasma normetadrenaline exceeding 1180 pmol/l without paraganglioma identified; seven patients had a level exceeding the upper limit of only the age-adjusted recumbent range which led to three radiological findings: two have $<$2cm phaeochromocytomas and one has a para-aortic cluster of cells with restricted diffusion suggestive of paraganglioma.
Conclusions
Utilising recumbent, age-adjusted reference ranges allows those patients with potential for a small secretory lesion to be highlighted to the reporting radiologist. Where recommended age brackets increment by decade until the age of 60, existing data does not provide a suitable range for those over 70 years. Given the low rate and small size of tumour detection in this cohort with "intermediate" normetadrenaline, the age-adjusted range is likely less useful for screening hypertensive patients without a familial syndrome so recumbency can be prioritised for those with a genetic predisposition.

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P47

In silico-based analysis of differentially expressed miRNAs involved in the ovarian cancer

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Ovarian cancer is one of the major cause of death among women worldwide with high incidence. Ovarian cancer can be categorized into epithelial, non-epithelial (germ cell and sex cord-stromal cell), and metastatic (usually develop from surrounding cancerous organs). Recently, several approaches have been studied to control ovarian cancer at the transcriptional or post-transcriptional levels using small non coding RNAs including microRNAs. We carried out a meta-analysis of previously published miRNA expression datasets (two human database GSE119055 and GSE216150 (Dong *et al*., 2019; Gumusoglu-Acar *et al*., 2023) to identify the miRNAs and its target genes with biological processes and pathways using several bioinformatic software. Meta-analysis of miRNA datasets revealed that a total of 270 differentially expressed miRNAs, including 164 upregulated and 106 downregulated miRNAs in cancerous samples in comparison to normal samples. As a result, 12 of the DE miRNAs were identified to be shared by two human datasets (GSE119055 vs GSE216150). miRWalk analysis showed a total of 140 common target genes for these miRNAs and their functional annotation revealed that these common genes were mainly associated with signal transduction as well as in ErbB and Estrogen signaling pathways. Moreover, among these genes, AKT3, which corresponded to the both pathways provided poor prognosis of the ovarian cancer patients in Kaplan-Meier Plotter website. These findings indicated that the defined miRNAs and their target genes could be used for future molecular studies which lead to identify an early effective treatment for the ovarian cancer.
References
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Gumusoglu-Acar, E. *et al*. (2023) 'Metabolic pathways of potential miRNA biomarkers derived from liquid biopsy in epithelial ovarian cancer', Oncol Lett, 25(4), p. 142.

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P48

MicroRNA drivers of resistance to androgen deprivation therapy in prostate cancer

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Introduction
Prostate cancer is the most prevalent malignancy affecting Western males. Initially an androgen-dependent disease, androgens bind to the androgen receptor and drive expression of genes that promote proliferation and evasion of apoptosis. Although advanced disease involves reduced androgen dependence, androgen receptor signalling remains a key driver of growth. Androgen deprivation therapy (ADT) is first line, but resistance inevitably develops. Abiraterone and Enzalutamide are drugs widely used in ADT and are androgen synthesis and androgen receptor signalling inhibitors respectively. The shortage of alternative treatment options means acquired resistance to these drugs is a major clinical problem. MicroRNAs (miRs) are important mediators of post-transcriptional gene regulation and show altered expression in cancer. Several have been linked to the development of resistance to ADT. Manipulation of such miRs may be a pathway to breakthrough treatments for advanced prostate cancer. This study aimed to validate ADT resistance-implicated miRs and their clinically relevant targets.
Materials and Methods
Small RNA-sequencing of Abiraterone- and Enzalutamide-resistant C42 prostate cancer cells identified miRs dysregulated as compared to parental cells. Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) was used to validate altered expression of candidate ADT resistance-implicated miRs 195-5p, 497-5p and 29a-5p in ADT-resistant and -responsive prostate cancer cell lines, patient-derived xenografts (PDXs) and primary prostate cancer explants.
Results and Discussion
This study suggests a possible role for miR-497-5p in the development of ADT resistance in prostate cancer. MiR-497-5p expression was increased in ADT-resistant vs ADT-responsive prostate cancer cells. Importantly, miR-497-5p expression was also increased in Enzalutamide-treated, castrated (ADT-mimicking) PDXs vs intact PDXs. Candidate clinically relevant targets of miR-497-5p in prostate cancer were identified by mining AGO-PAR-CLIP-seq data sets and may include AVL9 and FZD6.
Conclusion
In summary, this study identified microRNAs implicated in prostate cancer resistance to androgen deprivation therapy that may represent novel therapeutic targets for advanced disease.

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P49

Neuroendocrine cancer: An ideal patient pathway

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Neuroendocrine cancers represent the tenth most prevalent type of cancer in England. However, people with neuroendocrine cancer currently face significant inequities throughout the entire care pathway – from suspected cancer to follow-up care. Despite expert clinical guidelines, there is no currently available national Neuroendocrine Cancer Patient Referral and Care Pathway. Guiding principles of optimal patient pathways include the promotion of earlier, accurate diagnosis and care through earlier:

- recognition/suspicion of diagnosis
- access to disease appropriate diagnostics
- access to disease appropriate clinical expertise and treatment
- access to individualised supportive services and follow on care – whether cure is achievable or not.

To this end, Neuroendocrine Cancer UK, alongside a multi-stakeholder group,

including patients, advocates, expert clinicians, Health Policy Partnership, industry and NHS healthcare representatives, have developed a pathway to address and reduce the inequities identified. It aims to reduce the burden of these cancers and to support people with neuroendocrine cancer in seeking the right care, in the right place, at the right time. As the incidence and prevalence of Neuroendocrine Cancer continues to increase there is a consequent urgent need to accelerate the uptake of the care pathway to support earlier diagnosis, help standardise care, and reduce the cost burden to the health system, to ensure patients benefit from ongoing initiatives to improve cancer care across the UK. Having gained patient and multi-professional endorsement, including Society of Endocrinology members, the pathway was launched at a parliamentary event, held in June 2023, to demonstrate the importance of, and next steps for, integration within NHS England practice. It is vitally important that there is a consistent approach to the interpretation and implementation of this pathway, as national guidance across NHS organisations, to avoid the persistence and exacerbation of existing inequities. The Neuroendocrine Cancer: Ideal Pathway is available to read and download here: https://www.neuroendocrinecancer.org.uk/-campaigns/nc-pathway/

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P50

Survival rates in metastatic gastroenteropancreatic neoplasms after multidisciplinary approach

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Background
Prevalence of neuroendocrine neoplasms is increasing and multidisciplinary approach is mandatory. This study aimed to assess the outcome of patients with gastroenteropancreatic neoplasms (GEP NEN) presenting in a tertiary endocrine center.
Methods
Retrospective study on 36 patients (16 M/20 F) with pathology confirmed GEP NEN, aged 51.9 $\pm$ 12.7 years. Serum chromogranin A, serotonin, neuron-specific enolase, NT proBNP, urinary 24h 5 hydroxyindoleacetic acid were measured. Imaging with computed tomography, magnetic resonance were used for staging and assessment of tumour size. Whole-body somatostatin receptor (SSTR) imaging was performed in a subgroup.
Results
Metastatic disease was present in 21 patients (58.3%). Median progression free survival (PFS) was 36 months, with no significant differences between different localizations. Median PFS was not reached for G1 tumors, was 26 months for G2 tumors and 3 months for G3 tumors. Median overall survival was not reached, with 86% of patients' alieved at 3 years, and 80% of patients' alieved at 5 years. Tumor size and serotonin levels at diagnosis were significantly higher in patients that will progress later than in patients with no further progression, $P = 0.05$ and 0.01 respectively.
Conclusions
initial endocrine assessment is helpful in stratifying risk in gastroenteropancreatic tumors and early diagnosis with smaller tumors improved prognosis.

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P198

Evaluation of a national genetic testing service for monogenic endocrine disease in Scotland; enforcement of referral criteria may result in missed opportunities for genetic diagnosis

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Background
Establishing a genetic diagnosis in patients presenting with potential monogenic endocrine disorders can provide benefits for the individual and wider family. Next-generation sequencing (NGS) gene panels provide a time- and cost-efficient platform for testing. A Scottish NGS endocrine testing platform, comprising 30 genes (11 individual panels), was established in 2018. A national genomic test-directory provides eligibility criteria for testing, but these are yet to be evaluated against 'real world' referrals.
Methods
Index cases referred for Endocrine NGS gene panel testing (12/2018-12/2022) were evaluated for baseline clinical characteristics, indication for testing and test outcome. Referrals were assessed against national eligibility criteria (v1.0/2022).
Results
1131 endocrine gene panel requests representing 1057 index cases were identified (>1 panel for some patients), with a mean age of 45 years and a female predominance (~1:2 M:F). Of the most frequently requested panels (Familial Hyperparathyroidism (FHPT) ($n=329$), Familial Hypocalciuric Hypercalcaemia (FHH) ($n=220$), Multiple Endocrine Neoplasia1/4/Familial Isolated Pituitary Adenoma (MEN1/4/FIPA) ($n=196$) and Phaeochromocytoma/Paraganglioma (PPGL) ($n=121$)), the proportion of index cases with pathogenic/likely pathogenic variants varied markedly (i.e. 5.5%, 22.3%, 3.6%, 18.9%, respectively). Several patients referred for FHPT testing harboured pathogenic *CASR* variants, consistent with a diagnosis of FHH. Whilst the majority of requests met referral criteria, ~40% of FHH referral contained insufficient/in-consistent biochemical information to assess eligibility. Notably, ~30% of PPGL referrals did not meet testing criteria, including ~10% of cases with a positive genetic test result. Of the more commonly requested panels, PPGL and MEN1/4/FIPA panels were the most and least cost-effective (~£1300 and ~£7000 per positive test, respectively).
Conclusions
Combining panels improves diagnostic yields for disorders with overlapping clinical phenotypes (e.g. FHPT & FHH). Strict enforcement of testing eligibility criteria may result in 'missed' genetic diagnoses, the implications of which should be considered when reviewing and/or implementing future test criteria.

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P199

Stroke Risk in Childhood, Adolescent, and Young Adult (CAYA) Cancer Survivors who Received Cranial Radiotherapy

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Background
CAYA cancer survivors who received cranial radiotherapy have an increased risk of stroke. Traditional cardiovascular disease (CVD) risk factors likely contribute, but there are no guidelines for management of stroke risk in this population. It is unclear how general CVD risk calculators (QRISK3, Framingham Risk Score) compare to specific cancer survivors scores such as the Childhood Cancer Survivors Study Stroke Risk Calculator (CCSS).
Objective
To describe traditional CVD risk factors in an UK CAYA survivor population and compare outcomes of 3 risk calculator models (QRISK3, FRS and CCSS).
Results
99 CAYA patients (identified from consecutive late effects clinics at a tertiary oncology center: March-May 2021) were included; mean age 35.4 (SD 10.5) years old; mean age at diagnosis 11.8 (SD 5.6) years old, female (46%), Caucasian (86%), active smokers (7%), diabetic (12%), mean HbA1c 39.3 (SD 19.8) mmol/mol, Chol:HDL 3.9 (SD 1.1) and SBP 127 (SD 16) mmHg. Risk factor data available for 89.9%. 90% received cranial radiotherapy; mean dose 47.5 (SD 8.9) Gy. Neoplasms included astrocytoma (23.2%), medulloblastoma

Table 1: 10-year CVD risk (FRS/QRISK3) and stroke risk (CCSS)

10-year risk	FRS (calculable in 39/99)	QRISK3 (calculable in 85/99)	CCSS (calculable in 65/99)
<5 %	25	67	20
≥5%<10%	8	14	16
≥10%<20%	6	1	29
≥20%	0	3	0

(22.2%) and germinoma (13.1%).
For patients with calculable FRS, QRISK3 and CCSS scores, 94.4% ($n=17$) and 100% ($n=38$) who had CCSS 10-year stroke risk of 5-20% had a lower predicted risk of CVD using FRS and QRISK3, respectively. Patients who had cranial radiotherapy were more likely to have an underestimated common CVD calculator scores. 6 patients in our cohort had a stroke (CCSS score could not

be calculated as >40yrs).
Conclusion
Common CVD risk prediction tools underestimate the risk of stroke compared to the CCSS calculator.

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P200

SURvey of Surgeon's and Physician's experiences of GEnetic testing in patients with Familial Endocrine Syndromes: SurGe in UK and Abroad

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Introduction
Genetic testing for Familial Endocrine Syndromes has an important role in diagnosis, timing/extent of surgery, and follow-up. Our survey explored experiences and attitudes towards genetic testing in the UK and Abroad.
Methods
Attendees of 2022 Conferences of ESES, BSPED, SfE, BAETS and AsianAES were asked to participate in an online survey (31 questions on demographics; genetic testing availability and experiences; clinical scenarios).
Results
One-hundred-and-eight surveys were completed (male:51;47%). Most were ≥40years ($n=71$;66%); and majority were surgeons ($n=67$;62%). Fifty-one (47%) were from the UK and 57(53%) from Abroad; 56% worked in teaching hospitals. Most respondents (75%) had seen patients with potentially genetic endocrine disorders very/somewhat often, and <5% infrequently/rarely; similar for surgeons vs physicians; and UK vs Abroad (both $P>0.05$). Genetic services were generally available (88%), alike for surgeons vs physicians, and for UK vs Abroad (both $P>0.05$). Overall, 69% felt that genetics referrals were very/somewhat easy. Only 35% could request testing themselves, UK (49%) more than non-UK (23%;$P<0.05$), and surgeons (27%) less than physicians (49%; $P<0.05$). The majority (mean:84%) would request genetic testing in the scenarios for which it would be recommended by current guidelines; similar for surgeons vs physicians, and for UK vs Abroad (both $P>0.05$). Specifically for MEN-1, if ≥2 tumours, 54% would always request genetics, compared to 18% if one potentially associated tumour. In the latter scenario, 41% surgeons would always/sometimes request vs 7% of physicians ($P<0.05$). Geographically, UK (always:71%/never:5%) vs Abroad (39%/32%) always/never requested genetics in this scenario ($P<0.05$).
Conclusion
The respondents represent real-world evidence of genetic testing in endocrine patients. The majority had similar experiences and attitudes. However, physicians were more likely to request test than surgeons, and UK more than Abroad. This should be explored further, as it might delay timely performance of genetic testing.

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P201

Paraganglioma syndromes data from a single centre

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Paraganglioma syndromes (PGL) encompass a diverse group of rare neuroendocrine tumours that are characterised by hereditary predisposition and present unique diagnostic and management challenges. We performed an audit to assess the prevalence, presentation, testing, diagnosis, and treatment of these patients. We did a retrospective analysis of the genetic database and medical records of PGL patients diagnosed and managed at our hospital up till April 2023. A total of 119 cases were identified. 71% carried the SDHB mutation (PGL4), 18% carried SDHD (PGL1), 6% SDHC (PGL3) and 5% SDHA (PGL5) mutations. None were identified with SDHAF2 mutation (PGL2). All tumours presenting in 11 SDHD (PGL1) cases were head and neck tumours (HNPGLs), of which 31% were unilateral carotid body tumour (CBT), 9% bilateral CBT, 4% glomus jugulare tumour, and 4% skull base (SKB) tumour. Four cases were secretory with elevated plasma metadrenaline, plasma normetadrenaline and methoxytyramine. None of the 7 cases of SDHC (PGL3) had any tumours. Of the 84 cases of SDHB (PGL4), 8 had CBT, 5 had Pheochromocytoma-Paraganglioma (PPGL), 2 had SKB tumour, 2 had renal cell carcinoma and 1 had bladder tumour. 11% were secretory with high metanephrines. Of the 6 SDHA (PGL5) cases, 1 presented with pituitary macroadenoma and pheochromocytoma. 40 of the 119 cases were index cases and 79 family members. Penetrance by 60 years for developing PPGL/HNPGL was 58% in SDHB, 66% in SDHC and 74% in SDHD index cases. Penetrance in non-probands was 22.5% in SDHB, 25% in SDHC, 50% in SDHD. We offer screening and individualised treatment as per international guidelines. We measure plasma free or urinary fractionated metanephrines, MRI scan for imaging and for functional PGL we use [68Ga]-DOTA-SSA PET/CT. For children we start screening at 6-10 and 10-15 years for SDHB and SDHA/C/D mutation carriers, respectively.

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P202

Probing the functional role of peptidylglycine alpha-amidating monooxygenase (PAM) in the maintenance and transition towards neuroendocrine prostate cancer

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Castration-resistant prostate cancer (CRPC) is an androgen-independent subtype of prostate cancer (PCa) that develops in response to androgen deprivation therapy (ADT). In some advanced CRPC cases, tumors can develop the neuroendocrine (NE) phenotype and progress towards an aggressive PCa subtype known as treatment-induced NE PCa (NEPC), which is characterized by an increase in the population of NE cells that secrete neuropeptides promoting cancer progression. A key player in neuropeptide synthesis is peptidylglycine alpha-amidating monooxygenase (PAM), a bifunctional cuproenzyme responsible for the α-amidation-dependent activation of neuropeptides. Due to its use of copper as a co-factor for its activity, PAM is also implicated in copper homeostasis, a process that is dysregulated during PCa development. Given its function in pathways related to NEPC, we hypothesized that PAM may play a role in the maintenance and transition to NEPC. *In silico* analysis confirmed that *PAM* expression is upregulated in NEPC tumors. In cell line models for prostate adenocarcinoma and CRPC, we found that *PAM* expression is differentially regulated by androgen. Further, through *in silico* analysis, we identified four intronic *cis*-regulatory elements in the *PAM* locus that can mediate androgen-dependent differential regulation. To determine the functional role of PAM in PCa progression, we knocked down *PAM* in various prostate cell models and subjected hormone-refractory PCa cells with *PAM* knockdown to ADT to model the transition towards NEPC. *PAM* knockdown led to alterations in the expression of genes involved in NE differentiation and copper homeostasis. Using paracrine signaling and cancer hallmark assays, *PAM* knockdown reduced the secretion of growth-promoting factors and mitigated the aggressive nature of hormone-refractory and neuroendocrine PCa cells. Overall, our findings demonstrate the coordinated involvement of PAM in neuropeptide synthesis and copper homeostasis and how these two pathways may contribute to the maintenance and transition towards NEPC.

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P203

Selective use of mutational analysis helps with diagnostic challenge in hypercalcaemia

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A 34-year-old was referred for a second opinion regarding his incidental mild hypercalcemia ranging between 2.56 mmol/l and 2.88 mmol/l, with a corresponding PTH ranging between of 3.3 pmol/l and 6.8 pmol/l (laboratory reference range 1.3-9.3 pmol/l). He did not have a history of renal calculi or fractures. He reported chronic recurrent diarrhoea, weight loss, low mood and chronic headache. There was no known family history of calcium disorders. His examination did not reveal abnormalities. His 24-h calcium creatinine ratio was 0.02 and 24 h urinary calcium was high at 15.91 mmol/24 h. A previous ultrasound of the neck did not identify parathyroid lesion. Familial hypocalciuric hypercalcaemia was clinically unlikely due to the hypercalciuria. A germline mutational analysis was carried out to rule out monogenic causes of hyperparathyroidism using the available eight gene panel for monogenic causes of hypercalcaemia. He was found to be heterozygous for MEN1 mutation, c.758C>T p.(Ser253Leu), which is a known pathogenic mutation. The variant

has been reported with hyperparathyroidism and MEN1, with a biallelic loss being reported in a sporadic parathyroid tumour. The proband's first degree relatives have been offered mutational analysis. Imaging and biochemical investigations so far have not revealed other tumours or endocrine abnormalities associated with MEN1. Mutational analysis is associated with a low yield of positivity in isolated primary hyperparathyroidism. In this case, the single pointer of a likely underlying inherited cause is the relatively young age at presentation. There are numerous points of discussion in this case including the approach to diagnosis of hypercalcaemia in a person with a fluctuating level of calcium, with a low unsuppressed PTH and the indications for mutational analysis to aid diagnosis. Here, the diagnosis of MEN1 is likely to be transformative to his outcome and his affected first-degree relatives.

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P336

Ectopic ACTH-dependant Cushing's syndrome in MEN2A and metastatic medullary thyroid carcinoma: Challenges beyond Diagnosis

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Introduction
Multiple endocrine neoplasia, type 2A (MEN 2A) is a hereditary syndrome characterized by medullary carcinoma of the thyroid, pheochromocytoma, parathyroid hyperplasia or adenomas due to mutation in RET oncogene on chromosome 10. Complications can occur as a result of ectopic ACTH causing Cushings syndrome. We present here a case initially presenting to hospital with worsening shortness of breath on a background of metastatic medullary thyroid cancer and family history of MEN2A syndrome.
Case Presentation
A 57-year-old male presented to the hospital with a left-sided pleural effusion along with pericardial effusion, refractory hypokalemia and hypocalcemia. A pleural tap confirmed Chylothorax effusion. He also developed in-patient psychosis and subsequent investigations confirmed Cushings syndrome due to ectopic ACTH as seen on urinary collections ($>$27000 nmol/24hr) and overnight dexamethasone suppression test revealing cortisol $>$4000 nmol/l with high ACTH (290ng/l). He was started on metyrapone titrated up to the maximum recommended dosage, and steroids along with ketoconazole. He was discussed with surgeons and oncology for bilateral adrenalectomy but given the extent of disease spread and progressive frailty, this was deemed inappropriate. He was also offered tyrosine kinase inhibitor therapy (Selpercatinib) but was unable to complete the same due to worsening frailty. He developed chronic diarrhea due to high calcitonin levels and bile salt malabsorption and was eventually commenced on palliative treatment.
Conclusion
This case highlights the complications and challenges of managing a complex MEN2A syndrome. Despite quiescent disease for years, rapid deterioration despite treatment contributed to the patient's overall decline and frailty. A newer option would be the new drug osilodrostat (11-beta hydroxylase inhibitor). Although there is limited clinical experience in it, studies have shown promising results in controlling cortisol levels. This along with further details like complications of Cushings secondary to malignancy, challenges of managing these and their associated mortality would be discussed further.

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P337

Pilot study of liquid biopsy in paragangliomas: a feasible alternative to tissue biopsy in inoperable and multifocal lesions?

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Background
Phaeochromocytoma and paraganglioma (PPGL) are highly heritable, with 30-40% due to a germline pathogenic variant. An additional 40% of tumours will harbour a somatic variant. Understanding the variant status of a tumour enables molecular classification. Liquid biopsy offers a novel approach to non-invasive diagnostics by harnessing the ability to detect small amounts of circulating-free DNA (cfDNA) and performing genomic sequencing. There are few studies examining the use of liquid biopsy in PPGLs.
Methods
This pilot study was undertaken in a patient with congenital cyanotic heart disease and multifocal *in situ* PPGLs, likely driven by lifelong hypoxia. 30ml of peripheral blood was collected in Streck BCT® tubes. Extraction of cfDNA was performed by CeGaT GmbH and was used for next generation sequencing with a panel of 750 genes, including *BRAF, EPAS1, FH, HRAS, MAX, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127* and *VHL.*
Results
A 52-year-old female with a history of congenital cyanotic heart disease presented with a 15mm bladder paraganglioma and lymph node metastasis. Following resection, functional imaging with Gallium-68 DOTATATE demonstrated three further paragangliomas, one in the mediastinum and two in the neck. Her plasma normetadrenaline levels were raised. Germline genetic testing did not detect variants in 14 PPGL susceptibility genes. Due to high anaesthetic risk, she has been managed with long-acting somatostatin analogues and regular surveillance. From 30ml of peripheral blood, 34ng of cfDNA with an average length of 170bp was obtained. Next generation sequencing using a custom panel was successfully performed. Analysis of sequencing data will be presented.
Discussion
We have demonstrated that liquid biopsy may be feasible in patients with inoperable PPGLs. If underlying genetic drivers of the tumour can be detected, particularly when germline testing is negative, this may improve access to emerging targeted therapies and guide decisions in surveillance strategies and prognostication.

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P338

Papillary thyroid cancer occuring in thyroglossal duct cyst- a rare presentation

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Thyroglossal duct cysts are the most frequently occurring congenital cervical anomaly, however the development of Papillary Thyroid Cancer (PTC) in these are very rare, with an incidence around 1%. We present two cases of PTC identified in thyroglossal duct cysts from our services. A 26-year-old lady with a 1-year history of midline neck swelling, was investigated with a neck ultrasound which showed a 2.8cm septated thyroglossal duct cyst and U2 thyroid cyst. She underwent a Fine needle aspiration which was S/O of PTC within the cyst. She went on to have surgery with removal of the thyroglossal cyst, total thyroidectomy and level 6 Lymph Node dissection. Histology showed 15mm papillary thyroid cancer within the fibrous tissue of thyroglossal duct. The thyroid gland showed nodular hyperplasia and no evidence of PTC. She was staged pT1b N0 (0/9). A 28-year-old lady was referred with a midline neck swelling. She was found to have a complex cystic mass S/O thyroglossal cyst and a thyroid nodule U2, which was managed with a sistrunk operation. Histology revealed the presence of 1.5cm PTC arising from within the thyroglossal duct cyst and was staged pT1bR1. She then underwent completion total thyroidectomy and level 6 lymph node dissection. The histology of which revealed a background lymphocytic thyroiditis, and 1/16 lymph nodes showed a small deposit of PTC. Final staging was pT1b N1a(1/16) R1. Patient received RAI 978MBq 131-I. Both the patients were started on levothyroxine, calcium and vitamin D supplements, and is having regular reviews in the outpatient setup. These cases highlight the importance of awareness of the rare occurrence of PTC within a thyroglossal duct cyst. There needs to be a high index of suspicion when dealing with such cases, as this commonly encountered benign lesion, does have the potential to harbour malignant tissue.

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Innovation in Teaching

P51

Genomic notes for clinicians – A genomic testing resource for endocrinologists

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Introduction
Genomic testing is expected to become a part of mainstream testing in the not-too-distant future, with clinicians ordering genetics tests in the same way routine endocrine tests are requested today. Knowledge on how and what test to request needs to be gathered by a wide range of physicians. To support this, the Genomics Education Programme of NHS England is developing a resource for all endocrinologists to use in clinic as part it's Genomic Notes for Clinicians (GeNotes) programme. Two resources (tier 1 and tier 2) will be available on a dedicated section for Endocrinology on the GeNotes website, written and reviewed by specialists in the field. One will direct users to commonly encountered clinical scenarios. Each scenario is concise and gives a typical case, explains when genetic testing should be considered, what you need to do, and which type or panel of tests to order. Extra resources for clinicians and patients are also included. The second resource (tier 2) will be more knowledge based and expand on specific conditions with an overview; clinical features; genes; inheritance and genetic counselling; differential diagnosis and management. Further resources for clinicians and patients will be included.
Summary
The majority of endocrinologists feel apprehensive about ordering genetic tests. GeNotes will help endocrinologists identify patients in need and suitable for genetic testing and help navigate the National Genomic Test directory to empower clinicians to request the right genetic test for patients wherever they are.

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P339

Biomedical Kitchen – safely transitioning students to higher education laboratories through transdisciplinary simulation

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Laboratory skills are a critical part of science education, enabling students to develop practical competencies and to relate theoretical learning to the laboratory bench. However, practical learning is often daunting for students, particularly those making the transition from secondary school to higher education. To support this transition, we have developed 'The Biomedical Kitchen', which introduces first year Medical Biosciences students to laboratory practice through transdisciplinary simulation, where students are taken out of their chosen discipline (molecular biology) and engage in activities from another discipline (professional gastronomy). Students (>300 over 2-year cohorts) were asked to design a yoghurt fermentation experiment, handle delicate edible thin gels, and engage with precise cooking techniques to create 10 identical canapes. These techniques aligned with learning outcomes for Lab Pod 1, their first laboratory module. Quantitative data focussing on self-efficacy ($n=78$) before and after the course, indicated that the students who gained in self-efficacy ($n=31$) had lower initial-self efficacy than the rest of the cohort. Qualitative data (2 surveys – before and after the course, $n=148$, 87) revealed that whilst students reported apprehension about practical work and time management; they were excited, curious, and expected to learn and be challenged. In their view, BK created an authentic, low-stakes environment introducing them to practical laboratory work. Their responses indicate learning beyond practical work, and delivered outcomes focussing on teamwork (notably with new colleagues), time management and laboratory book write ups. A final survey ($n=75$) performed during the Lab Pod 1 module confirmed that The Biomedical Kitchen effectively prepared them for learning in laboratories. The Biomedical Kitchen offers an innovative approach to laboratory skill acquisition. It is an inclusive, and affordable programme that delivers its learning outcomes and is well-received by students, with wide possibilities of adaptation and implementation across undergraduate science education.

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P340

New Teaching and Assessment Practices in an Undergraduate Medicine Intercalated BSc in Endocrinology

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The General Medical Council's publication 'Outcomes for Graduates' places emphasis on doctors being able to integrate biomedical science, research, and scholarship with clinical practice. In response, a new paradigm of assessment was introduced for the intercalated Bachelor of Science (iBSc) in Endocrinology program at Imperial College School of Medicine. The approach involves authentic "active learning" assessments analogous to tasks encountered in a research environment and intends to test a wider range of applied scientific skills than traditional examinations. Written assessments on themes in Endocrinology include a "Letter to the Editor", a scientific abstract, and production of a lay summary. Scientific presentation skills are developed through tasks including an endocrinology research proposal pitch, discussion of therapies or diagnostics, or review of a paper. A data management assignment develops skills in endocrinology hypothesis generation, performing analysis, and drawing conclusions. Finally, students conduct an exciting and original endocrinology research project which is assessed via a written report in the format of a research paper and an oral presentation involving critical analysis of their project. We aspire to train clinicians in endocrinology who apply scientific principles to critique the evidence base of medical practice and possess the skillset to conduct high-quality research. The Endocrinology BSc at Imperial is open to undergraduate medicine students from other UK universities, and overseas.

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Metabolism, Obesity and Diabetes

P52

Non-invasive, nanodroplet, ultrasound imaging of gut permeability

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The term Leaky Gut Syndrome (LGS) describes a collection of a range of symptoms, including abdominal pain, bloating, recurring diarrhoea, bloody stools and weight loss, when a diagnosis has not been, or cannot be, made. It can be associated with inflammatory bowel disease (IBD), celiac disease, chemotherapy and radiation therapies, and endocrine conditions including obesity and diabetes. The common underlying features of LGS are gut inflammation and an increase in gastrointestinal tract permeability. Currently, gut permeability is measured in two broad approaches, absorption from the gut to the blood or biopsy. Not only can these procedures be highly invasive and uncomfortable, but they only allow very small and limited sampling, and may not distinguish between specific diseases. We have tested a novel methodology in rodents that non-invasively measures gut permeability in real time with the ability to spatially map the level of permeability throughout the gut. This is achieved through the use of ultrasound imaging and phase change contrast agents. In their condensed state nanodroplets are undetectable and ~100 nm in diameter. Nanodroplets are injected into the bloodstream and remain within the blood vessels that vascularise healthy tissues. However, in diseased tissue these nanodroplets can extravasate and become trapped within the tissue. Once the nanodroplets remaining in the circulation have been cleared, these extravasated droplets can be activated through acoustic pressure, providing a high contrast signal. This signal thus highlights areas of high vessel wall permeability. Within the gastrointestinal tract, our data show that this method provides a non-invasive measure of LGS that we have validated using microscopy. Ultrasound is cost efficient, non-ionising and provides real time results, and this represents a non-invasive tool to quantify gut permeability and diagnose LGS which has the potential to change the monitoring and treatment of the millions of people it affects worldwide.

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P53

The role of glycated haemoglobin in predicting disease severity in non-alcoholic fatty liver disease

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Introduction
The relationship between non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes is well-established. However, the precise impact of glucose control on the severity and progression of NAFLD remains largely unexplored. Currently, none of the non-invasive scoring systems used to assess NAFLD severity incorporate glucose control markers, such as glycated hemoglobin (HbA1c).
Methods
Data were collected from a cohort of 857 patients with NAFLD, including liver histological staging, HbA1c levels, and body mass index (BMI). Generalized linear regression models and binomial regression analysis were employed to assess the relationships between histological NAFLD severity, age, HbA1c, and BMI. Furthermore, paired biopsies from interventional studies involving 421 patients were utilized to evaluate the impact of weight changes, HbA1c levels, and active vs placebo treatment on improvements in steatosis, non-alcoholic steatohepatitis (NASH), and fibrosis.
Results
In our discovery cohort ($n=687$), we found a positive correlation between HbA1c levels and the risk of severe steatosis, NASH, and advanced fibrosis, even after adjusting for obesity and age. These findings were confirmed through analysis of a separate validation cohort ($n=170$). Predictive modeling incorporating HbA1c and age was found to be non-inferior to the established non-invasive biomarker, Fib-4. Furthermore, we developed risk charts adjusted for HbA1c, age, and BMI to predict NAFLD severity. Within the interventional cohort, reductions in HbA1c were associated with improvements in both steatosis and NASH, independent of weight changes and treatment. However, changes in fibrosis were only associated with weight changes and treatment, not HbA1c levels.
Conclusion
Our study highlights the high informativeness of HbA1c in predicting NAFLD severity, surpassing the significance of BMI alone. We propose that HbA1c assessments should be an integral part of the holistic evaluation of NAFLD patients. Combined with age, HbA1c can effectively identify patients at the highest risk of advanced disease.

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P54

Unveiling the metabolic benefits of GLP-1 analogues in alström syndrome: implications for monogenic syndromic obesity management

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Background
Glucagon-like-peptide-1 (GLP-1) has been shown to improve body weight and glycaemic control in patients with common obesity and type 2 diabetes. Whether it confers the same metabolic benefits in monogenic syndromic obesity is unknown. This observational study aimed to examine the real-world efficacy of GLP-1 analogues in Alström syndrome (ALMS), a form of monogenic obesity.
Method
We screened all 72 UK adult patients with ALMS and offered treatment to 34 patients meeting one of the following criteria: body mass index >25, sub-optimal glycaemic control on oral hypoglycaemic medications, non-alcoholic fatty liver disease or insulin resistance. Metabolic parameters were measured at baseline and six months post-treatment.
Results
30 patients completed 6 months of treatment with GLP-1 analogue either in the form of semaglutide or exenatide. Treatment with GLP-1 analogue reduced body weight by 5.4 ± 3.81 kg and HbA1c by 12.0 ± 4.85 mmol/mol (mean $\pm$ SEM) equating to c.6% weight loss ($P<0.01$) and c.18% reduction in HbA1c ($P<0.01$). Significant improvements were also observed in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and alanine aminotransferase. The improvement of metabolic parameters was more pronounced than data from polygenic obesity irrespective of weight loss. A modest increase was noted in post-treatment c-peptide levels with a treatment duration of 6 months. Preliminary experiments demonstrate that ALMS1 silenced EndoC-βH1 cells (to model ALMS) exhibit exaggerated glucose-responsive insulin release vs control cells, perhaps explaining the modest increase in plasma c-peptide with GLP-1 analogue treatment.
Conclusion
GLP-1 analogue can be considered a treatment option in patients with ALMS and perhaps other monogenic forms of syndromic obesity. Loss of ALMS1 function impacts human pancreatic beta cell function.

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P55

Investigating chemogenetic manipulation of spinal astrocytes within a high-fat diet-induced hyperglycaemic model during neuropathic pain development

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The spinal cord dorsal horn acts as a hub for the modulation of sensory information, relying heavily upon the interplay of a heterogenous cell population (endothelial cells, astrocytes) with sensory neurons. We have identified in rodent models of hyperglycemic neuropathic pain that spinal microvasculature is damaged. A pathological hallmark of chronic pain is astrogliosis, acting as a potent source of inflammatory response and impacting vessel integrity and sensory neuronal activity. To date, it remains unclear how diabetic neuropathic pain develops and how microvessels are damaged. Here we use chemogenetic manipulation of astrocytes in healthy and hyperglycaemic rodents to elucidate the role of astrogliosis in the modulation of the blood-spinal cord-barrier and nociception. For spinal astrocyte activation, intrathecal injection of AAV GFAP-hM3D(Gq)-mCherry in C57/Bl6J male mice ($n=10$). Clozopine-N-Oxide (CNO, $n=10$) or vehicle (PBS, $n=5$) was delivered via intraperitoneal injection 2 weeks later. Hargreaves latency testing was performed prior to and 30minutes post-CNO/vehicle delivery to evaluate nociceptive withdrawal behaviours. To investigate the inactivation of spinal astrocytes during hyperglycaemia, C57/Bl6J male mice ($n=10$) were intrathecal injection of AAV GFAP-hM4D(Gi)-mCherry and fed on a 60% high-fat diet for 8 weeks. CNO ($n=5$) or vehicle (PBS, $n=5$) was delivered via intraperitoneal injection (2.5mg/kg) in week 8 for 4 consecutive days. Hargreaves latency testing was performed before diet feed, each week during diet feed and 30mins post-CNO/vehicle delivery to evaluate nociceptive withdrawal behaviours. Reduced heat-induced paw withdrawal thresholds were demonstrated post-CNO dosing compared to vehicle treatment within the spinal astrocyte activation cohort (hM3D(Gq)). Whereas during astrocyte inactivation (hM4D(Gi)) via CNO delivery, high-fat diet-induced thermal hypersensitivity was alleviated compared to vehicle treatment in hyperglycaemic mice. This data indicates that spinal astrocyte activation mediates nociceptive behavioural changes which can be targeted in a hyperglycaemic state for pain alleviation.

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P56

3α-hydroxysteroid dehydrogenase type 1 (AKR1C4) is upregulated in patients with non-alcoholic fatty liver disease and AKR1C4 silencing improves hepatic metabolic phenotype *in vitro*

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. It represents a spectrum of disease, ranging from steatosis to non-alcoholic steatohepatitis, progressing to fibrosis, cirrhosis, and hepatocellular carcinoma. BAs, as well as their intermediary products (oxysterols), are metabolic modulators exerting their effects through activation of nuclear receptors (NRs),

including the farnesoid-X- (FXR) and liver-X-receptors (LXR). Crucially, dysregulated BA synthesis has been associated with NAFLD. 3α-hydroxysteroid dehydrogenase type 1 (AKR1C4) is an enzyme exclusively expressed in the liver and plays an important role in BA synthesis. We hypothesised that AKR1C4 plays a crucial role in the pathogenesis of NAFLD. Genetic manipulation of AKR1C4 was performed in human Huh7 liver cells, and mRNA expression was determined by qPCR and RNA-sequencing. Serum and medium BA- and oxysterol concentrations were measured by LC-MS, and cholesterol levels by biochemical assays. Nuclear receptor activation was determined by luciferase assays. AKR1C4 expression and total BAs were increased in liver biopsies and serum samples from patients with advanced NAFLD, respectively. Supporting these data, data mining of genome-wide association studies (GWAS) identified protein-inactivating single nucleotide polymorphisms (SNPs) at the AKR1C4 locus associated with lower circulating triglyceride levels. In Huh7 cells, AKR1C4 knockdown reduced BA and oxysterol synthesis downstream decreasing LXR activation with no changes in total cholesterol, whilst RNA-sequencing analysis identified dysregulated pathways impacting upon a variety of cellular phenotypes, including cell cycle, lipid/carbohydrate metabolism, and insulin sensitivity. Complementing these data, mRNA expression analysis in AKR1C4-knockdown Huh7 cells revealed decreased expression of lipid and carbohydrate metabolism genes (*SCD1*, *PEPCK*, *G6PC*) and increased expression of insulin signalling genes (*AKT1*, *IRS1*). In conclusion, AKR1C4 is upregulated in advanced NAFLD, and AKR1C4 silencing improves BA homeostasis and metabolic gene expression profile *in vitro*. Taken together, these data suggest an as yet unexplored role of AKR1C4 in NAFLD.

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P57

Transcriptional regulation of hepatic circadian rhythm and metabolism: determining the role of nutritional challenge

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Metabolic fluxes in the liver demonstrate circadian rhythms. The hepatic circadian clock is a cell- autonomous protein network that governs the switch between the fasted and fed states via a series of transcriptional-translational feedback loops (TTLs). Diet is a powerful zeitgeber which can reprogramme the liver clock to follow eating schedule rather than the geophysical day-night cycle. Diet- induced circadian disruption has been implicated in the pathogenesis of common metabolic diseases including type two diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) which may be ameliorated via ROR-α and cryptochrome (CRY) stabilisation. Reciprocity between nutrition, core clock gene (CCG) expression, and hepatic metabolic flux exists. However, precise mechanisms of this relationship, particularly the actions of nutritional challenges, are not well characterised. In this study, two mammalian hepatocyte-derived *in vitro* models of circadian metabolism were used to profile how individual nutritional challenges interact with the liver clock, and if these can be potentially manipulated for therapeutic benefit. Gene expression analysis demonstrated that nutritional challenges individually disrupt mRNA expression of different CCGs, and the clock is sensitive to fatty acid (FA) composition. Glucose and FA challenges were found to directly attenuate CRY and ROR-α gene expression. ROR-α agonism and CRY stabilisation during modelled hyperglycaemia were both found to antagonistically modulate hepatic circadian amplitude (CA), and attenuate expression of genes are known to regulate insulin resistance (IR): PPAR-γ and glycogen synthase respectively. This study reveals that diet-induced hyperglycaemia and free FAs may alter hepatic circadian metabolism and suggests that pharmacological agonism of these CCGs may provide therapeutic benefit in T2DM and NASH.

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P58

EarLy Surveillance for Autoimmune type 1 diabetes (ELSA) – paediatric, general population screening in the UK

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Background
Children with pre-symptomatic type 1 diabetes (T1D) can be identified through testing for circulating islet autoantibodies (AAb). Identifying children at risk reduces diabetic ketoacidosis at onset and allows participation in trials aiming for immunoprevention. The EarLy Surveillance for Autoimmune diabetes (ELSA) study is exploring feasibility and acceptability of UK paediatric general population screening.
Methods
The ELSA study runs from July 2022 to August 2024 and aims to recruit 20,000 children aged 3-13 years. ELSA is screening for AAb via dried blood spot (DBS) and subsequent staging via oral glucose tolerance testing. ELSA is exploring feasibility and acceptability of UK paediatric general population screening.
Results
In total, 6104 children are consented, including 5968 for home testing and 136 for community settings (school, general practice). Families are principally White European (89%) and 54% have a family history of T1D. Thus far, 3421 kits are returned with 3324 children screening negative and 86 screening positive for AAb. Only 2 DBS kits failed due to insufficient sample. On confirmatory AAb testing, 5 are false positive (8%), 18 are single (28%) and 41 (64%) are multiple AAb positive. Of the multiple AAb children, 27 are stage 1, 2 are stage 1 and 1 child is stage 3. All families agreed to confirmatory testing, staging and education and all expressed interest in INNODIA for monitoring.
Conclusion
Social media is an effective route to recruitment. Community outreach to schools and general practices is underway. Exploring acceptability and barriers to screening are key outcomes for this study.

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P59

Activation of AMPK & p38MAPK Pathways with a Novel Agonistic Compound in LHCN-M2 Skeletal Muscle Myotubes

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Introduction
Pharmacological targeting of skeletal muscle to enhance metabolism through signalling pathways independent of insulin could be effective in treating metabolic diseases such as obesity and type 2 diabetes. BI-9774 is an allosteric agonist which has been shown to have high potency in enhancing 5' AMP-activated protein kinase (AMPK) activity. The purpose of these experiments was to establish the effects of BI-9774 on AMPK signalling and mitochondrial capacity in LHCN-M2 human skeletal muscle cells.
Methods
LHCN-M2 human skeletal muscle cells were cultured and differentiated into multinucleated myotubes. Following 10 days of differentiation, time (0-12 h) and dose response curves (0-1μnM) were conducted to establish phosphorylation of AMPK (Thr172), Acetyl-CoA carboxylase (ACC) (Ser79) and p38 MAPK Kinase (Thr180/Tyr182) in response to BI-9774.
Results
Time course experiments showed an increase in the phosphorylation of AMPK at 15, 30 and 60 minutes and phosphorylation of ACC at 30 ($P = 0.006$), 60 ($P = 0.004$), 300 ($P = 0.010$) minutes when stimulated with 10nM of BI-9774. Despite being described as a selective AMPK agonist, there was an increase in p38 MAPK phosphorylation at 15 minutes of stimulation at 10nM ($P = 0.015$). Dose response curves showed a significant increase in AMPK and ACC phosphorylation at concentrations of equal to and greater than 10nM ($P < 0.05$) and 1nM ($P < 0.05$), respectively. Preliminary seahorse data suggests that concentrations of BI-9774 up to 1μM induce no changes to basal or maximal oxygen consumption rates.

Conclusions
These experiments show for the first time that BI-9774 can induce phosphorylation of the AMPK-ACC and p38 MAPK signalling pathways in human skeletal muscle myotubes. Further experiments are required to investigate the effects of BI-9774 on enhancing skeletal muscle metabolism as a potential therapeutic for treating metabolic disease.

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P60

Predictors of weight loss in a secondary care tier 3 specialist weight management service

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Background
A four-tiered system is currently in place for weight management in the National Health Service (NHS). Tier 3 comprises specialist weight management services and aims for a clinically meaningful weight loss of $\geq$5%, as recommended by the National Institute for Health and Care Excellence (NICE). Within the Imperial Weight Centre (IWC), patients receive support from a multi-disciplinary team including endocrinologists, surgeons, dietitians, nurses, psychologists and psychiatrists.
Methods
Demographic data, anthropometric measurements and other baseline characteristics were collected for patients who completed the IWC Tier 3 programme between March 2019 and October 2022. Fisher's exact tests were used to identify predictors of $\geq$5% weight loss, and statistically significant variables were used in a multivariate logistic regression model.
Results
In total, 404 patients (79% female, 56.6% White, median age 41.5 (interquartile range (IQR) 17.8) years, median baseline body weight 123.7kg (IQR 29.0)) completed Tier 3, and 23.3% achieved $\geq$5% weight loss. Among the cohort, sixty-seven patients (17%) were receiving GLP-1 analogue medication. Hypertension (OR 1.96 (95% CI 1.17 to 3.31), $P<0.05$) and GLP-1 analogue use (OR 2.14 (CI 1.13 to 3.99), $P<0.05$) were independently associated with $\geq$5% weight loss.
Discussion and Conclusions
Increased motivation to achieve greater weight loss in patients with hypertension may be a possible explanation for the independent association of hypertension with $\geq$5% weight loss. GLP-1 analogue use was also independently associated with $\geq$5% weight loss, consistent with results from clinical trials. Current NICE criteria for eligibility for NHS-funded GLP-1 analogue treatment limit their use to a subset of patients with obesity and there is currently a supply shortage of this medication to the United Kingdom. Therefore, in addition to these agents, effective strategies are required to support long-term weight management.

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P61

Neurotensin improves glucose tolerance via NtsR1-expressing enteropancreatic neurons

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Neurotensin is expressed throughout the gastrointestinal tract and acts as a gut hormone. Recent work has established neurotensin modulates lipid absorption at the gastrointestinal lumen, but its role in the control of glucose homeostasis remains unclear. Neurotensin acts via three receptors, including the NtsR1 and is endogenously released following the ingestion of olive oil. Previous work in our group has identified that neurotensin acutely improves glucose tolerance in both lean and diet-induced obese mouse models via the NtsR1. This glucoregulatory effect is mediated by increased levels of insulin. We have previously demonstrated that this effect is unaffected by central administration of an antagonist or ablation of vagal NtsR1 and is therefore peripherally mediated. Using a NtsR1::Ai9 reporter model and RTF tissue clearing, we have visualised a population of NtsR1-expressing neurons extending from the proximal duodenum to the pancreas. Though these enteropancreatic neurons were first identified in the 1970s and subsequently found to be present in both mice and humans, their function has remained unknown. To investigate a functional role for these neurons, we used a diphtheria toxin receptor (DTR)-mediated ablation approach. Cre-dependant DTR-AAV or control was surgically injected into the pancreas adjacent to the proximal duodenum of NtsR1 NeoCre mice. Ablation of these neurons prevented the glucoregulatory effect of both neurotensin at pharmacological doses, and exacerbates the glucose excursion following a fast-refeed study in which mice were given chow rich in carbohydrate and olive oil. Surgical separation of the pancreas from the proximal duodenum also prevents the glucoregulatory effect of neurotensin, providing strong evidence that these effects are mediated by NtsR1-expressing enteropancreatic neurons which originate from the proximal duodenum. These data suggest that neurotensin modulates glucose homeostasis in response to lipid ingestion via enteropancreatic neurons and that these neurons represent potential targets for interventions to improve glucose homeostasis.

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P62

Metabolite-dependent regulation of HCAR1 at a spatial level and its potential to influence local gut barrier integrity

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The Hydroxycarboxylic Acid Receptor 1 (HCAR1) is a Gαi/o-coupled GPCR known to be activated by both L- and D-lactate; metabolites produced by gut microbiota and anaerobic metabolism. Elevated D-lactate levels are indicative of dysbiosis and inflammatory bowel disease. As lactate can be transported into cells, it has the potential to activate HCAR1 at the plasma membrane and within intracellular locations resulting in diversified responses. Whether HCAR1 signalling is spatially regulated and if this influences gut barrier integrity is unknown. Here, we characterise the effects of distinct lactate isomers on HCAR1 trafficking and investigate its role on intestinal barrier function. In HEK293 cells expressing human HCAR1, both BRET and HTRF assays indicated L- and D-lactate differentially activate HCAR1-mediated Gai signalling. Confocal imaging and flow cytometry measurements demonstrated HCAR1 internalised from the plasma membrane in both a constitutive and ligand-independent manner, with L-lactate inducing 2.5 times greater internalisation than D-lactate. Neither internalisation (ligand-independent and dependent) nor ligand-induced signalling was altered in cells lacking β-arrestins. HCAR1 internalisation was dynamin-dependent, and its signalling was partially inhibited by the dynamin GTPase inhibitor, Dyngo-4a, implying HCAR1 may continue signalling following internalisation. Despite isomer-dependent differences in the levels of ligand-induced HCAR1 internalisation, both forms of lactate trafficked HCAR1 to a similar endosomal compartment. HCAR1 poorly co-localised with an early endosome marker, EEA1, and partially localised to APPL1 endosomes. The human intestinal epithelial barrier model cell line, Caco-2, expresses HCAR1 in both differentiated and undifferentiated cells, and preliminary data suggest HCAR1 is constitutively internalised. Sustained exposure to low concentrations of lactate increased transepithelial electrical resistance readings, suggesting improved barrier function. Translating the spatial regulation of HCAR1 into Caco-2 cells will enhance our knowledge of how HCAR1 responds to L- and D-lactate to influence local control of gut barrier integrity and inflammatory responses in the gut.

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P63

Androgens potently regulate sterol 12α-hydroxylase (CYP8B1) expression in mouse and human liver

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Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders affecting 6-15% of women of reproductive age. The syndrome is characterised by a variety of reproductive and metabolic features, including hyperandrogenism, chronic anovulation and hirsutism as well as insulin resistance, dyslipidaemia, and non-alcoholic fatty liver disease (NAFLD). Specifically regarding NAFLD, androgen excess is hypothesised to have a direct effect on hepatic lipid storage, thus making patients with PCOS more prone to develop fatty liver. Bile acids (BAs) have been shown to play a central role in the

pathogenesis of NAFLD, and elevated serum primary BA levels have been recently observed in patients with PCOS. However, the cellular processes that drive alterations in BA profiles in PCOS are unknown. We hypothesised that androgen excess modulates BA synthesis in the liver. C57BL/6J female mice were treated with either dihydro-testosterone (DHT) or placebo for 90-120 days, and liver samples were collected for downstream analyses. Primary human hepatocytes were treated with either testosterone (50nM) or dihydrotestosterone (10nM) for 24 h. mRNA and protein expression of BA-synthesising and BA-regulated enzymes were measured by qPCR and western blotting, respectively. In C57BL/6J female mice, DHT treatment significantly increased sterol 12α-hydroxylase (CYP8B1) expression at both mRNA and protein level. However, no significant differences in the expression of other BA-synthesising and BA-regulated enzymes were observed (Cyp7a1, Cyp27a1, Akr1d1, Nr0b2, Nr5a2). Supporting these data, both testosterone and DHT treatment significantly increased CYP8B1 protein levels in primary human hepatocytes compared to vehicle-treated cells. In conclusion, these data suggest an as yet unknown role of androgens in the regulation of BA synthesis. More experiments are now required to elucidate the importance of these findings on hepatic metabolic phenotype both *in vivo* and *in vitro*.

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P64

Female AKR1D1 knockout mice are protected against diet induced obesity and insulin resistance but not hepatic steatosis

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Bile acids and steroid hormones are potent regulators of metabolic phenotype. 5β-reductase (AKR1D1) is highly expressed in the liver where it catalyses a fundamental step in bile acid synthesis and inactivates steroid hormones. We have previously shown that male, but not female, AKR1D1 knockout (KO) mice on a normal chow diet are leaner than wildtype littermates but are not protected against diet induced obesity. Here we investigate the impact of a high fat diet on female AKR1D1KO mice. Female wildtype and AKR1D1KO mice were challenged with a 60% high-fat diet for 20-weeks. AKR1D1KO mice were protected from diet induced obesity (weight gain: 27.2 ± 0.5 g [WT], 15.8 ± 1.2 g [KO], $P < 0.01$), with reduced adipose tissue mass (gonadal: 4.0 ± 0.2 g [WT], 2.4 ± 0.4 g [KO], $P < 0.005$; subcutaneous: 3.9 ± 0.3 g [WT], 2.4 ± 0.5 g [KO], $P < 0.05$). Female AKR1D1KO mice were also protected against glucose intolerance (ipGTT AUC: 3216 mmol × min [WT], 2601 mmol × min [KO], $P < 0.05$) and insulin resistance (ipITT AUC: 1171 mmol × min [WT], 947 mmol × min [KO], $P < 0.05$). Despite being protected against diet induced obesity, female AKR1D1KO mice had a similar degree of steatosis as the wildtype mice. Suggesting an increase in lipogenesis, the mRNA expression of *Acc1* (relative expression: 0.85 ± 0.10 [WT], 0.19 ± 0.11 [KO], $P < 0.05$) was increased. There was no change in the expression of genes involved in b-oxidation (*Acc2* and *Cpt1*), lipid uptake (*Lipc*) or export (*Apoa4*). In summary, despite being protected against diet induced obesity female AKR1D1KO mice have a similar degree of steatosis to high fat fed wildtype mice. Gene expression analysis suggests this is, at least partially, driven by an increase in lipogenesis but further studies are needed to confirm the underlying mechanisms.

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P65

Differential DNA methylation during postnatal development establishes a subpopulation of pancreatic beta cells with expression of the insulin secretion-enhancing gene, neuronatin

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Subpopulations of beta cells dictate overall 'pacing' of insulin secretion across the islet and therefore the control of glycaemia. Functional beta cell subpopulations also exist in human islets and have an altered subtype distribution in type 2 diabetes. However, the molecular control of the establishment and maintenance of beta cell hierarchy is poorly understood. We hypothesised that the epigenome would govern this heterogeneity. We have identified a novel subpopulation of beta cells with 'on/off' expression of neuronatin (*Nnat*), a gene required for normal insulin synthesis and secretion. Beta cell heterogeneity at the level of *Nnat* expression is established via *de novo* CpG methylation at the *Nnat* promoter during early postnatal life. $NNAT^+$ beta cells have a discrete transcriptome, appear to be functionally specialised for insulin production, and we have demonstrated their presence in the developing human pancreas. We therefore demonstrate that differential DNA methylation at the *Nnat* locus represents a novel means through which beta cell heterogeneity is established. Changes in methylation at this locus may thus contribute to a loss of heterogeneity, and defective insulin secretion, in some forms of diabetes. Furthermore, epigenome-modifying compounds may provide a way of enhancing beta cell function and the ensemble behaviour of the islet to stimulate insulin secretion.

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P66

Developing flare-responsive intra-articular steroid injections

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Intra-articular (IA) glucocorticoids (GCs) injections are effective in controlling joint inflammation but limited by short duration of action and off-target side effects. Gellan sheared hydrogels (SHs) area drug delivery vehicle, with unique thinning properties and enhanced release kinetics. We hypothesise that a combination of SHs and pre-receptor metabolism activated GCs provide slow-release drug delivery to target inflammation and minimise side-effects. We the release kinetics of GC loaded SHs and examined their IA application in a murine model of polyarthritis. SHs containing either vehicle, active prednisolone (10 mg/ml) and metabolism activated prednisone (10 mg/ml) were generated under shear gelling conditions. Steroid release properties *in vitro* over time were examined by ELISA. GCs loaded SHs, vehicle loaded control or GC only were examined in the TNFtg model of polyarthritis after IA injection(10ul) of animals at six weeks. After 21 days, animals were culled, and measures of disease activity, joint inflammation score, body weight and joint histology were examined. GC hydrogels released steroids *in vitro* for 12 days, whereas the neat GC was detectable for 48 h by ELISA. The IA injection visualisation was done using a dyed hydrogel. IA Gel injection was tolerated with irritation or tissue break down. No changes were detected in body weight, global disease, and inflammatory paw scores in treated animals. Histological knee analysis has shown that synovitis and pannus($P \leq 0.001$) were reduced in Prednisolone gel group and cartilage was preserved in the Active/Inactive GC gel($P \leq 0.05$) groups compared to control and vehicle injected groups. GC delivery by gellan sheared hydrogels were well tolerated by intra-articular injection. Prednisolone hydrogel showed effective suppression of joint destruction in TNFtg mice relative to standard solution and reduced synovitis and collagen loss. However, metabolism activated gels failed to show efficacy relative to Prednisolone gels *in vivo*.

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P67

The effect of snack foods containing rare sugars on glycaemic response, gut hormones and satiety in healthy UK adults

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Dietary guidelines in the UK and worldwide recommend reducing the quantity of free sugars in the diet. The consumption of foods high in free sugars can lead to postprandial hyperglycaemia and hyperinsulinemia, which have been implicated in the development of metabolic diseases including type 2 diabetes and obesity.

Rare sugars (naturally occurring monosaccharides which hardly exist in nature) have been found to suppress the postprandial elevation in blood glucose and improve glycaemic control when consumed alongside a carbohydrate load. However, the effect of rare sugars when consumed as part of a confectionery product has not been widely studied. Additionally, there is limited research on the effects of rare sugar consumption on appetite. Here we conducted a double-blind, randomised controlled study to investigate the effects of replacing sucrose with the rare sugars tagatose or arabinose in sweet snacks. We measured liking of the snacks and postprandial blood glucose, insulin and gut hormones alongside effects on appetite and satiety. We observed that there was no difference in liking of the products as indicated by a 9-point hedonic scale, while results to date indicate significant differences in peak glucose concentration between samples, and differences in satiety after consumption of samples. Our results will demonstrate whether the replacement of sucrose with tagatose or arabinose can reduce the elevation in blood glucose after eating a sweet snack, and whether satiety or food intake are affected. We anticipate this will aid in the development of reduced- sugar confectionary which could be beneficial for those at risk of or living with metabolic disease.

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P68

Investigating the pancreas-projecting enteric neurons in the regulation of metabolic homeostasis

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The regulation of insulin and glucagon secretion has traditionally been attributed to the gut-brain axis and direct sensing of blood glucose levels by pancreatic islets. However, the enteric nervous system may directly modulate pancreatic hormone release. This study focuses on a specific population of enteric neurons that exhibit the capability to transmit signals from the gut to the pancreas, potentially revealing new pathways of metabolic regulation. The gastrointestinal tract senses various nutrients, triggering the release of hormones and neuropeptides. This research aimed to investigate the impact of enteric neuronal signalling on pancreatic hormone regulation, particularly in response to nutrient intake. In this investigation, we found that both whey and olive oil decreased blood glucose levels and improved glucose tolerance. Subsequently, we performed a surgical procedure to physically separate the proximal duodenum from the adjacent pancreas, severing the enteric neurons that project directly to the pancreas. This resulted in the attenuation of the observed effect of olive oil on glucose tolerance. Further confirmation is needed to determine the effect of whey protein in this context. To examine the specific enteric neuronal projections to the pancreas, we isolated and cultured the longitudinal muscle myenteric plexus (LMMP) of the enteric nerve. This isolation allowed us to investigate the effects of specific nutrients on the LMMP, potentially uncovering their role in pancreatic hormone regulation. Additionally, following injection of an adeno-associated virus encoding a fluorescent marker into the pancreas, we were able to identify enteric neurons with projections to the pancreas in the duodenal LMMP, and to isolate these cells and characterize their gene expression using Fluorescence-Activated Cell Sorting. This isolation will enable us to comprehensively characterize these neurons and identify their likely functions. These findings will contribute to a better understanding of pancreatic hormone regulation and offer potential therapeutic targets for metabolic disorders.

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P69

Pattern of diabetes and diabetic foot admissions in a tertiary centre in Nigeria: A five-year review

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Introduction
The prevalence of type 2 diabetes mellitus (DM) is increasing worldwide. As a result, there is also an increased incidence of complications of diabetes at the clinics and emergency rooms. This study seeks to know the proportion of medical admissions due to diabetes-related causes, to determine the pattern of DM-related admissions, assess the pattern and outcome of diabetic foot syndrome (DMFS) and their determinants.

Method
We conducted a retrospective descriptive study at the Federal Medical Centre Owo, South-West Nigeria. Medical records of patients admitted for medical conditions from 2016 to 2020 were obtained. We recorded the total number of medical cases and specifically noted diabetes-related conditions. Demographic data, clinical history, examination findings and laboratory results of patients admitted for DMFS were recorded.
Results
Four hundred and fifty subjects were admitted due to diabetes-related causes. Of these, DMFS accounted for 20.2%, Diabetic Ketoacidosis (DKA) 1.8%, Hypoglycemia 4.2%, Hyperglycemic hyperosmolar state (HHS) 18.2%, cerebrovascular accident (CVA) 0.4%, DM nephropathy 17.8%, DM hand 0.7%, poor glycemic control 35.8% and gluteal ulcer 0.9%. Nearly an equal number of males and females had DMFS. Among these patients, 55% presented with Wagner grades 4 and 5 ulcers, of which 81.8% eventually had amputation. We employed a multinomial logistic regression model to assess the risk factors associated with mortality from DMFS. The analysis revealed that higher grades of ulcer, elevated levels of serum urea, serum creatinine, TWCC, adSBP, adRBS, and lower PCV were all associated with an increased mortality risk.
Conclusion
The study highlights a high proportion of diabetic-related admissions related to diabetic foot ulcers. The study findings indicate that most cases presented with foot gangrene, leading to limb amputation. It emphasizes the need for prioritizing foot care education in diabetes clinics to address this issue effectively.
Keywords
Diabetes mellitus, Diabetic foot ulcer, Diabetic foot outcome
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P70

How do healthcare professionals represent obesity and overweight on social media? Exploring the perspective of persons living with the disease

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Background
Predictions estimate that the majority of the global population will be living with overweight and obesity by 2035. Due to its widespread use and ability to disseminate information, social media has a potentially prominent role in obesity care and education. Regulatory bodies issue ethical guidance on social media use. However, it is unknown how healthcare professionals' (HCP) online activity affects people living with obesity. By exploring their perspectives, we can gain insight and develop a framework to inform good practice around social media use.
Methods
We conducted semi-structured interviews with people living with overweight and obesity who use social media. Participants were recruited via the Irish Coalition for People Living with Obesity and three clinical sites offering weight management services. Thematic analysis was employed to identify key themes.
Findings
Fifteen interviews took place with 12 female and 3 male participants between April and June 2023. We identified four key themes of how people living with obesity perceive HCPs' online representation of the disease: (i) Negative and Stigmatising Perception – HCPs perpetuated bias and fat-phobia while using simplistic and generalizing language that caused people living with obesity to feel shame, fear, and anger. (ii)Empowerment and Disparity– social media allows HCPs to educate, inform and change public perception. However, there is a limited presence currently, leaving a desire for access to accurate medical information. (iii) Credibility and Expertise– qualifications, professional titles and academic association affected the perceived trustworthiness of information and its impact on readers. (IV) Engagement and Responsibility – Risk of retaliation and perceived responsibility were barriers for HCP engagement.
Conclusion
People living with overweight/obesity are adversely affected by HCPs stigmatising representation on social media, which is characterised by outdated conceptualisations and misinformation. There is a desire for increased presence by specialist HCPs to enhance disease awareness and reduce stigma.

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P71

HbA1c assessment and inpatient diabetes management for people diabetes and moderate/severe frailty: audit results from a UK teaching hospital

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Introduction
Inpatient admission presents an opportunity to deintensify treatment in people with diabetes and frailty. The Joint British Diabetes Society recommends checking HbA1c in people with diabetes and frailty during admission if it had not been checked in the preceding six months. The audit aimed to identify the proportion of people who had their HbA1c checked upon admission and, if appropriate, what proportion had their treatment deintensified.
Methods
We retrospectively collected data on people with diabetes and clinical frailty score (CFS) ≥ 6 discharged from the medical unit in 2022. HbA1c data prior to and during admission were collected. Deintensification was defined as any reduction in blood glucose lowering medication or switching of medications to those with less risk for hypoglycaemia. Descriptive statistics were performed.
Results
Four-hundred and thirty-six patients were included in our analysis [Age: 79.5 years (IQR = 71-86). 52.1% ($n = 227/436$) were women and the median CFS was 6 (IQR = 6-7). 29.4% ($n = 128/436$) of the admissions were due to falls. 35.6%($n = 155/436$) of patients admitted to the hospital did not have their HbA1c assessed in the preceding six months. Of these, only 9.0% ($n = 14/155$) had it checked during this admission. In patients with HbA1c $< 7.0\%$, only 10.6% ($n = 22/207$) were deintensified during admission.
Conclusion
Despite National recommendations, only a small proportion of patients had their HbA1c assessed during inpatient care, when appropriate, and there were low rates of treatment deintensification. Quality improvement programs are warranted to improve inpatient care for people with diabetes and moderate/severe frailty which includes assessment of HbA1c which in turn will guide decision-making regarding further deintensification.

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P72

Correlation of metabolic syndrome with human papilloma virus infectivity in pregnant women

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Human papillomavirus (HPV) is one of the most common sexually transmitted viruses in reproductive age. About 80% of women will get at least one type of HPV at some point in their lifetime. Pregnancy is highly susceptible because decreased immunity during this period. There are few studies available from Indian sub-continent indicating a link between HPV infection and pregnancy. Association with various demographic factors in women would help in categorising those women who are more vulnerable to the disease.
Objective
The Objective was to study association of features of Metabolic Syndrome with HPV infection in both the groups. Secondary objective of this study was to find out prevalence of HPV infection in non-pregnant vs pregnant women.
Material and Method
This was a prospective cohort study, at a tertiary level institution in an out-patient setting. We recruited 200 women in two groups:- 1. Non pregnant women in reproductive age ($n = 100$) and pregnant women ($n = 100$) after consent clearance. Clinical history and examination was documented. Cervical swab samples(in non-pregnant women) and High Vaginal Swab (in pregnant women) used for the detection of HPV DNA infection by using the hybrid capture technique. Prevalence in both groups was calculated and association of features of Metabolic Syndrome like PCO, Obesity, Presence of Prediabetes or diabetes. GDM, studied with respect to each group.
Result
The Study revealed prevalence in two groups was significantly different in two groups. (9% in Group 1 vs 16% in group 2). In Group 2, apart from nutritional and socioeconomic status, co-morbid ailments like Diabetes, Obesity played a significant role.

	HPV negative	HPV positive	P_value
AGE	30(28,32)	32(30,33)	0.816
BMI	25.6(24.5,26.8)	27.875(26.7,27.856)	<0.001

Conclusion
Our study concluded that HPV prevalence is higher in pregnant women than non-pregnant women being associated with features of Metabolic Syndrome.

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P73

Fulminant diabetic ketoacidosis occurring one year after immune checkpoint inhibitor-induced hypothyroidism while on pembrolizumab: a case report

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Introduction
Pembrolizumab is an immune checkpoint inhibitor (ICI) used to treat advanced cancers. While improving survival rates, ICIs also cause immune-related adverse events (IRAEs). The endocrine system remains the most vulnerable to IRAEs: thyroid involvement is the commonest while pancreatic involvement is rare, affecting less than 1% of individuals. Risk factors for IRAEs include, personal or family history of autoimmune conditions, presence of another IRAE, most commonly thyroiditis, and being on ICI combination therapy. We describe a man who developed pembrolizumab-induced diabetic ketoacidosis (DKA) a year after developing pembrolizumab-induced hypothyroidism.
Case presentation
A 62-year-old man presented with three days of weakness, weight loss, polyuria, and polydipsia. His medical history included a recurrence of oropharyngeal cancer and pembrolizumab-induced hypothyroidism. Current medications included intravenous pembrolizumab, started two years ago, levothyroxine 150 mg daily started a year ago, alendronic acid and a calcium-vitamin D supplement. He was a non-smoker and had no family history of diabetes mellitus. His blood glucose levels had been normal prior to this presentation. On examination he was dehydrated and tachypnoeic. Laboratory analysis demonstrated severe hyperglycaemia (glucose 35.3 mmol/l), metabolic acidosis (pH 7.01, bicarbonate 5.5 mmol/l) with ketonaemia (6.6 mmol/l) consistent with DKA. Further tests revealed a slightly raised glycated haemoglobin level (70 mmol/mol), a low C-peptide level (0.13 nmol/l), with negative anti-islet cell and anti-glutamic acid decarboxylase antibodies, consistent with fulminant onset type 1 diabetes. He responded rapidly to treatment according to the DKA treatment guidelines and was discharged on a basal-bolus insulin regimen.
Conclusion
Antibody-positive and antibody-negative endocrine IRAEs can occur even after a year of initiating ICI-therapy. Affected individuals can developed more than one endocrine IRAE. This case highlights the need for clinicians to remain vigilant about the occurrence of life-threatening endocrine IRAEs, even beyond a year after initiating ICI-therapy.

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P74

Hypoglycemia box awareness among clinical staff - where is the hypoglycemia box?

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Hypoglycemia during hospital admission remains a common complication of diabetes. Hypoglycemia is associated with increased morbidity and mortality, increased length of stay, increased admission rate and increased cost to the NHS. Prompt treatment of inpatient hypoglycemia is imperative to avoid such complications. The Hypoglycemia box is an important tool to manage hypoglycemia on the wards. It is crucial for all clinical members to be aware of the hypoglycemia box; its contents, location aswell as access to the hypoglycemia guidelines. We have organised a quality improvement project at our trust, Doncaster and Bassettlaw Teaching Hospital NHS Trust, to assess and ultimately improve timely management of what could be a life threatening event. We did 2 cycles of this QIP. In cycle one, we found 60-70% of the staff were

aware of the hypoglycemia box, its contents and the hypoglycemia guidelines. After cycle one, we conducted practical education classes following which we noted an improvement to above 95%. We are hopeful that following this quality improvement project, we can improve the management of inpatient hypoglycemia which will improve patient outcomes.

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P75

Severe non-diabetic hypoglycemia unawareness, explained by a large fibrous tumor

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Background
Hypoglycaemia unawareness is thought to be due to very tight control of diabetes but may also be due to very longstanding slowly progressive hypoglycaemia. We describe a patient who had no warning of very severe hypoinsulinaemic hypoglycaemia.
Case Presentation
A 65-year-old gentleman presented with recurrent hypoglycemia that responded to IV glucose. A chest X-ray revealed a space occupying lesion and further investigations during short fast are in the table below. He was managed with continues glucose monitoring (CGM) and his family were alerted to hypoglycemia before he became confused. The family described repeated episodes of him being unarousable in the morning. He was able to have regular meals as needed until he underwent left hemi-clamshell thoracotomy with the resection of the solitary tumor that resulted in complete cure.
Discussion
Insulin levels while hypoglycemic were low and ketones were 0.1 mmol/l,

Table The normal IGF-II to IGF-I ratio should be <10, Calculated ratio is 15 which indicates an ectopic source of IGF-II. Results are consistent with non-islet cell tumor hypoglycemia

	Before surgery	After Surgery
Glucose	1.8 to 2.7 mmol/l	7 mmol/l
Insulin	2.4 mU/l (3.0-15.0)	
IGF-I	9 nmol/l (5.9-25.0)	
IGF-II	134.9 nmol/l	

suggesting non-insulin derived hypoglycemia. He was managed with regular meals and CGM which enabled his family to feed him whenever his glucose fell below 3 mmol/l until surgery

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P76

Point prevalence of undiagnosed cardiovascular risk factors in an urban market in lagos metropolis, Nigeria

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Introduction
Major risk factors for cardiovascular disease and outcome include, though not limited to, hypertension, diabetes mellitus and obesity. In the wake of present urbanization, the prevalence of these risk factors has increased, impacting greatly on disease burden.
Objectives
To determine the prevalence of undiagnosed Diabetes, Hypertension, Obesity and associated demographic factors in a market population in Lagos, Nigeria.
Method
A cross-sectional study was conducted among 85 Traders in Lagos, Nigeria. Data were collected on age, gender, blood glucose levels, blood pressure, height and weight. Data were analyzed using Statistical Package for Social Science version 26. Variables were presented with frequency and percentage. Bivariate analysis was carried out using chi-square test.
Results
The majority of recruited participants were females, with a male: female ratio of 1: 2.5. The mean age is 46.31 ± 10.9 with one-fourth of the participants less than 40 years (28.2%). The prevalence of undiagnosed Hypertension was 54.12%, with no association between age and gender. The prevalence of obesity was 52.94% with a higher rate in older adults age ($P=0.003$) and female gender ($P=0.023$). The prevalence of diabetes was only 10.6 % with a significant association with age. The commonest combination of risk factors was hypertension and obesity (30.6%) with 72.9% of participants having at least one of the risk factors. Overall 98% of participants with hypertension, 95% with obesity and 100% of participants with diabetes mellitus were **unaware** they had these conditions.
Conclusion
The study captures the increased prevalence and low awareness of cardiovascular risk factors within an urban population in Lagos, Nigeria, Regular screenings are needed in these populations for early detection and management of cardiovascular risk factors, to reduce morbidities and mortalities.

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P77

A retrospective audit on the adherence of Trust guidelines in the management of Hyponatremia at a DGH

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Background
Hyponatremia is the most common electrolyte disorder encountered in clinical practice. Vulnerable cohorts tend to be hospitalised patients where it tends to occur in 15-20% of the patients and the other category being nursing home residents. Significant risk factors are increasing age, and polypharmacy.
Aims
We aimed to look at the management of hyponatremia at our hospital, check adherence with the trust guidelines and assess the standards of referrals to the endocrine team.
Methology
Retrospective data was collected over the past 4 months (from January 23 to April 23) by compiling clinical information from patient notes and biochemistry from lab database. 34 online referrals were done to the endocrinology for specialist input regarding hyponatremia. Standards looked at were the trust guidelines.
Outcome
Of the 34 patients referred to the endocrinology, 29 cases (85.35) had severe hyponatremia. Only 3 patients amongst these were symptomatic.18 referrals did not have volume status assessed.17 cases had all recommended investigations carried out as per guidelines. Twenty instances (58.8%) had fluid charts while 14 cases (41.2%) did not. Only 8 cases (23.5%) used hypertonic saline. Culprit drugs were ACE I/ARB. 16 patients had a possible diagnosis of SIADH (47%) with screening investigations done beforehand. Endocrine causes of hyponatremia were identified in 2 patients. Treatment of hyponatremia was documented in 27 cases. 6 patients did not have the cause of hyponatremia noted in the discharge summary.
Conclusion
Hyponatremia in hospital setting is often overlooked. Early referral to specialist remains pertinent. Our results could be skewed by small sample size but this was a pilot study done prior to a larger prospective cohort study.

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P78

Endocrine consequences of inherited metabolic disorders: Experience from a joint clinic

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Introduction
Substrate accumulation, energy deficiency or complex molecule defects characterize inherited metabolic disorders (IMDs), accounting for their multi-system manifestations. One important aspect of this is endocrinopathy, which is relatively common but underestimated in IMDs, presenting in childhood following diagnosis or sometimes a presenting symptom in adults where there is multi-system or multi-gland involvement. Endocrinopathies may be secondary to treatment (eg chemotherapy used for Hematopoietic Stem Cell Therapy (HSCT)). Given the physical and psychological burden of these conditions and the advent of new treatments for IMDs, it is important that clinicians are aware of endocrine manifestations of IMDs and their management.

Methods
Individuals were reviewed in our joint supra-regional endocrinology/metabolic clinic. The hospital digital care record and national summary care record was used to review diagnoses, endocrine manifestations, blood results, imaging and treatment.
Results
36 people were reviewed in the combined endocrine/metabolic clinic; 19 were female and 17 were male. The most common groups of metabolic conditions represented were disorders of carbohydrate metabolism ($n=7$), fatty acid disorders ($n=6$) lysosomal storage disorders ($n=6$) and mitochondrial disorders ($n=4$). The most common endocrine complication was primary or secondary hypogonadism ($n=22$) followed by thyroid disorder (hypo/hyperthyroidism or thyroiditis) ($n=5$), diabetes T1/T2 ($n=4$) and adrenal insufficiency ($n=4$). 8 individuals had 2 or more endocrine complications. In all, 25 individuals received specific endocrine treatments.
Discussion
This study highlights the utility of hormonal profiling of IMD patients in general metabolic clinics with subsequent referral to a specialist joint endocrine/metabolic clinic. Endocrine problems account for significant morbidity so early identification can identify treatable complications. Hormonal dysfunction may also be the first sign of an IMD, such is in our cohort (X-linked adrenoleukodystrophyand Lesch-Nyhan). IMDs should also be considered where a patient presents with an endocrinopathy and multi-system or multi-glandular involvement.

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P79

An audit on management of inpatient hypoglycemia among diabetic patients

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Aim
To know the compliance on management of inpatient hypoglycaemia among diabetic inpatients admitted for non-critical illness at Bronglais General Hospital based on JBDS guidelines
Method
A retrospective collection of data of diabetes patients from EMR and patient files over the period of 6 months from September 2022 to March 2023, who were admitted for various conditions and developed hypoglycemia during their stay in hospital.
Results
The median age of patients was around 81 years; with equal male: female ratio. The median length of stay in hospital was around 23 days. Out of 30 patients, 28 were type 2 and 2 were Type 1 Diabetes Mellitus Insulin in combination with oral diabetic agents was prescribed in 46 % of type 2 Diabetes patients and 28 % of patients were on Glicazide. Majority of hypoglycemic episodes fall under mild (77 %) with 13 % and 10 % in moderate and severe categories, respectively. Nine patients were treated with oral glucose preparations based on guidelines and rest of patients' management plan were not recorded. Repeat blood glucose after 15 mins of initial hypoglycemic episode were done in all of them. None of them died from any hypoglycemic event.
Conclusion
There is wide range of missing data from the files regarding management of hypoglycemic episodes. Overall compliance with respect to management of JBDS guidelines is about 30 %. All patients were correctly categorized based on the level of severity of hypoglycemia. About 70 % have missing documentation which led us to implement a proper documentation tool for inpatient hypoglycemia which should be easily accessible and also clearly stating the treatment given. Also, staff education on the latest guidelines is important as well as proper tritration of insulin based on blood glucose level for the doctors. We plan to Re-audit within 6 months after implementation of the above action plan.

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P204

Investigating the role of CaSR in mediating effect on glucose tolerance via α-cell and β-cell signalling

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High protein diets are hypothesised to improve glucose tolerance by modulating the secretion of gastroenteropancreatic hormones via amino-acid sensing. Glucagon, traditionally associated with hyperglycaemia, has beneficial effects on glucose homeostasis, potentially due to its role as an insulin secretagogue via intra-islet signalling and as a regulator of pulsatile insulin secretion. The calcium sensing receptor (CaSR), known for its role in calcium homeostasis, also functions as an amino-acid sensor and modulates secretion of gastroenteropancreatic hormones. We hypothesize that CaSR also functions as an amino-acid sensor in the pancreatic islets to mediate protein's beneficial effects on glucose tolerance. To test this hypothesis, we examined the effects of different amino-acids on mobilization of intracellular calcium ($[Ca^{2+}]_i$) in α-cells and β-cells in islets isolated from preproglucagon promoter-driven (PPG-Cre;GCaMP6f) and insulin promoter-driven (Ins1Cre;GCaMP6f) $[Ca^{2+}]_i$-reporter mice, respectively. The role of CaSR signalling in mediating the effect of oral administration of 10% whey on glucose tolerance was assessed *in vivo* in the PPG-Cre;flox-CaSR mice, characterized by deletion of exon 7 of the *Casr* gene in PPG-expressing α-cells and gastrointestinal L-cells. Our results showed various potencies of amino-acids in mobilizing $[Ca^{2+}]_i$ in the α-cells in the order of glutamic acid > ornithine > alanine. L-phenylalanine, which is the most potent amino-acid modulator of CaSR, also increased $[Ca^{2+}]_i$, but to a lesser extent. Similar effects of amino acids on $[Ca^{2+}]_i$ were observed in β-cells, except that activation with 6mM-glucose was required for some amino acids. Whey-induced improvement on glucose tolerance was blunted in PPG-Cre;flox-CaSR mice, supporting a role of CaSR in α-cells and/or L-cells in mediating the actions of protein on glucose tolerance. These data suggest that CaSR signalling in PPG-expressing cells partially mediates protein-induced beneficial effects on glucose tolerance. We are investigating the *in vivo* action of CaSR in β-cells using Ins1Cre;flox-CaSR mice.

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P205

Metabolic signatures of selective hepatic insulin resistance are not evident in humans across a range of liver fat content

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Background
Fasting hyperglycaemia and hypertriglyceridemia are characteristic of insulin resistance (IR), type 2 diabetes, and non-alcoholic fatty liver disease, but the underlying mechanisms remain unclear. Rodent work has suggested this is due to selective hepatic IR; defined by increased hepatic gluconeogenesis (GNG) and *de novo* lipogenesis (DNL). The aim of this study was to determine if signatures of selective hepatic IR were associated with hyperinsulinemia or liver fat content in humans.
Methods
182 medication-free participants were classified as hyperinsulinemic or normoinsulinemic (HI or NI) and as having high or low liver fat (HF or LF). Magnetic resonance spectroscopy was used to measure liver fat content and stable isotope tracer methodology was used to measure fractional GNG and hepatic DNL following an overnight fast.
Results
HI and HF groups had higher fasting plasma glucose and triglyceride concentrations compared to the NI and LF groups, respectively. Despite this, there was no difference in fractional GNG between the HI and NI groups. HF compared to LF participants, tended ($P=0.08$) to have lower fractional GNG. HI participants had higher fasting hepatic DNL compared to NI participants (6.7 vs 5.0 %, $P=0.013$) but no difference was observed between the HF and LF groups. There was no association between fractional GNG and DNL across all participants ($r=0.05$, $P=0.5$).
Conclusions
Hepatic glucose production, from gluconeogenic and glycogenolytic pathways, contributes to hyperglycaemia in the fasting state and GNG is often suggested to be the major contributor. From our observations, both pathways appear to be equally upregulated in hyperinsulinemia but glycogenolysis may play a greater role in those with HF. DNL may contribute to hypertriglyceridemia in individuals with HI but not those with HF. Taken together, this suggests that selective hepatic IR may be driven more by hyperinsulinemia than liver fat content alone and glycogenolytic pathways should also be considered.

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P206

New approaches to imaging metabolic heterogeneity in cultured adipocytes

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Introduction
Adipocytes have been shown to exhibit considerable heterogeneity. In humans, they vary in size from <20 to 300 μm in diameter, which equates to a several hundred-fold difference in cell volume within the same tissue. Population based studies indicate larger adipocytes are associated with metabolic diseases, but how cell size is related to metabolism is poorly understood. Recent studies measured glucose levels in individual cells in culture and showed larger fat cells were less insulin sensitive than smaller cells. However, this technique is limited in its applications and required genetic manipulation of the cells, rendering it of limited use in primary tissues. Hence, there is an unmet need to study metabolism non-invasively at the single cell level in living tissues.
Results
Using Stimulated Raman Scattering (SRS) microscopy, we have shown that we can identify and quantify heterogeneity in a label free manner using 3T3-L1 adipocytes for proof-of-concept. Furthermore, by utilizing deuterated glucose-d7, we identify heterogeneity in glucose incorporation into lipid droplets within individual cells, and individual lipid droplets. Combining this approach with spectral phasor analysis, we have begun to develop methodology to quantify cell size, lipid droplet size and number, and quantifying specific metabolic steps all within the same sample set.
Future work
We will also outline the use of a ratiometric Raman sensor that incorporates into the mitochondria ('mitokyne'). This mitokyne is able to determine real time pH changes within mitochondria during treatment conditions; our goal is to develop a system which captures this information from a single field of cells.
Conclusion
Here, we have developed and validated a workflow of experimental systems to quantify distinct aspects of adipocyte biology which can be applied across a range of experimental research and cell types.

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P207

Vertical sleeve gastrectomy: Attenuating cortisol activation in mice and humans via pro-inflammatory cytokine reduction

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Background
Cortisol is a hormone produced by the adrenal cortex and is essential for the maintenance of metabolic homeostasis. Cortisol activation is catalysed by 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and excess cortisol is associated with insulin resistance and hyperglycaemia. Previous studies from our group have shown that Vertical Sleeve Gastrectomy, a gastrointestinal procedure known to improve insulin sensitivity, causes cortisol inhibition in mice, independent of weight loss. The aim of this study was to investigate the underpinning mechanisms of this observation in mice and humans.
Methods
High Fat Diet mice underwent Vertical Sleeve Gastrectomy ($n=5$) or sham ($n=5$) surgery. 11βHSD1 knockout mice were generated on a C57/BL6 background using CRISPR/Cas9. Cortisol, cytokines and 11βHSD1 levels were measured in intra and post-operative plasma and adipose tissue. Adipose tissue biopsies were obtained from patients undergoing Vertical Sleeve Gastrectomy at intra and 6 months post-operative timepoints. All biopsies were analysed using Magnetic Luminex Screening Assays and quantitative real-time PCR (qRT-PCR).
Results
Both HFD VSG and 11βHSD1-/- mice displayed significantly improved glucose and insulin tolerance ($P<0.001$). Cortisol secretion in plasma, and 11βHSD1 expression in adipose tissue, was significantly reduced in VSG mice, as previously shown. This was confirmed in liver and muscle biopsies. Cytokines interleukin-6 (IL-6), leptin and Transforming growth factor beta (TGF-β) were significantly inhibited in plasma and adipose tissue in both VSG and 11βHSD1-/- mice, while anti-inflammatory peptide FGF-21 concentration was increased. Expression of 11βHSD1, leptin and IL6 was also significantly reduced in human adipose tissue post- Vertical Sleeve Gastrectomy.
Conclusion
Vertical Sleeve Gastrectomy is shown to be inhibiting cortisol secretion and 11βHSD1 activity in both mice and humans, an effect that may represent an additional contribution to the health benefits of the surgery. The mechanism underlying this observation could involve a decrease in inflammatory cytokines, both circulating and at tissular level.

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P208

Screening for paediatric type 1 diabetes: a qualitative exploration of parent and stakeholder views [ELSA 1 Study]

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Background
The EarLy Surveillance for Autoimmune diabetes (ELSA) study is screening 20,000 children in the UK aged 3-13 years for type 1 diabetes through measurement of islet autoantibodies. Screening aims to prevent diabetic ketoacidosis at clinical onset of disease, reducing mortality, and identifies the population who could benefit from prevention trials. The ELSA-1 study aimed to explore the perspectives of parents and stakeholders on the relative benefits and limitations of type 1 diabetes screening.
Methods
Qualitative interviews were conducted with parents and stakeholders. Stakeholders included general practitioners, paediatricians, adult diabetes consultants, allied health care professionals, policymakers, and other non-healthcare setting stakeholders. Thematic analysis was undertaken using N-Vivo software to help identify themes.
Results
Sixty interviews were conducted, including 33 family interviews (F) (38 parents and 14 children) and 27 stakeholder interviews. Overall, parents were supportive of screening ($n=33/36$). Parents cited the following benefits of screening; 1) better prepared for the future, 2) prevent emergency presentation at diagnosis and 3) monitoring follow-up to track progression. Concerns included the burden of 'living with risk' and harms of screening older children. There was emphasis on the education and support needed for families with children at-risk. The lack of preventative treatment negated the benefits of screening for a third of stakeholders. The major concern was around managing children at-risk within current NHS system pressures. Consensus guidelines for a monitoring programme were needed, including recommendations for management in primary and secondary care. Appropriate psychological support was also important for families with a child at-risk. Overall, screening stakeholders agreed screening was an important area of research.
Conclusion
ELSA-1 provides the first qualitative interview data in the UK to show that parents are supportive of screening and stakeholders recognise the importance of screening research. Barriers raised in ELSA-1 will be addressed through co-production workshops.

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P209

Inpatient hypoglycaemia in patients with diabetes and moderate/severe frailty is associated with prolonged length of stay

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Introduction
National guidance states that people with diabetes and frailty require personalised targets and less aggressive treatments due to the limited evidence for benefits and the high risk of hypoglycaemia. Studies have shown a low rate of deintensification in this cohort of patients that may increase the risk of inpatient hypoglycaemia, contributing to morbidity and mortality. The audit aims to assess the frequency of inpatient hypoglycaemia and its association with length of stay in people with diabetes and moderate/severe frailty.

Methods
We retrospectively collected data on patients with diabetes and clinical frailty score (CFS) of ≥ 6 that were discharged from the medical unit in 2022. Data including patients' baseline characteristics, their medications, number of inpatient hypoglycaemia (capillary blood glucose $<$ 4mmol/l), and length of stay were collected. Multivariate regression was conducted using StataSE v1.7 to assess the association between patient factors, inpatient hypoglycaemia and the length of hospital stay.
Results
Four-hundred and thirty-six patients were included in our analysis [Age: 79.5 years (IQR=71-86). 52.1% (n=227/436) were women and the median CFS was 6 (IQR=6-7). 29.4% (n=128/436) of the admissions were due to falls. 17.2% (n=75/436) had mild/moderate hypoglycaemia during admission and 6.0% (n=26/436) had severe inpatient hypoglycaemia (capillary blood glucose $<$ 3mmol/l). The median length of stay was 8 days (IQR=4-16 days). Adjusted for age, insulin use and CFS, Multivariate regression showed a positive association between the occurrence of any episode of inpatient hypoglycaemia and the length of stay [β=6.65, $P<0.001$].
Conclusion
This audit shows a high rate of inpatient hypoglycaemia in patients with diabetes and moderate/severe frailty. Inpatient hypoglycaemia is also associated with increased length of stay highlighting the importance of early review of HbA1c, medication history and pro-active deintensification when appropriate. Systems to identify high-risk inpatients allowing targeted specialist support should be developed and implemented where possible.

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P210

The contribution of glucocorticoid metabolism by 11β-HSD1 towards muscle wasting in chronic kidney disease

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Background
Skeletal muscle wasting is a characteristic feature of chronic kidney disease (CKD), associated with increased hospitalisations and premature mortality. Excess glucocorticoid signalling is a major contributor to the pathogenesis of muscle wasting in conditions of renal impairment. This study aimed to validate a murine model of CKD and utilise this to determine if deletion of 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) provides protection against muscle atrophy.
Methods
8-week-old male mice with wild-type (WT) or 11β-HSD1 knockout (11βKO) genetic background received either normal chow diet or chow treated with 0.15% adenine for 7-weeks to induce renal impairment. Model validation involved histological analysis of kidney tissue, measurement of urea and creatinine serum concentrations and inflammatory markers. The effects of 11βKO on skeletal muscle weights, fibre size distribution, steroid metabolism, catabolic pathways and inflammation were assessed ex vivo.
Results
Adenine induced increased urea and creatinine concentrations in both WT (fold changes 3.16 and 2.79, $P<0.0001$ respectively) and 11βKO mice (fold changes 4.69 and 4.10, $P<0.0001$ respectively) with reduced functional tissue (fold changes WT: 0.35; 11βKO: 0.22, $P<0.0001$). Adenine treatment led to reduced myofiber area (WT: -13.83%, $P<0.05$; 11βKO: -16.79%, $P<0.01$) with no protection observed in 11βKO mice. No significant changes were observed in markers of catabolic signalling or inflammation.
Conclusions
The Adenine diet model of CKD effectively induced renal impairment for both WT and 11βKO. This resulted coincided with marked muscle atrophy, mirroring observations in human disease. The metabolic, catabolic and inflammatory markers provided limited insight into the underpinning biochemistry. 11βKO offered no protective properties against skeletal muscle wasting.

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P211

miR-10b as a novel negative regulator of brown adipogenesis

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Improved knowledge of adipogenesis is necessary to gain insight into brown and white fat physiology. Interest in adipocyte differentiation has increased markedly over the past few years with emphasis on intersection between microRNAs (miRNAs) and the transcriptional cascade that controls adipogenesis and metabolic dysfunction. The aim of this study is to identify miRNAs that regulate white and brown adipocyte differentiation and define miRNA action in a stem cell model of adipogenesis. Small RNAseq analysis of primary mouse brown and white adipocytes identified miR-10b to be upregulated in brown adipocytes. We generated two model systems: 1) immortalized brown pre-adipocytes (BAT) treated with miRCURY miRNA Inhibitors and 2) CRISPR/Cas9 KO of miR-10b in E14 mouse embryonic stem cells (ES). Both cell models were differentiated to mature adipocytes using optimized protocols. To unravel the pathways that are affected by miR-10b depletion, a transcriptomic analysis was performed at key time points. Both cell models demonstrated that miR-10b depletion severely compromised differentiation into mature adipocytes as judged by lack of lipid droplet accumulation and low expression of white and brown adipocyte marker genes. Further examination showed that miR-10b directly affects BMP/WNT signalling pathway, which plays a crucial role during the differentiation of ES cells into adipocytes. Intriguingly, this mechanism is not affected in the BAT model. GSEA Analysis (GSEA) based on KEGG pathways revealed that fatty acid metabolism, Citrate cycle, AMPK signalling pathway and regulation of lipolysis in adipocytes were amongst the most significantly affected pathways by the depletion of miR-10b in BAT. Our research was the first to identify the importance of miR-10b upregulation during adipogenesis. miR-10b appears to control distinct molecular pathways during preadipocyte commitment and terminal differentiation. Understanding the miR-10b-mediated regulatory mechanism during adipocyte commitment and differentiation may help to generate adipose tissue-engineering strategies for cellular therapies for lipodystrophy and obesity.

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P212

Insufficiency of vitamin B12 affects m6A methylation of mRNA and their related gene expression in human placenta

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Background
Vitamin B12 is crucial for placental development and fetal growth. B12 deficiency is associated with maternal obesity and adverse pregnancy outcomes. B12 is essential for the synthesis of S-Adenosyl methionine (SAM) which serves as a methyl donor in various cellular processes including DNA and RNA methylation. Pregnant women with low B12 have higher triglycerides, lower HDL and lower DNA methylation of cholesterol transcription factor. However, the influence of B12 on m6A (N6-methyladenosine) methylation of mRNA has not been explored. M6A methylation, the most prevalent modification of mRNA in mammals is regulated by methyltransferase complex including writers, erasers and readers. Here we aim to investigate whether low B12 affects m6A levels and gene expression involved in methylation in mRNA.
Methods
Human placental explants derived from 10 healthy pregnant women and trophoblastic cells (BeWo) were cultured for 7 days in CMRL or DMEM media, respectively, supplemented with sufficient (500nM-Control) and low B12 (25pM-low B12). RNA isolation, cDNA synthesis and qRT-PCR assays were performed to assess the expression of genes and m6A levels by Epiquick m6A RNA methylation kit.
Results
Placental trophoblasts cultured in low B12 showed decreased levels of m6A in total RNA. Placental explants and trophoblasts cultured in low B12 showed a significant increase in expression of m6A methylation genes: (1)writers that catalyse mRNA methylation (METLL3, METLL5, WTAP), (2)erasers that catalyse demethylation process (FTO, ALKBH5), and (3)readers that captures

m6A methylation sites (YTHDF1, YTHDF3), when compared to control ($P < 0.05$).
Conclusion
Our novel data show that low B12 status in placenta significantly impacts m6A levels in mRNA and the expression of genes including writers, readers, and erasers. Modulation of m6A methylation levels and understanding the underlying mechanisms of its regulation may offer new avenues for developing novel therapeutic strategies for preventing adverse metabolic programming due to B12 deficiency.

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P213

Super-resolution ultrasound imaging approaches to visualise changes in gut structure

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The gut plays an important role in energy homeostasis, and gut function is under intensive neuroendocrine control. The non-invasive imaging techniques contrast enhanced ultrasound (CEUS) imaging and super resolution ultrasound (SRUS) have the potential visualise the gut and provide novel insight into its structure and function. We aimed to demonstrate that changes in duodenal villi structure can be monitored using CEUS and SRUS, providing an insight into the structural of the gut. Rats ($n = 8$) received twice daily vehicle control or the GLP-2 analogue teduglutide (0.3mg/kg; sc), known to drive small intestinal growth, for six days. In a separate experiment, rats ($n = 5$) received once daily vehicle control or the gut-damage inducing drug methotrexate (2.5mg/kg; sc) for three days. Animals were imaged before and after using a high-frequency L22-14Vx probe (Verasonics, Kirkland WA). Following data processing, villi length increased by 22% by day 6 of the teduglutide treatment compared to a 9% decrease in the control group. Villi length was found to have decreased by 12.0% (SEM = 4%) following MTX treatment, while the controls showed no significant change (2.8%; SEM = 2.6%) from baseline. These results were in line with histology. This work demonstrates that SRUS can track structural changes in the duodenum and has potential, as a tool, to longitudinally study the gut and its role in homeostasis.

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P214

The effects of physiological and pathophysiological concentrations of fatty acids on lipid droplet accumulation and metabolic function of LHCN-M2 human skeletal muscle cells

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Introduction
Skeletal muscle (SkM) is a major site of carbohydrate and fatty acid (FA) utilisation, where efficient selection between these two substrates is paramount in maintaining metabolic homeostasis. The accumulation of FA in SkM has been suggested to contribute to metabolic diseases such as obesity and type 2 diabetes mellitus. Consequently, there is significant interest in SkM FA metabolism and importantly, how FAs contribute to the metabolic function of SkM.
Methods
LHCN-M2 human skeletal muscle cells were cultured and differentiated into multinucleated myotubes. After a total of 8 days differentiation, LHCN-M2 cells were cultured for a further 2 days with 0.25% fatty acid-free bovine serum albumin alone or conjugated to oleic, palmitic, linoleic, and α-linoleic acid (OPLA; physiological ratio 45:30:24:1%) at a concentration of 200μM and 800μM. Immunofluorescence confocal microscopy was used to determine the presence of lipid droplets in SkM and Immunoblotting to determine the expression of oxidative phosphorylation (OXPHOS) protein complexes (II-V). Cell respiration analysis was used to determine the effects of OPLA in mitochondrial function.
Results
Immunofluorescence based microscopy showed an increased in the presence of lipid droplets following exposure to increasing concentrations of OPLA. However, analysis of cellular respiration found no significant differences in basal or maximal respiration, coupling efficiency or spare capacity between conditions ($P > 0.05$). The expression OXPHOS protein complexes (II-V) was not different between conditions ($P > 0.05$).
Conclusions
Preliminary data from these experiments would suggest that although exposure to increasing concentrations of OPLA leads to an increase in the presence of lipids droplets, there are no differences in cell respiration or expression of OXPHOS protein complexes. Further experiments are needed to determine how changes in composition of lipids at these concentrations effect the metabolic function of human skeletal muscle *in vitro*.

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P215

Trends in the rate of complications and outcomes in DKA management following modifications in JBDS national guidelines-Results from DEKODE study

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Introduction
Joint British Diabetes Societies Inpatient (JBDS-IP) recommended reducing fixed-rate intravenous insulin infusion (FRIII) rate to 0.05units/kg/hr when blood glucose falls <14 mmol/l to avoid hypoglycaemia during diabetes-related ketoacidosis (DKA).
Aim
We studied the impact of guideline change on complications and outcomes of DKA.
Methods
We included all DKA episodes from July 2021 to March 2023 across five hospitals participating in the DEKODE programme. The number of hypoglycaemia, hypokalaemia, and hyperkalaemia during each DKA episode was included in our study. Data regarding dates and times of admission, discharge, DKA diagnosis and resolution were used to calculate DKA duration and length of stay. The differences in the proportion of complications and outcomes between DKA episodes where FRIII was and was not reduced were calculated using the chi-square test in SPSS 29.0.
Results
A total of 753 DKA episodes were included in the study. FRIII was reduced as per JBDS recommendations in 49.7% of DKA episodes during the last quarter of 2022. However, this declined to 19.2% in the first quarter of 2023. There were no significant differences in the frequency of hypokalaemia (those with reduced rate FRIII vs those without; 33.5% vs 30.7%, $P = 0.448$) or hyperkalaemia (29.4% vs 29.9%, $P = 0.881$). While there was no significant reduction in hypoglycaemia (16.5% vs 13.8%, $P = 0.344$) the overall cohort, hospital D had an increase in the rate of hypoglycaemia (18.2% vs 7.8%, $P = 0.016$). There were no difference in the DKA duration (hours, median (IQR): 17 (12-25) vs 17(11-27)) or length of admission (days: 3.4 (2.4-5.6) vs 3.4 (2.1-6.8)) between the two groups.
Conclusion
There was no significant benefit of FRIII reduction over complication during DKA or its outcome. Although there was a positive trend in guideline uptake, this dropped in the last quarter of the study, suggesting the need for better implementation strategies.

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P216

Junior doctor knowledge and awareness of management strategies for inpatients with diabetes and moderate/severe frailty

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Introduction
unior doctors (JDs) are important part of the multidisciplinary team when managing people admitted with diabetes and frailty. Several guidelines have recommended a target HbA1c of between 7.0-8.5% for this group of people with diabetes. We aimed to assess junior doctors' knowledge and awareness of management guidelines for people with diabetes and moderate/severe frailty.
Methods
Survey was conducted among JDs working in the medical department of a large acute teaching hospital at the beginning of their rotation. Data collected included participants' grade and their knowledge of inpatient management of people with diabetes and moderate/severe frailty. Responses were recorded on a 5-point Likert scales.
Results
Sixty-eight junior doctors completed the survey and were included in the analysis. The majority were foundation year (63.2%; $n=43/68$) followed by core trainees (20.6%; $n=14/68$) and specialist registrars (11.8%; $n=8/68$). 82.4% ($n=56/68$) of the JDs stated that they were aware that people with diabetes and moderate/severe frailty required an HbA1c target range which was different to standard care. Of these, 67.9% ($n=38/56$) were able to correctly state/identify the correct target range for these people (7.0-8.5%). Only 19.1% ($n=13/68$) of the JDs stated that they would always/often check the HbA1c for people with diabetes and frailty during admission, and only 20.6% ($n=14/68$) of the JDs would always/often consider deintensification of treatment during the inpatient stay. 22.1% (15/68) had some experience of direct involvement with deintensification.
Conclusion
This study identifies gaps in knowledge and awareness of the management of patients with diabetes and moderate/severe frailty among junior doctors. Junior doctors were unlikely to (consider) deintensification or have direct experience of deintensification. Educational interventions to improve the knowledge and awareness are needed to improve the inpatient care of patients with diabetes and moderate/severe frailty admitted to the hospital.

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P217

Acetate supplementation improves adipose-hepatic gluco-lipid dysregulation in experimental PCOS model by repression of NF- κB/NLRP3 immunoreactivity

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Background
Endocrine-metabolic disorders, especially polycystic ovarian syndrome (PCOS) has been linked with increased risk of non-alcoholic fatty liver disease (NAFLD) among reproductive age and implicated hyperandrogenism-driven adipose/hepatic insulin resistance (IR). Gut microbial metabolites such as short chain fatty acids (SCFAs) are crucial modulators of metabolic regulation. However, the impact of SCFAs, in particular, acetate on hyperandrogenism and/or adipose/-hepatic IR in PCOS model is unclear. This study therefore hypothesized that acetate would break the vicious cycle that drives adipose-hepatic metabolic dysregulation in a rat model of PCOS, possibly by suppression of NF-κB/NLRP3 inflammasome.
Methods
Female Wistar rats (eight-week-old) were randomly allocated into 4 groups of $n=$six/group, which received vehicle, sodium acetate (200 mg), letrozole (1 mg/kg) and letrozole plus sodium acetate respectively. The animals were treated by oral gavage, once daily for a period of 21 days.
Results
The PCOS animals were insulin resistant, hyperandrogenic and hypoestrogenic with decreased SHBG. In addition, the liver had increased lipid profile and decreased glycogen synthesis, while the adipose tissue showed decreased lipid profile with elevated glycogen synthesis. Besides, the results also showed increased malondialdehyde, γ-glutamyl transferase, lactate dehydrogenase, inflammatory mediators with corresponding decrease in antioxidant system in the liver and adipose tissues. Immunohistochemical evaluation also demonstrated severe expression with BAX/NLRP3 antibodies. Nonetheless, concomitant acetate supplementation attenuated these derangements.
Conclusion
The present data collectively suggest that acetate reverses adipose-hepatic glycolipid dysregulation in experimental PCOS model by attenuating androgen excess and NF-κB/NLRP3 immunoreactivity.

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P218

High but not low molecular weight FGF-2 levels are increased in response to epididymal white adipose tissue (eWAT) dysfunction caused by a chronic high fat diet

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Fibroblast growth factor (FGF) 2 (FGF-2) has been implicated in the regulation of adipogenesis and in epididymal fat development. However, FGF-2 exists as multiple high (Hi; >20 kD) and low (Lo; 18 kD) molecular weight isoforms, as a result of alternative codon usage from a common RNA. Furthermore, HiFGF-2 and LoFGF-2 isoforms can possess opposing activities and dose-dependent effects have been described. In this context, LoFGF-2 possesses proliferative and cytoprotective properties including against cellular senescence, as well as adipogenic activity. By contrast, HiFGF-2 has been associated with hypertrophy, dysregulation of the extracellular matrix, fibrosis and cell death. Despite this, the production of HiFGF-2 vs LoFGF-2 is not well described in adipose tissue, and thus, the nature of FGF-2 involvement remains unclear. Here we have used protein immunoblotting to assess FGF-2 levels in eWAT from outbred 4-week-old male CD-1 mice maintained on a high fat diet (HFD) vs regular chow diet (RCD) for up to 24 weeks. By comparison, mice on a HFD displayed increased total body weight and adiposity, evidence of fatty liver and impaired glucose clearance. More specifically, HiFGF-2 but not LoFGF-2 was detected in eWAT and levels were increased significantly in mice fed a HFD. This increase was associated with evidence of eWAT dysfunction (increase in adipocyte size and altered production of leptin and adiponectin) as well as increased levels of senescence-related p21 and extracellular matrix-related collagen type 5 and 6 RNAs. Complementary studies in the 3T3-L1 mouse cells, as a model for preadipocyte differentiation, are in progress. Our observations indicate a complex role for FGF-2 isoforms and/or levels in adipocyte biology in response to diet which warrants further study.

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P219

Broccoli extract as an agent to protect against endoplasmic reticulum stress and mitochondrial dysfunction in human adipocytes

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Background
Endoplasmic reticulum (ER) stress and associated mitochondrial dysfunction contribute to the pathogenesis of obesity and type 2 diabetes mellitus (T2DM). Studies show broccoli can reduce inflammation in cancer and may therefore mitigate inflammation-induced cellular disruption that precedes insulin resistance in human adipocytes. Therefore these studies investigated the impact of freeze-dried broccoli extracts (BE) on ER stress and mitochondrial dysfunction in human adipocytes.

Methods
Differentiated human adipocytes (Chub-S7 cell line, $n=6$) were treated with tunicamycin (Tun; 750ng/ml) alone, to induce ER stress, or combined with a freeze-dried broccoli extract (BE; hybrid Brassica oleracea var. italic; 10ng/ml) acutely (24hr), and chronically (48hr, 72hr). ER stress changes were measured through marker genes (ATF4, ATF6 and CHOP) and proteins (BiP, p-eIF2α and eIF2α). Mitochondrial function was assessed via a Mito Stress Test, measuring oxygen consumption, and through marker genes (SIRT3). Mitochondrial morphology was assessed using live cells on a Nanolive microscope.
Results
Tun increased ER stress marker genes up to 4.5-fold (CHOP, 72hr, $P<0.001$), whilst BE+Tun reduced this expression up to 64% ($P<0.001$). Tun increased mitochondrial oxygen consumption rate by 77% (24hr, $P<0.05$) whilst BE mitigated this by 37%. BE increased the expression of SIRT3 up to 3-fold, regardless of Tun presence. Live cell imaging highlighted Tun-induced mitochondrial fragmentation, indicative of dysfunction, which progressed with time (48hr, 72hr). BE+Tun treated cells displayed a more efficient, elongated mitochondrial phenotype, similar to control.
Conclusion
These studies highlighted that BE can alleviate ER stress and associated mitochondrial dysfunction in human adipocytes. BE reduced markers of ER stress, prevented excessive mitochondrial oxygen consumption and maintained morphologically healthier mitochondria than cells exposed to Tun alone. These impacts occurred both acutely and chronically, with most notable protection from BE observed at 72hr. As such, BE may offer an agent to relieve obesity-induced inflammation and associated insulin resistance.

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P220

Hepatic dysmetabolism in polycystic ovarian syndrome: Impact of paraoxonase-1 modulation by butyrate

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The complications of endocrine-metabolic disorders among women of reproductive age, such as polycystic ovarian syndrome (PCOS), are cascade of events leading to cardiovascular diseases, as well as non-alcoholic fatty liver disease (NAFLD) which is the leading cause of liver cirrhosis and hepatic carcinoma that often necessitates organ transplant. Paraoxonase-1 (PON-1) has been shown to be protective against metabolic assaults. However, its role in hepatic glucolipid regulation particularly in PCOS model has not been documented. Short-chain fatty acid (SCFAs) particularly butyrate, are essential modulators of metabolic health. The present study hypothesizes that butyrate would ameliorate hepatic dysmetabolism by upregulation of PON-1. Female Wistar rats (8-week-old) were allotted into groups; control (CONT), butyrate (BUTY), letrozole (PCOS), and PCOS+BUTY. Letrozole (1 mg/kg) was used to induce PCOS for 21 days. After confirmation of PCOS, butyrate (200 mg/kg) was administered for 6 weeks. Rats with PCOS showed multiple ovarian cysts, hyperandrogenism, reduced insulin sensitivity, hyperleptinemia, hypoadiponectinemia, dyslipidemia, and hepatic lipid peroxidation, lipotoxicity, as well as increased hepatic caspase-6, proinflammatory markers (NF-kB, SDF-1), and decreased antioxidant defense/sirtuine-1(NrF2), and HIF-1α with corresponding expression of inflammasome as evaluated immunohistochemically. These alterations were accompanied by suppressed level of PON-1. However, administration of butyrate attenuated these hepatic metabolic/cellular perturbations. The results of the present study demonstrate that butyrate mitigates hepatic glucolipid dysregulation and its attendant oxidative/inflammation in PCOS model through upregulation of PON-1 expression.

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P221

Crosstalk between preadipocytes and macrophages modulate depot-specific adipose tissue responses to oestrogen

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Fat distribution influences metabolic risk. Accumulation of fat in the upper body increases metabolic risk, while lower body adipose expansion is protective. Oestrogen promotes lower body adiposity; transgender women on oestrogen therapy show increases in gluteal adipose, while transition to the menopause is associated with a shift in fat distribution towards the upper body, concurrent with changes in metabolic risk. Still, mechanisms governing the depot-specific effects of oestrogen on fat distribution are poorly understood but likely to involve cell-to-cell communication between preadipocytes and resident immune cells. To investigate crosstalk between adipose tissue cell types, we have explored single cell RNA sequencing data taken from paired abdominal and gluteal adipose biopsies from healthy male and female subjects. By running a differential gene expression analysis paired with an interactome analysis, we have identified a limited number of depot- and gender-specific ligand receptor interactions between preadipocytes and macrophages. To test the functional significance of ligand-receptor pairs we are performing *in vitro* co-culture studies using depot-specific human preadipocyte cell lines together with human monocytes. The lead ligand candidate is an oestrogen-inducible peptide secreted by preadipocytes, subsequently conveying an anti-inflammatory response in resident macrophages. The detailed knowledge of this signalling system will provide opportunities for novel therapeutics for metabolic disorders.

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P222

The impact of using self-selected non-weight loss goals in sustainable obesity management

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Background
Most obesity management programs use short term weight loss as the main monitoring parameter. Change in weight can be a misleading measure as it can be impacted by various factors and most participants regain weight after exiting such programs[1]. The aim of this project is to assess the efficacy of focusing on self-selected, non-weight loss goals in encouraging long term obesity management.
Methods
From December 2022 to April 2023, 4 "Enhance obesity education sessions" were delivered online. All sessions were delivered on zoom and recorded then uploaded to the Program's landing page. The program was set-up based on the Transtheoretical Model of Cycle of Change, educating patients on obesity, healthy lifestyle and how to create their personalized SMART goal. Participants submitted pre- and post- program survey to monitor their adherence to their chosen healthy lifestyle goal.
Results
In total, out of 41 participants, 6(14%) filled the post-program questionnaire. On average, participants' confidence in attaining set goals increased by 67%($P=0.04$). Participants scored the ability to stick to their SMART goal during the program 7.57/10 and the effectiveness of the SMART goal model 8.57/10. While weight loss was not a focus, 2 participants (29%) lost weight. 100% of the participants "strongly agreed"/"agreed" the program "helped understand obesity and its management", "helped build an achievable goal", and "helped focus on aspects of obesity other than weight loss", "helped develop a sustainable healthy lifestyle", and "tailored to needs and priorities". 86% of participants "strongly agreed"/"agreed" the program: "helped participants stay consistent with their goal"
Conclusion
Non-weight based, self-selected healthy goals are an effective way of encouraging participants to maintain sustainable healthy lifestyle choices. By allowing participants to focus on their chosen goal and tailoring care accordingly, obesity management is easier to achieve and sustain.

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P223

Prevalence of Vitamin B12 deficiency in Kano, northwestern Nigeria with reference to diabetes mellitus status and metformin use

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Background
Metformin has been shown from observational studies to cause vitamin B12 deficiency and its complications. However there is no such study in Kano, Northwestern Nigeria which has a large population of patients with type 2 diabetes mellitus on metformin.

Objective
To determine the prevalence of Vitamin B12 deficiency among patients with type 2 diabetes mellitus on metformin therapy compared with metformin-naïve patients with diabetes and healthy individuals
Methods
It was a hospital-based, case-control prospective, analytical, observational study. Three hundred participants were recruited, 100 metformin-treated patients with diabetes, 100 metformin-naïve patients with diabetes and 100 non-diabetic patients. Questionnaire was used to evaluate the clinical and laboratory features of the participants. Vitamin B12 was assayed using Beckman access immunoassay system. Peripheral neuropathy was tested using biothesiometer. Data was analysed using SPSS.
Results
Most of the participants were females above 40 years of age. Vitamin B12 deficiency occurred among 24% of metformin-exposed patients with diabetes mellitus, 8% of metformin-naïve patients with diabetes and 5% of participants without diabetes mellitus. Metformin exposure, dose and duration of the drug therapy were found to be significantly associated with the development of vitamin B12 deficiency ($P<0.05$). However, among metformin-naïve participants, the duration of diabetes mellitus was significantly associated with vitamin B12 deficiency. The dose of metformin was an independent predictor for the development of vitamin B12 deficiency among metformin exposed participants (OR 3.5, 95% CI 1.330-9.368). There was a statistically significant relationship between the vitamin B12 deficiency and the development of peripheral neuropathy and macrocytic anaemia among the three groups of participants.
Conclusion
High doses of metformin causes vitamin B12 deficiency among patients with type 2 diabetes mellitus. Hence there is need for regular screening of these individuals when they are on long term therapy to prevent and alleviate the complications of vitamin B12 deficiency.

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P224

Metabolic profiles of children of mothers with and without gestational diabetes at age of 5 years

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Aims
Epidemiological studies have demonstrated that Indian babies born to mothers with gestational diabetes mellitus (GDM) have adverse metabolic profiles. The anthropometric and metabolic profiles in children of women with and without GDM were compared at age 5 years.
Methods
Children born to mothers with GDM (CGDM) and without GDM (WGDM) were included in this prospective study. We examined maternal gestational BMI, GDM, offspring height, weight, BMI, subscapular skinfold (SSF) and triceps skinfold (TSF) thickness, fasting (FBS) and post glucose blood sugar (PPBS), lipid profile and liver function tests at age 5 years.
Results
Maternal BMI was positively associated with adiposity in both groups. The risk of being overweight/obese was increased 3.27-fold if mothers were overweight/-obese (95% CI 1.56-416) compared to 4.35-fold (95% CI 2.50-9.88) if mothers additionally had GDM. CGDM had higher measures of SSF and TSF as compared to WGDM($P<0.001$). A higher FBS (92 $\pm$ 4.6 mg% vs 88 $\pm$ 3.22 mg%) but not PPBS was seen in CGDM vs WGDM. HDL was lower (37 $\pm$ 2.3 mg% vs 43 $\pm$ 1.96 mg%) and triglycerides (133 $\pm$ 4.4 mg% vs 127 $\pm$ 3.37 mg%) levels were higher in CGDM vs WGDM. There were no differences in the LDL levels. Irrespective of treatment regimens used for GDM there were no differences in anthropometric or metabolic parameters. No significant gender specific differences were found although males had higher SSG, TSF and lower HDL levels as compared to females.
Conclusions
CGDM had higher anthropometric measures - SSF and TSF- and higher fasting glucose, lower HDL and higher triglycerides as compared to WGDM at age of 5 years. These children may be more likely to have adverse metabolic outcomes later in life. Interventions focused on obesity prevention in women and effective management of GDM could help reduce childhood obesity.

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P225

Retrospective case review of patients treated with semaglutide for weight management

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Introduction
Obesity, a chronic disease, is recognised as a major public health problem. In 2023, the National Institute for Health and Care Excellence (NICE) recommended semaglutide, a weekly glucagon-like peptide-1 (GLP-1) agonist, as a pharmacological option for weight management. This case series aims to evaluate the real-world effectiveness and safety profile of semaglutide therapy for weight loss.
Methods
Retrospective case review of patients treated with semaglutide for weight management in an outpatient endocrine clinic in Athens, Greece. Patients were adults with either a body mass index (BMI) $>$ 30 kg/square meter or 27-29.9 kg/square meter and, at least, one weight-related complication. Patients with diabetes mellitus were excluded.
Results
Analysis included 36 individuals (25 females, 11 males) with a median age of 48 years, weight of 109.2 kg and BMI 39.7. The commonest comorbidities were dyslipidaemia (75%), prediabetes (61%), non-alcoholic fatty liver disease (50%), and obstructive sleep apnoea (25%). Analysis of 36 patients showed a median 12-week percentage weight loss of 6.9%, with 72% and 19% of patients achieving $>$ 5% and $>$ 10% weight loss, respectively. Six-month data were available for 21 individuals. The median 24-week percentage weight loss was 13.3%, with 90%, 67%, and 29% of cases losing more than 5%, 10%, and 15% of the baseline weight, respectively. After 24 weeks of treatment, 8 patients received weekly semaglutide dose of 2.0 mg, with the remaining 13 being administered 1.0 mg dose. Side effects were generally mild, with only 1 case of drug discontinuation due to vomiting.
Discussion
Real-world data confirm the great effectiveness and safety of semaglutide for weight management. The availability of medications, such as semaglutide, with this unprecedented degree of efficacy could constitute a new paradigm for obesity care. This case series reports great potency of the lower 1.0 mg semaglutide dose which warrants further evaluation.

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P226

Diabetes Management in Dialysis patients - JBDS guidance

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Diabetic nephropathy is a major cause of end stage renal failure requiring haemodialysis. Diabetes patients undergoing haemodialysis are at a high risk of adverse cardiovascular outcomes and therefore require close follow-up and ongoing monitoring which involves clinical staff working on dialysis units, GPs and diabetic nurses/specialists. We conducted an audit to assess service provision given to dialysis patients at Doncaster Royal Infirmary as per JBDS guidelines. This was a questionnaire led audit and involved enquiring whether patients are under the care of a named DSN, aware of insulin reduction on the day of dialysis, undergo routine retinal and lipid screen and to assess general control of their diabetes. We found that of the patients receiving dialysis at Doncaster Royal Infirmary, 40% of patients had not been seen by diabetes team, 55% were not under a named DSN, 80% were not aware of dose reduction while 90% of patients had undergone routine eye and lipid screening. Following this audit, we have made certain recommendations to improve the standard of care given to dialysis patients. This included individual patient education, making appropriate referrals and active communication with the Diabetic team to ensure close follow-up. Our next step would be to re-audit this cohort to ascertain improvement.

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P227

Altered glucose homeostasis and the acute porphyrias

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Background
Carbohydrate loading is used to manage the neurovisceral attacks of the acute porphyrias. This presents difficulty when treating those with altered glucose homeostasis.
Case history
A 17-year-old female presented with 5 days of abdominal pain and vomiting, her third acute presentation in eight months; the first with a seizure and second with bilateral lower limb weakness. All attendances were preceded by reduced oral intake, strenuous physical exercise and surrounded her menses. She had antibody-negative diabetes diagnosed aged 14 with an Hba1c 73mmol/mol (20-41) and Hb 66g/l (120-150) at the time. C-peptide 2592 pmol/l (370-1470), MODY screen negative. There was a family history of type 2 diabetes. Aged 17, her BMI was 17.54kg/m2. She had acanthosis nigricans and hypercholesterolemia (total cholesterol 7.3mmol/l (0-5). She had stopped insulin and was normoglycaemic (Hba1c 35mmol/mol, haemoglobin 112g/l). Abdominal pain improved three days following cessation of menses and hyperglycaemia associated with improved oral intake necessitated restarting insulin. Sustained improvements in symptoms and biochemistry were seen. Urine porphobilinogen 28.5μmol/mmol (<1.5) confirmed an attack of acute porphyria.
Discussion
The acute porphyrias manifests as neurovisceral crises due to provoked build-up of neurotoxic heme precursors. Reduction in carbohydrate intake is a well-known trigger. Small observational studies report a high incidence of abnormal glucose homeostasis in those with acute porphyrias, with levels of insulin resistance positively associated with reduced disease activity. Molecular studies have shown that glucose and insulin downregulate heme synthesis synergistically, and a small clinical study reports clinical improvement with concomitant insulin and carbohydrate administration during an acute attack. Though the mechanism is not fully elucidated, hyperinsulinemia seems positively associated with clinical and biochemical disease activity. Therefore, insulin therapy alongside a carbohydrate rich diet may be a therapeutic option to support disease quiescence in those with acute porphyrias and altered glucose homeostasis without aggravating glycaemic control.

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P228

Association of Vitamin D deficiency and gestational diabetes mellitus

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Introduction
Vitamin D deficiency is known to cause adverse outcomes in Pregnancy and has shown to have an association with Gestational Diabetes Mellitus
Aim
To evaluate the relationship between GDM and Vitamin D
Materials and Methods
Retrospective study where we looked into the Vitamin D levels (deficient <25 nmol/l - G1, Insufficient 25-50 nmol/l - G2, Sufficient >50 nmol/l - G3), GTT results, diabetes status and pregnancy outcome of 250 pregnant women of multiple ethnicities who attended the antenatal clinic in between 2018 and 2022.
Results
Mean Vitamin D in G1 was 20.15 ± 3.37 nmol/l, in G2 was 38.39 ± 7.26 nmol/l and in G3 was 64.13 ±10.27 nmol/l. The mean fasting sugar in severely Vitamin D deficient group (G1) was 5.73±1.24 mmol, in insufficient group (G2) was 5.13 ± 0.82 mmol and in Vitamin D sufficient group (G3) was 5.00 ± 0.70 mmol, $P=0.003$, G1 vs G2 +G3. $P=0.005$, G1 vs G2. Caucasian group had a mean Vitamin D of 45.15 ±16.75 nmol/l, GTT 0 min –5.05 ± 0.82 mmol, GTT 2 h – 7.03 ± 2.20 mmol; meanwhile South Asian (SA) group had mean Vit D of 41.17±18.03 nmol/l, GTT 0 min – 5.28 ± 0.92 mmol, GTT 2 h – 8.11 ± 2.17 mmol. *P* Values (GTT 0 min) 0.05;(GTT 2 h) 0.0007, Caucasians vs SA. Mean BMI was 31.24 ± 7.25 and baby birth weight 3308.58 ± 484.37 g in the Caucasian group and mean BMI 28.64 ± 5.08 and baby birth weight 3058 ± 604.23 g in the Asian group. $P=0.01$ for BMI Caucasian Vs Asian. $P=0.004$ for baby birth weight Caucasian Vs Asian.
Conclusion
Pregnant women with low Vitamin D were found to have elevated fasting sugars irrespective of the ethnicity and South Asians are more prone to have GDM when compared with the Caucasians. Caucasians had higher BMI and bigger babies.

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P229

A Case report of the rare non-diabetic euglycaemic ketoacidosis (NDEK) in patient with acute pancreatitis

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Non-diabetic euglycaemic ketoacidosis (NDEK) is a rare condition defined as euglycaemia, metabolic acidosis and elevated serum ketones occurring in patients without diabetes mellitus. It is less well known compared to diabetic ketoacidosis (DKA) and euglycaemic diabetic ketoacidosis (EDKA), both happening in patients with diabetes. Here we describe a case of a 35-year old woman, previously fit and well, who presented with unidentified cause of pancreatitis leading to severe metabolic acidosis. Despite the conventional medical treatment for pancreatitis, she was still in resistant metabolic acidosis status. Intensive care input was sought and she was taken there for further management. In view of unexplained and ongoing metabolic acidosis, a finger prick point of care capillary blood ketone reading was found to be elevated at 4.7mmol/l despite being normoglycaemic in the last 23 h post-admission. Urgent Diabetologist input was requested. A diagnosis of NDEK was made. Blood glucose throughout admission remained below 10mmol/l. Serum Beta-Hydroxybutyrate level was analysed retrospectively on her admission blood sample which confirmed elevation at 8.03mmol/l. Glycated haemoglobin level was normal at 37mmol/l. She was started on fixed rate insulin infusion with intravenous dextrose fluid therapy and later stepped down to variable rate insulin infusion. Within a few hours of starting intravenous insulin, point of care blood ketones had significantly reduced with normalisation of serum bicarbonate. Due to low awareness of NDEK, there was delay in serum ketones checking, right diagnosis and implementation of correct treatment plans until the involvement of a Diabetologist. Given the complexity of the presentation, metabolic management and potential complications associated with delayed diagnosis and correct care plan, we propose early involvement of Diabetologist in all NDEK cases. This case also serves as another learning example of challenging NDEK presentation and to raise more awareness amongst clinicians of this condition.

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P230

Case report - success story of GLP-1 agonist (liraglutide) treatment in someone with type 1 diabetes: A life transformed

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Introduction
Glucagon-like peptide-1(GLP-1) agonists are widely used for treatment of type 2 diabetes(T2D). To date a number of reports have described improvements in glucose control with the addition of a GLP-1 agonist to the insulin regime in treatment of type 1 diabetes(T1D). From a physiological perspective there is credence to the notion that a GLP-1 agonist will lower glucose levels in people with T1D as they do in T2D. GLP-1 is an endogenous hormone that regulates secretion of both insulin and glucagon in response to meals. GLP-1 agonists also slow gastric emptying through effects on the autonomic nervous system/act centrally to increase satiety. Liraglutide is the most widely studied GLP-1 agonist in adults with T1D, as add-on therapy to insulin.
Report
Our patient has experienced challenges with their T1D management for a number of years in spite of being maintained on a basal bolus regime and recently developed a foot ulcer (now healed). He works long hours in his own business. With the addition of Liraglutide to the basal bolus regime, by 8 weeks there was a frameshift in glucose profile as evidenced by FreeStyle® glucose monitoring. Time in range glucose (3.9-10.0mmol/l) increased from 43% to 80% with the percentage in the range >10.0mmol/l decreasing from 35% to 15%. Also variability decreased from 42.3% to 32.4%% and estimated HbA1c from 72mmol/mol to 52mmol/mol. The change in glucose levels was associated with a self-reported enhancement of sense of control of the T1DM day to day. In his own words 'I feel in control of my diabetes for the first time in 20 years'.
Conclusion
We here report a 'good news story' of the benefits of GLP-1 agonist treatment in T1D in relation both to quantitative glucose profile and an individual's sense of agency in their self-management.

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P341

The ameliorative effects of aqueous allium sativum on acrylamide-induced neurotoxicity in drosophila melanogaster model

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Background
Drosophila Melanogaster is a prominent animal model due to its short life cycle, ease of culture, and genetic makeup similar to that of humans. Acrylamide (ACR) is a naturally occurring, widely used chemical that is generated during high-temperature carbohydrate-rich meal. Significant doses of ACR have been associated with a variety of health problems, including neurotoxicity, reproductive toxicity, and immunotoxicity. Garlic (Allium Sativum) is an ancient medicinal plant, is used for disease treatment and spice worldwide due to its unique aroma.
Aim
This is to study ameliorative effect of Allium sativum on acrylamide-induced neurotoxicity in drosophila melanogaster model.
Methodology
Flies were divided into four groups; each with three vials and fifty flies. The three vials per group were to have a balanced and also variable data for the experiment. Control group fed with normal meal (CT), treatment group TGA fed with (200mg/kg of allium sativum), toxicant group TOA fed with (50mg/kg of acrylamide), treatment and toxicant group GAC fed with (200mg/kg of allium sativum + 50mg/kg of acrylamide). Behavioural assays and biochemical assays were then checked across all groups. GraphPad Prism statistical software package version 9.0, One-way ANOVA followed by post hoc ''Turkey'' test were used for data analysis
Result
Acrylamide exposure significantly reduced flies' life span, muscular integrity, locomotory, exploratory activities, total thiol, catalase activity, and protein levels; garlic intervention improved these aspects ($P < 0.05$). The study shows increased MDA activity and ACh e in the acrylamide group TOA, while co-administration of garlic extract lead to a significant reduction in MDA and ACh e activity.
Conclusion
According to the findings of this study, Allium sativum & antioxidative properties improve flies' life span, behavioural deficits and oxidative stress.

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P342

Importance of metabolic control in diabetic patients infected by covid-19 from a south american hospital

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Introduction
Type 2 diabetes is an important comorbidity during the course of COVID-19. However, the impact of blood glucose control on the degree of medical interventions required and on mortality in patients with COVID-19 remains uncertain.
Methods
Single-center retrospective study of 306 cases of COVID-19, of which 43 had pre-existing type 2 diabetes for 6 months. Qualitative variables were assessed using the Chi-square test or Fisher's exact test, and in the case of numerical or quantitative variables Student's T or Mann-Whitney tests were used. We found that subjects with type diabetes required more medical interventions and had significantly higher mortality (9.6% vs. 3.4%; adjusted hazard ratio, (1.8)) and multi-organ injury than non-diabetic individuals.
Results
Discovered We found that subjects with type 2 diabetes required more medical interventions and had significantly higher mortality (9.6% vs. 3.4%; adjusted hazard ratio, (1.8)) and multi-organ injury than non-diabetics. Furthermore, we found that well-controlled glucose (glycemic variability within 3.9 to 10.0 mmol/l) was associated with markedly lower mortality compared with those with poorly controlled glycemia (upper limit of variance). glycemic stability greater than 10.0 mmol/l) (adjusted HR, 0. 14) during hospitalization.
Conclusion
These findings provide clinical evidence correlating optimized glycemic control with better outcomes in patients with COVID-19 and pre-existing diabetes.
Keywords
Mortality, Endocrinology, Diabetes.

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P343

Familial hypercholesterolaemia patients in a lipid clinic: Characteristics and outcomes

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Objective
The NHS long term plan aims to identify 25% of the Familial Hypercholesterolaemia (FH) patients in England by 2025. This study aimed to identify patients with FH, assess their classification according to the Dutch Lipid Clinic Network (DLCN) criteria, and evaluate treatment outcomes.
Methods
We conducted a retrospective analysis of patients referred for assessment of possible FH who went on to have genetic testing.
Results
The study cohort included 26 patients between 2019 and 2022 (16 females and 10 males) with a mean age of 46 ± 13 years. Among the total 26 patients, the following characteristics were noted: eight were smokers (30.8%), five were drank alcohol (19.2%), one had a history of myocardial infarction prior to the first visit (3.8%), two had hypertension (7.7%), and one had type 2 diabetes (3.8%). According to the DLCN criteria, 12 patients (46.2%) were classified as definite familial hypercholesterolemia (FH), 5 patients (19.2%) as probable FH, and 9 patients (34.6%) as possible FH. Subsequent genetic testing confirmed FH in 14 out of the 26 patients, representing a FH positivity rate of 53.8%. Among the 14 patients with a positive FH gene result, the treatments are as follows: 13 patients (85.7%) on statin, 4 patients (28.6%) on ezetimibe, 3 patients (21.4%) on PCSK9 inhibitors. One patient was intolerant to any cholesterol-lowering agents and was referred to tertiary centre for consideration of plasmapheresis. Additionally, 4 out of the 14 patients had mild coronary atheroma on CT angiogram. The baseline and final lipid profile (median + SD) of the 14 patients were total cholesterol 8.49 ± 1.19 and 6.1 ± 1.37 mmol/l, LDL 6.9 ± 0.93 and 3.85 ± 1.49 mmol/l, HDL 1.25 ± 0.33 and 1.1 ± 0.31mmol/l.
Conclusion
FH gene was positive in more than 50% of patients. The NICE recommended target LDL reduction >50% was achieved in 57%.

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P344

An unexpected food-aversion in mice lacking functional leptin signalling

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Defending body weight is a fundamental homeostatic process. Indeed, countless studies have demonstrated weight-maintaining hyperphagia in response to either increased energy expenditure or a reduction in the caloric density of available food. The principal effector of this adaptive food intake is thought to be the adipose tissue-derived hormone, leptin. According to the classical 'adipostat' model, the hypoleptinemia resulting from weight loss drives food intake to restore body weight. In line with this hypothesis, animals and humans lacking functional leptin signalling display profound hyperphagia and obesity. However, during our recent studies on adaptive feeding behaviour in mice, we unexpectedly made two observations concerning leptin physiology. First, we found that hypoleptinemia is not responsible for the normal hyperphagia observed in response to a reduction in the caloric density of food. Second, mice lacking leptin signalling appear to display a profound aversion to food with low caloric density. Therefore, we propose herein that explaining these observations may require a fundamental re-evaluation of the classical 'adipostat' model of leptin action.

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P345

The effects of bariatric surgery on blood pressure management in Type 2 Diabetes: Insights from a ten-year follow up study

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Background
The prevalence of obesity associated comorbidities, such as Type 2 Diabetes(T2D) and hypertension, continues to rise globally. Our study aimed to describe the long-term effects on blood pressure management in individuals with T2D post bariatric surgery in a single centre prospective observational cohort study in North-West England.
Methods
We undertook a 10-year prospective cohort study on people who underwent bariatric surgery (gastric bypass/sleeve gastrectomy) between 2009 - 2012 at a single tertiary surgical centre in North-West England, UK. Baseline preoperative/follow-up postoperative data were obtained from electronic patient records including blood pressure (BP) readings and initiation of pharmacological treatment. Parameters include BP readings, HbA1c, BMI and antihypertensive medication use was obtained from electronic patient records at regular intervals up to 10 years, to ascertain longitudinal outcomes in BP, BMI and HbA1c.
Results
119 individuals were included in the study. Optimal metabolic health state was achieved at 12 months post-surgery for BMI (-14.8kg/m2 (95%CI: 10.4-16.2, $P<0.001$)), systolic BP (sBP) (-15.0mmHg 95%CI: 8.2-21.8mmHg, $P<0.001$)), diastolic BP (dBP) (-8.1mmHg, 95%CI: 4.3-11.9, $P<0.001$)) and HbA1c (-24.4mmol/mol, 95%CI: 18.3-30.6, $P<0.001$). A sustained reduction in both sBP/dBP was maintained for up to 5years, mirroring a reduction in concurrent use of antihypertensive medications (164 prescriptions v 66 at 5years). At latest follow-up, there was an observed increase in antihypertensive prescription (95 v 66) yet there was no statistically significant change in mean BP. Furthermore, the number of individuals with clinically diagnosed hypertension (BP 140/90 or more was lowest at 5years ($n=53$ v 86 pre-op) before rising at the latest follow-up ($n=64$) in hand as did BMI($+3.1$kg/m2) and HbA1c($+7.5$mmol/mol).
Conclusion
Our study demonstrates that bariatric surgery has a sustained positive impact on BP management as reflected by both absolute measurements/reduction in antihypertensive medication use, with slight reduction in benefit beyond 5year follow-up.

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P346

Modelling muscle wasting in chronic kidney disease under conditions of acidosis and steroid exposure

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Introduction
Chronic kidney disease (CKD) is characterised by an ongoing reduction in kidney function and is associated with comorbidities such as muscle wasting that greatly increase mortality. Both acidosis and elevated glucocorticoids levels are hallmarks of CKD and implicated as having a synergistic role in driving muscle wasting. We investigated the synergistic effects of acidosis and the glucocorticoid cortisol on muscle metabolism and fibre size using primary human muscle culture.
Methods
Primary human muscle cells from a single osteoarthritic donor were collected after surgery and exposed to a pH of 7.1 or 7.4 in combination with cortisol (100 or 1000 nmol/l) for 48h. 3H-tyrosine assays were utilised to determine protein synthesis and degradation. Histological analyses of primary muscle culture diameter were determined using ImageJ software and genes regulating muscle metabolism were assessed by quantitative RT-PCR.
Results
In primary muscle culture, no changes in protein synthesis or protein degradation were evident when cells were exposed to pH7.1 or cortisol (100-1000nmol/l) alone. In contrast, the combination of pH 7.1 and cortisol at 1000 nmol/l significantly reduced protein synthesis (21.2%, $P=0.0321$) and increased protein degradation (13.34%, $P=0.0066$). These changes were matched by a significant decrease in muscle fibre diameter *in vitro* after exposure to pH7.1 and cortisol at 100 nmol/l (13%, $P<0001$), but not with individual interventions. RT-PCR analysis indicated a trend towards an increase in the catabolic FOXO-1 and TRIM63 genes in response to acidosis and cortisol.
Conclusion
This data reveal for the first time in primary human muscle cultures, that the combination of glucocorticoids and acidosis possess an increased capacity to induce muscle wasting than either factor independently. This study will inform future strategies aiming to prevent muscle wasting in CKD.

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P347

The ameliorative effects of aqueous allium sativum on acrylamide-induced neurotoxicity in drosophila melanogaster model

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Background
Drosophila Melanogaster is a prominent animal model due to its short life cycle, ease of culture, and genetic makeup similar to that of humans. Acrylamide (ACR) is a naturally occurring, widely used chemical that is generated during high-temperature carbohydrate-rich meal. Significant doses of ACR have been associated with a variety of health problems, including neurotoxicity, reproductive toxicity, and immunotoxicity. Garlic (Allium Sativum) is an ancient medicinal plant, is used for disease treatment and spice worldwide due to its unique aroma.
Aim
This is to study ameliorative effect of Allium sativum on acrylamide-induced neurotoxicity in drosophila melanogaster model.
Methodology
Flies were divided into four groups; each with three vials and fifty flies. The three vials per group were to have a balanced and also variable data for the experiment. Control group fed with normal meal (CT), treatment group TGA fed with (200mg/kg of allium sativum), toxicant group TOA fed with (50mg/kg of acrylamide), treatment and toxicant group GAC fed with (200mg/kg of allium sativum + 50mg/kg of acrylamide). Behavioural assays and biochemical assays were then checked across all groups. GraphPad Prism statistical software package version 9.0, One-way ANOVA followed by post hoc ''Turkey'' test were used for data analysis
Result
Acrylamide exposure significantly reduced flies' life span, muscular integrity, locomotory, exploratory activities, total thiol, catalase activity, and protein levels; garlic intervention improved these aspects ($P<0.05$). The study shows increased MDA activity and AChe in the acrylamide group TOA, while co-administration of garlic extract lead to a significant reduction in MDA and AChe activity.
Conclusion
According to the findings of this study, Allium sativum & antioxidative properties improve flies' life span, behavioural deficits and oxidative stress.
Key Words
Drosophila melanogaster, Allium sativa, Acrylamide, Behavioural assay.

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P348

Examining hyperglycaemia and its management through a clinical audit

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Glucose is the primary source of energy for cells and its levels are tightly regulated by the hormone insulin. In people with diabetes, the body either doesn't produce enough insulin or doesn't respond to insulin properly. Hyperglycemia can occur which carries high morbidity and mortality. Some common signs and symptoms include polyuria, polydipsia, polyphagia and fatigue. Diabetic ketoacidosis and hyperosmolar hyperglycaemic state are serious medical emergencies associated with uncontrolled levels of blood glucose. The management of acute hyperglycemia in a hospital setting has improved in recent years but still poses a clinical challenge and requires proper evaluation. Measuring blood ketone levels and blood gas remains the important steps when hyperglycaemia is

encountered. Short acting insulins are used frequently but require clinical assessment because of the serious risks associated with giving short acting insulin, most importantly hypoglycaemia and symptoms of the patients. Owing to insufficient awareness of guidelines and on-call busy shifts, doctors may prescribe doses of insulin without proper clinical assessment. We gathered data to assess and compare if prescription of short acting insulin was done according to the guidelines to ensure best quality of care to the patients. It is also important to check blood glucose after treatment is given. We audited the management of acute hyperglycemia in clinical settings and found that assessment of clinical features was not done in as many as half of the patients. Also vital investigations like checking for blood ketones was not done in one fifth of the patients and almost half of the patient's didn't have their blood glucose checked after giving short acting insulin. This demonstrates a significant gap in clinical understanding and assessment on part of clinicians and through this audit we are trying to highlight the importance of following respective guidelines in the acute management of hyperglycaemia

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P349

Effect of Oral Semaglutide on Weight & Cardiac Biomarkers In patients With Hypothyroidism Treated Using Liothyronine + Levothyroxine Combination Therapy

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Aim
To asses the role of oral semaglutide (Sm) on weight & cardiac biomarkers (CB) in 69 patients with hypothyroidism optimally controlled using Liothyronine (T3) + Levothyroxine combination (T4) therapy (T3/T4).
Methods
Between January 2022 and March 2022, 69 hypothyroid patients, who were treated using T3/T4 while on regular follow up, initiated Sm with the intention of weight loss and were retrospectively analysed. Hypothyroidism was defined as TSH $>$ 4.2 (irrespective of their thyroid antibody status) on $\geq$ 2 occasions $\geq$ 2 weeks apart. Protocol: Patients were on T3 (25 mg/day) along with varying doses of T4 to optimise the TSH (lower limit of normal reference range). Patients initiated Sm with 3mg and were asked to self titrate up to 14mg based on their symptoms. They were followed up every 2-3 mths for clinical & CB: weight-kg (W), body mass index (BMI-kg/m2), systolic BP (SBP-mm of Hg), diastolic BP (DBP-mm of Hg), TSH (mIU/ml), Lipid profile mg/dl (TC, LDL-C, TG, HDL) & Hs-CRP mg/l for 6 months. Continuous variables were analysed using paired t-test expressed as mean $\pm$ standard deviation. Bonferroni's correction was applied & P value $<$0.007 was considered significant (S).
Results
Baseline (B) characters: Female:Male ratio 56/11 (84%/16%). Average [Age (42.59 $\pm$ 10.81), BMI (31.92 $\pm$ 6.75), W (82.43 $\pm$ 19.23), SBP (119.89 $\pm$ 13.09), DBP (82.8 $\pm$ 9.73), TSH (1.79 $\pm$ 1.67), TC (170.63 $\pm$ 41.92), LCL-C (103.54 $\pm$ 38.53), TG (121.68 $\pm$ 54.52), HDL (48.86 $\pm$ 7.97) & hs-CRP (5.95 $\pm$ 7.97)]. Comparison between B & 6 mths: S reduction in W (-5.07 $\pm$ 5.16), BMI (-1.96 $\pm$ 2.01), TC (-11.79 $\pm$ 30.3), LDL (-10.21 $\pm$ 28.86), TG (-10.22 $\pm$ 29) & hs-CRP (-1.97 $\pm$ 5.32) was seen with Sm. There was no difference seen in SBP, DBP & HDL.
Conclusion
Oral Semaglutide is effective in causing weight loss and improving cardiac parameters (lipid profile) in patients with hypothyroidism. Sm might have beneficial long term cardiovascular effects in patients with hypothyroidism.

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P350

Impact of SGLT2 inhibitor prescription on DKA in patients with T2DM in NHS Lothian

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Diabetic Ketoacidosis (DKA) in patients with Type 2 Diabetes Mellitus (T2DM) is relatively rare and usually associated with intercurrent illness but can cause significant morbidity and mortality. SGLT2 inhibitor (SGLT2i) use has been implicated as a potential risk factor for developing euglycaemic DKA, particularly in sepsis, surgery and starvation. We aimed to investigate the common causes of DKA in T2DM in NHS Lothian to identify whether SGLT2i use was having a significant impact. We retrospectively reviewed casenotes for T2DM patients admitted with DKA to the Royal Infirmary of Edinburgh and Western General Hospital in 2020-21. Demographic and biochemical data was collected and notes were reviewed for precipitants and relevant medication. 69 T2DM patients were admitted with DKA. Common precipitants included infections, insulin omission and alcohol. 43% were on regular SGLT2i treatment with 26.6% first prescribed in the preceding six months. Patients on SGLT2i had lower glucose levels (median 15.65 vs 30.5mmol/l), higher ketones (median 5.2 vs 5.0mmol/l) and more severe acidosis (median H+ 72.9 vs 56nmol/l). C-peptide was measured in 49.3% of patients on SGLT2i with median level 621 pmol/l. Only 17% had documentation of sick day rules in clinical letters. Just under half of all recorded DKA episodes in T2DM were associated with SGLT2i therapy. Patients were more acidotic, ketotic and had lower blood glucose levels. This may simply reflect increasing prescription of these drugs but raises the possibility that the threshold for DKA is lowered. We have highlighted the importance of regular discussion of sick day rules in clinic along with providing patient information leaflets. We have liaised with primary care to ensure these alerts are clear on community prescriptions. Finally, we have used our electronic prescribing system to include an alert to prescribers to consider SGLT2i suspension for patients admitted with acute illnesses or for major surgery.

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P351

Time-restricted eating in polycystic ovarian syndrome: a randomised crossover feasibility study of real-world clinical advice

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Objective
Time-restricted eating (TRE) represents a novel intervention that may improve insulinaemia and reduce weight, but is untested in polycystic ovarian syndrome (PCOS). In a randomised interventional study (NCT05126199), we investigated the feasibility of TRE in PCOS. Secondary objectives included effects on insulin and metabolic indices.
Methods
Participants were randomised to 12-week TRE (18h fast/6h eating window) or 'ab-libitum' (no time-restriction) and crossed over. Primary outcomes assessed recruitment, compliance, safety, and drop-outs. Secondary outcomes were insulin resistance, androgens, lipids, anthropometrics, and nutritional intake.
Results
We found TRE was a feasible intervention with near-total compliance in those completing the intervention; however, there were considerable difficulties with recruitment. Of $n=68$ eligible to participate, $n=40$ declined. Ultimately, $n=15$ were recruited, with $n=9$ completing data collection to date ($n=4$ (27%) drop-outs due to commitment/study duration). There were no serious adverse events in the TRE group. Compliance(%(SD)) with TRE was 94(4.6)%, and $n=8$ were keen to continue TRE. There was no significant difference with TRE on insulin-related parameters. There was significant decrease in weight (-1.5kg (-2.7, -0.1), $P=0.01$), BMI (-0.52 (-0.99, -0.04), $P=0.02$) and hip circumferences (-2cm (-4, -2), $P=0.01$) in the TRE vs ab-libitum eating group. There was significant weight gain seen in the ad-libitum eating group (2.65kg (0.3, 3.5), $P<0.001$). Those following TRE had favourable changes in SHBG (2.4nmol/l (0.25, 6.2), $P=0.04$) and Apolipoprotein A1 (-0.02g/l (-0.06, 0), $P=0.01$) in androgen and lipid profiles. Those in the TRE group consumed significantly less energy (calories) ($P=0.002$), carbohydrate ($P=0.03$), saturated fat ($P=0.03$), and calcium ($P=0.02$) with no difference in sugar, protein, fat, or vitamin D consumption.
Conclusion
TRE was a safe and feasible intervention, however there was poor recruitment (13.2% of eligible group). With limited numbers, the TRE group had improvements in metabolic indices and lost more weight than the 'ad-libitum' group.

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P352

Metabolic phenotyping of the polygenic mouse model (NON-cNZO10/LtJ) of type 2 diabetes to mimic the process of diabetes development and remission in human

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Background and Aims
Obesity is a major risk factor for type 2 diabetes (T2D). Remission of diabetes can be achieved by dietary weight loss although the underlying molecular mechanism(s) are unknown. These beneficial effects could be related to decreasing hepatic fat delivery to the pancreas and eventually restoring β-cell function. We hypothesised that hepatic de novo lipogenesis (DNL) is the primary driver of pancreas "lipotoxicity" and the process can be reversed during weight loss. We therefore aimed to mimic the process of T2D development and remission in human using this model and assess the change in DNL rates.
Methods
The first stage of the study was designed to optimise nutritional and stable isotopes conditions to induce T2D in this model (NONcNZO10/LtJ). 12 male mice were imported from the Jackson Laboratory at 5-6 weeks of age and were placed for 12 weeks on either high sucrose or corn starch diet with moderate fat content (Research Diet). The diet was also enriched with ^{13}C-labelled palmitic acid and deuterated water (^{2}H2O) for tracking of dietary and endogenous sources of fatty acids, respectively. Fat and lean mass were determined by TD NMR, and Glucose Tolerance Testing (GTT) was carried out by oral gavage at baseline and 12 weeks. Stable isotopes were analysed by high resolution LC-MS.
Results
At 12 weeks, mice on the high sucrose diet gained more body weight and total fat mass accompanied with higher liver fat and impaired glucose tolerance. Sucrose diet also promoted high rate of DNL as measured by deuterium incorporation into plasma palmitic and stearic acids. Analysis of liver tissues confirmed high DNL and expression of lipogenic genes.
Conclusion
Our findings suggest that this high sucrose model is useful to study DNL in T2D. Work is underway to mimic the remission process by calorie restriction.

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P353

Ex-vivo immune responses of blood cells with autologous stem cell derived beta cells in Type 1 Diabetes: a pilot study

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Introduction
Type 1 Diabetes Mellitus (T1DM) causes autoimmune destruction of insulin producing b-cells, affecting approximately 8.4 million individuals worldwide. Autologous stem cell derived b cell (sc-b cell) transplantation is a promising treatment, however receipient immunological responses remain a challenge. This pilot study utilised mass cytometry (CyTOF) to assess immune responses in co-cultures of peripheral blood mononuclear cells (PBMC) with autologous sc-b cells from T1DM patients.
Methods
PBMCs were isolated from three T1DM donors at two time points one year apart, and co-cultured with sc-b cells differentiated from each donor's stem cells. For each donor, the positive stimulation control was phorbol 1-myristate 13-acetate (PMA), while the negative control was sc-a or progenitor cells. Post-incubation, samples were labelled with metal conjugated antibodies for CyTOF analysis. Manual gating and unsupervised clustering models were used to identify immune subsets.
Results
The relative proportions of CD4 and CD8 T-cell subsets (naïve, memory) were similar with each stimulation condition, whilst differing across individuals. Notably, donor 1 had a higher proportion of memory CD8 T-cell subsets. The immunological response of PMA stimulation was different from the response to co-culturing with sc-b or sc-a cells. T-cell cytokines abudances, IFNg and granzyme B, were elevated in response to all stimulation conditions. However, abundance of CD25, CD137, and PD-1, in naïve and memory CD4 and CD8 T-cells, were higher in PBMCs co-cultured with sc-b or sc-a than when treated with PMA.
Conclusion
This pilot study demonstrated highly individualized immune profiles, further highlighting the immunological heterogeneity within T1DM patients. Within this small donor subset, no specific immune signatures were identified that indicated an autoreactive response to sc-b cells. Further research should aim to study responses in a larger donor subset and assess the clinical correlates of these immune signatures, which could have practical implications for T1DM prevention and treatment.

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P354

Anti-diabetic properties of the ethanolic extract of unripe Artocarpus heterophyllus fruit regulates glucose homeostasis in high-fat-fed diet-induced obese mice

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The prevalence of type 2 diabetes (non-insulin dependent diabetes) has been universally acknowledged as a chronic public health concern and the leading cause of mortality on a global scale. Plant-based bioactive compounds have made significant contributions to the management of diabetes mellitus globally. Artocarpus heterophyllus, also known as "kathal" in the subcontinent, is rich in dietary fibre and has traditionally been used as a diabetes remedy. The current study aimed to investigate the anti-hyperglycaemic and anti-hyperlipidaemic properties of ethanol extract of Artocarpus heterophyllus (EEAH) using high-fat-fed (HFF) diet-induced obese type 2 diabetic mice as well as phytochemical screening. Acute oral gavage of glucose (2.5 gm/kg) with EEAH (250 and 500 mg/kg) or glibenclamide (5 mg/kg) improved ($P<0.05$-0.001) oral glucose tolerance and food intake ($P<0.05$-0.001), and these acute *in vivo* investigations led to additional chronic studies. Twice daily oral gavage of EEAH (250 and 500 mg/kg) for 60 days showed remarkable improvements ($P<0.05$-0.001) in fasting blood glucose, body weight, glucose tolerance, food, and fluid intake in HFF mice. EEAH (500 mg/kg) promoted ($P<0.001$) gut motility, increased ($P<0.05$-0.01) high density lipoprotein, and decreased ($P<0.05$-0.01 total cholesterol, triglyceride, and low density lipoprotein at 250 and 500 mg/kg respectively. The phytochemical screening of EEAH depicted the presence of tannins, saponins, and flavonoids. These phytoconstituents may have a role in the anti-hyperglycaemic and anti-hyperlipidaemic properties of EEAH. Thus, the findings of this study support the notion of A. heterophyllus as a dietary supplement that might be useful in the treatment of type-2 diabetes in people.

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P355

Long-term audit of PCSK9 inhibitor therapy: impacts on LDL-C and HbA1c in clinical practice

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Background
The PCSK9 inhibitors (PCSKi), evolocumab and alirocumab, were approved by NICE in 2016, and have since proved to be efficacious in lowering LDL-C. Yet little is known about their long-term adverse effects. Genetic studies have shown patients with PCSK9 loss-of-function variants are at increased risk of T2DM. Similarly, analyses of an adverse event database found increased reports of PCSK9i-related hyperglycaemia. Meta-analyses have suggested that PCSK9i increase fasting blood glucose and HbA1c; but have not shown increased incidence of new-onset diabetes, a result that was attributed to the short duration of the follow-up.

Aims
To establish whether long-term use of PCSK9i a) maintains LDL-C reductions b) is associated with increased HbA1c and new-onset diabetes.
Methods
This was a retrospective audit of non-diabetic, lipid clinic patients, initiated on PCSK9i between June 2016 to November 2020 at UHB Trust. HbA1c and LDL-C laboratory values were analysed for 1-5 years following initiation.
Results
Spearman's correlation showed % LDL-C change was unaffected by duration of PCSK9i treatment ($n=135$, $r=0.0493$, 95% CI: -0.126 to 0.221, $P=0.2850$). Overall mean reduction in LDL-C was -59.4%, over a mean duration of 4.45 years. Paired t-tests showed pre/post LDL-C changes were significant for evolocumab, and alirocumab. A mixed-effects model for repeated measures data was used to investigate an association between duration of PCSK9i therapy and HbA1c. Cumulative increases in HbA1c from second to fifth year were found for evolocumab, but not alirocumab, and the increase was significant at five years of treatment (mean difference between HbA1c before evolocumab vs. after 5 years: -2.456, CI: -3.788 to -1.124, $P=0.0002$). The incidence of new-onset diabetes in patients on PCSK9i was 1.48% during follow-up.
Conclusion
PCSK9 inhibitor treatment sustained significant reductions in LDL-C over the long-term. At five years of treatment, evolocumab, but not alirocumab, was found to significantly increase HbA1c.

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P356

Ketoacidosis with hyperglycemia but not DKA

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We present an interesting case of a 50-year-old woman with previous history of alcohol dependence, depression & oesophagitis who was brought to the emergency department by ambulance with vomiting, back pain and feeling generally unwell. Her GCS was 14/15, HR128/min, RR 32/min, BP 111/60, temperature 35.2 & CBG 11.2mmol. She reported consuming one bottle of Vodka every day. Initial venous blood gas analysis showed severe metabolic acidosis (pH 6.79, HCO3 3, Lactate 15, Ketone 5.7) Urgent blood tests showed various biochemical abnormalities. The highlights of the results were severe metabolic acidosis with high osmolar gap and anion gap. The calculated serum Osmolality was 297mmol/mol & measured serum osmolality was 368 (osmolar gap 71). The anion gap was 54 which could not be completely explained by the significantly high Lactate & Ketones alone. An initial diagnosis of alcoholic ketoacidosis was made & she was treated with IV Saline & IV Dextrose after giving IV Pabrinex. She was pre-emptively started on IV Fomepizole while awaiting results of the toxicology screen. Interestingly the capillary and serum Glucose level and ketones steeply rose after starting IV Dextrose (administration of IV Dextrose is part of standard treatment of alcoholic ketoacidosis). Patient was started on fixed rate IV Insulin infusion which led to resolution of hyperglycaemia and ketosis over the course of the next 24-36 h. Interestingly HbA1c, Fructosamine & serial fasting plasma glucose levels were normal during the course of the long hospital admission. This meant that the hyperglycaemia during early admission was of recent onset. The initial worsening of hyperglycaemia & ketonemia with IV Dextrose infusion (which in retrospect, was not due to diabetes) was not completely understood and thought to be because of 'transient beta cell dysfunction' secondary to the severe metabolic derangement.

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Neuroendocrinology and Pituitary

P45

Phaeochromocytoma/Paraganglioma – Call for Education and More Screening

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Background
Phaeochromocytomas & paragangliomas (PPGL) are rare neuroendocrine tumours presenting with symptoms of sympathetic overactivity, hypertension, or as adrenal incidentalomas.
Study and results
A 24-year retrospective review of a U.K. single-centre PPGL service (2009 -2023) identified 61 cases (53 phaeochromocytomas/8 paragangliomas). Among these, 35 (57%) were females. Mean age of diagnosis was 56.35 ± 16.2 (SD) years. Only 13 (21%) presented with symptoms and were screened, while 48 (79%) were incidental findings. Of those incidental, 8 (17%) had hypertension/cardiovascular disease, 15 (31%) had phaeochromocytoma symptoms, and 13 (27%) had both. 95% had raised metanephrines at diagnosis and lesion identified with CT/MRI (mean size 42.5mm, range 8-90). MIBG scans were undertaken in 52 cases (85%) with increased uptake in 47 (92%) including metastatic disease identified in three cases. Diagnosis was made through histology in three cases following intervention for other reasons. Genetic screening was performed in 38 (62%) cases, with 13 identified to have mutations associated with PPGLs. Six cases (46%, $n=13$) had neurofibromatosis type 1 (NF1), all presenting as adrenal incidentalomas. All biochemically active cases were treated with alpha-blockers. 53 patients underwent surgery (89% laparoscopically), two are awaiting surgery, six were treated conservatively (five unfit for surgery, one declined). Perioperative blood pressure stability was observed in 52 patients, with no mortalities. Four patients experienced recurrence, and one had metastasis after surgery. Post-surgery, patients exhibited a mean weight gain of 3.3 ± 6.02 (SD) kg, likely due to reduced sympathetic activity and basal metabolic rate.
Conclusion
The study highlights the increasing diagnosis of PPGLs through incidentaloma screening. Missed symptoms were prevalent in 70% of incidental cases. NF1 patients comprised 46% of those with positive gene mutations, emphasising the need for phaeochromocytoma screening in this population. MIBG imaging was valuable for identifying active lesions, and thorough preoperative optimisation was crucial for favourable outcomes.

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P80

Integrated multi-omics data reveals distinct regulatory signatures and signaling pathways of aryl hydrocarbon receptor interacting protein (AIP) knockout cells

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Introduction
Aryl hydrocarbon receptor interacting protein (AIP) is a multifunctional co-chaperone protein with wide-ranging effects. It acts as a tumour suppressor in the pituitary, but may have other roles including oncogenic function in other tissues. To explore the molecular mechanisms, we have performed transcriptomic and phosphoproteomic analysis of Aip-knockout mouse embryonic fibroblasts (Aip-KO MEFs) cells and integrated these data sets.
Method
RNAseq was performed using Illumina NovaSeq 6000 and phosphoproteomics analysis performed by mass spectrometry (MS). Ingenuity Pathway Analysis (IPA), gene set enrichment analysis (GSEA) and Kinase-Substrate Enrichment Analysis (KSEA) were used.
Results
We identified 6,747 transcripts and 2,156 phosphopeptides altered in Aip-KO MEFs. GSEA analysis revealed enrichment of adherens junction, tight junction and cytoskeleton. KSEA revealed multiple kinases (significantly altered at the transcript levels), involved in the adherens junction, tight junction, cytoskeleton and vesicle trafficking. The top hyperphosphorylated peptide is Heart of glass (HEG1, Ser486, 12 log fold) corresponding to 3.3 log fold increased mRNA expression. HEG1, involved in Wnt/β-catenin signaling pathway. TJP2/tight junction protein 2 (Ser898, 3.5 fold), a member of the membrane-associated guanylate kinase homolog family, crucial for tight junction's assembly and involved in cell adhesion pathway. CAMKK2/calcium/calmodulin dependent protein kinase 2 (Ser495, 2 fold), a novel modulator of Golgi vesicle trafficking. GOLGA5/golgin A5 (Ser155, -10.28 fold), a coiled-coil membrane protein with potential role in vesicle tethering and docking. Both CAMKK2 and GOLGAA5 are involved in vesicle trafficking. NME1/nucleoside diphosphate kinase A (T94, 2 fold), a known AIP interacting partner, a tumor suppressor that negatively regulates cell motility.
Conclusions
Integration of multi-omics data of transcriptional and post-translational events in Aip-Ko cells has revealed the potential role of AIP in remodelling of the adherens junction, tight junction, vesicle trafficking and cell migration. This study has broaden our understanding of AIP-mediated tumorigenesis.

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P81

Osilodrostat: Effective and Safe Management of ACTH-Dependent Cushing's Syndrome - A UK single centre experience

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We present three cases of ACTH-dependent Cushing's syndrome, successfully managed with osilodrostat.

Case 1

A 42-year-old woman diagnosed with ACTH-dependent Cushing's disease was initially treated with osilodrostat dose-titration approach, as MRI of the pituitary did not identify a clear surgical target. By week five, serum cortisol levels fully normalised. Salivary and 24 hr urinary free cortisol (UFC) normalised on a maintenance dose of 10 mg/24 h (Table1). After 11 weeks of treatment, 11C-Methionine PET CT revealed a methionine-avid lesion in the pituitary gland. She underwent a successful trans-sphenoidal surgery (TSS).

Table 1 UFC on osilodrostat

Week	1	5	14
Total Daily Dose (mg)	2	12	10
UFC nmol/24hr	1271	232	76

Case 2

A 65-year-old woman diagnosed with a grade 2 neuroendocrine tumour presented with florid Cushing's syndrome, characterised by elevated ACTH 169 ng/l and cortisol >1000 nmol/l. Gallium-DOTATATE PET/CT imaging confirmed liver metastases and a presumed metastatic deposit in the pituitary gland. She was started on osilodrostat dose-titration regimen and eventually required a block and replaced regimen with osilodrostat and prednisolone. Osilodrostat fully suppressed her endogenous cortisol production allowing her to undergo chemotherapy for her neuroendocrine tumour.

Case 3

A 38-year-old woman was diagnosed with ACTH-dependent Cushing's disease secondary to pituitary macroadenoma. However, pre-operative evaluation revealed an internal carotid artery aneurysm which required a period of flow diversion and dual antiplatelet therapy, thus delaying TSS for one year. During this period, her serum and UFC levels fully normalised using an osilodrostat dose-titration regimen (Table 2).

Table 2 UFC on osilodrostat

Week	1	4	7
Total Daily Dose (mg)	4	8	10
UFC nmol/24hr	379	179	81

Conclusion

These cases highlight the extraordinary efficacy and safety of osilodrostat, a potent inhibitor of 11-beta-hydroxylase, in the management of ACTH-dependent Cushing's syndrome.

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P82

The effect of gamma knife radiosurgery on the endocrine profile in patients with non-sellar pathologies: A short-term study

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Introduction

Hypopituitarism is the most frequent side effect of radiation or gamma knife radiosurgery (GKRS) for sellar diseases. There is a paucity of literature on the impact of GKRS on the hormonal profile of non-sellar diseases, even though the impact of radiation on pituitary hormones has been widely explored in sellar as well as non-sellar pathologies. In patients receiving treatment for non-sellar diseases, we assessed the effect of GKRS on hormonal profile.

Methods

100 patients receiving GKRS for non-sellar pathologies between 2013-2017 were included in this study. Calculations were made for the maximum and average dose fall to the pituitary gland using a dose volume histogram (DVH) plot. Endocrine examinations at the baseline and follow-up (1 year) were carried out, compared to the normal reference range, and associated with the DVH.

Results

Sixteen patients showed hypocortisolism and we observed a significant decrease ($P=0.0027$) in serum cortisol levels post-GKRS (106.7 ± 14.27) as compared to baseline (288.9 ± 50.29). At follow-up, male ($n=5$) patients had ($P=0.007$) lower ACTH levels (22.6 ± 2.65) compared to baseline (45 ± 4.37). Six percent of patients showed new onset of IGF-1 deficiency in 6% (6/100). Hypothyroidism was not observed in our cohort. In the gonadotrophic axis, females had lower mean LH (25.2 ± 4.34) after treatment as compared to pre-treatment (32.64 ± 4.54) ($P=0.04$) in the supratentorial group, and this decrease in LH levels was more pronounced in infratentorial group ($P=0.006$). There was a significant increase in post-GKRS mean serum prolactin (20.66 ± 6.69) in comparison to baseline (15.69 ± 6.23) in females receiving 2-5 Gy radiation ($P=0.04$), indicating hypothalamic damage.

Conclusion

In patients receiving treatment for non-sellar diseases, our data demonstrate a considerable alteration in hormonal profile. Even at exposure levels of 1Gy, the clinical effects of this damage are most noticeable in the corticotroph and gonadotroph axis.

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P83

The use of overnight fasting copeptin and glucagon stimulated copeptin to diagnose arginine vasopressin deficiency in a tertiary centre

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Introduction

Distinguishing arginine vasopressin deficiency (AVD) from primary polydipsia (PP) can be challenging in clinical practice. Copeptin is produced in equimolar amount to AV and is considered diagnostic biomarker to establish the diagnosis of AVD with and without provocative testing.

Methods

Patients referred with polydipsia, hypotonic polyuria (>3L/day) and normonatraemia had overnight fasting plasma copeptin measured. Those with level of <3 pmol/l underwent glucagon-stimulated copeptin test (GSC) to confirm AVD. Copeptin was measured at baseline, 30, 60, 90, 120, 150, and 180 minutes after administration of 1mg glucagon subcutaneously with peak level <4.6 pmol/l was considered diagnostic of AVD.

Results

Eight patients were referred to our centre, 6 (75%) were male, median age was 42 years (range 26-72). Four patients (50%) had overnight fasting copeptin above the diagnostic cut-off (>3 pmol/l) with a median level 7 pmol/l (range 4.6-9.4). These patients were diagnosed with PP and managed with reduction of fluid intake and careful monitoring of clinical and biochemical parameters. Three patients (38%) had low fasting copeptin and one couldn't tolerate fluid abstinence. These patients underwent GSC. Results are shown in the table: The two patients diagnosed with AVD were treated successfully with desmopressin and had significant improvement in their symptoms. GSC test was tolerated easily by all patients with no adverse consequences reported.

	Baseline Copeptin (pmol/l)	Peak Copeptin (pmol/l)	Diagnosis
Case 1	<1.2	<1.2	AVD
Case 2	2.6	2.8	AVD
Case 3	2.4	6.2	PP
Case 4	1.5	5.9	PP

Conclusion

Recent evaluations demonstrated high distinctive accuracy of measuring copeptin in the differential diagnosis of polyuria polydipsia syndrome. In our centre, we have replaced the water deprivation test with copeptin based tests due to reliability, tolerability, and precision. GSC can be utilised when there is inconclusive overnight fasting copeptin result or uncertainty.

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P84

Prevalence of cancer in a cohort of patients with prolactinoma compared to acromegaly

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Background
While growth hormone (GH) is involved in oncogenic transformation and IGF1 inhibits apoptosis, studies and case reports have shown an association between prolactin (PRL) and prostate cell proliferation, breast, gynecological, colorectal and hematopoietic cancer.
Aim
To compare the cancer rates in prolactinomas vs. acromegaly.
Methods
Retrospective study by analyzing the files of patients with acromegaly (ACM) and prolactinomas (PRM) who were followed-up within a tertiary endocrine center between 2018-2023. IGF1, GH and Prolactin were measured by chemiluminescence. Thyroid US, cytology exam by fine needle aspiration in suspicious nodules, colonoscopy, PAP, mammography were performed according to the latest guidelines as well as pathology exam in patients who underwent surgery. Patients with long distance between cancer and pituitary tumors (>5 years) were excluded.
Results
161 patients had acromegaly (F=104, M= 57) and 95 had prolactinoma (F=46, M= 49; 68 macroadenomas and 27 microadenomas). Globally, cancer prevalence was 7.42% [n= 19, 15 cancers in acromegaly (9.32%) and 4 in prolactinomas (4.21%)]. In our prolactinoma group, 3 out of 4 cancers (bladder, breast and renal) had macroprolactinoma and only one cancer (endometrial cancer) had a microprolactinoma One out of 3 macroprolactinomas had underwent irradiation due to resistant prolactinoma. Macroprolactinomas who underwent irradiation did not have an increased risk in developing cancer in our cohort. (P= NS, chi-sq). Also, no statistical difference was found in cancer risk between ACM and PRL (P=NS, chi-sq), however patients with acromegaly are at a higher risk to develop thyroid nodules than those with prolactinomas (P= 0,02, chi-sq).
Conclusion
In our retrospective series, patients with GH excess had a higher incidence of thyroid nodules compared to those with prolactin excess. Irradiation in the prolactin group did not increase the risk to develop cancer, however larger and prospectives studies might clarify this aspect.

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P85

Development of an optimal imaging pathway for management of somatotroph tumors in acromegaly

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Background
Acromegaly is associated with significant excess morbidity and mortality. Surgery and radiotherapy (including radiosurgery) aim to reduce the burden of growth hormone excess while preserving normal pituitary function, but their effective deployment is dependent on high quality imaging that allows accurate localization of site(s) of active de novo or residual/recurrent disease. Despite the existence of several comprehensive guidelines on the management of acromegaly, there is little consensus regarding imaging, and protocols are heterogeneous. A standardized and optimized imaging pathway could have a positive impact on routine clinical practice and facilitate comparative studies in this rare disorder.
Methods
We summarized existing acromegaly guidelines and performed a systematic review of the literature on cranial imaging for somatotroph adenomas in MEDLINE for studies published between January 1, 1966 and May 1, 2023. Based on the results, we set up a framework and performed a further hybrid search employing Semantic Scholar.
Results
We identified 4 guidelines and 1103 studies, of which 64 were included in our final analysis. The results confirmed a large variability of protocols between studies and centers. Merging the guideline suggestions and results of the systematic review, we have developed a novel hierarchical imaging algorithm for patients with somatotroph tumors, which incorporates advanced anatomical as well as molecular (functional) imaging.
Conclusion
In summary, we propose the use of a common, optimized imaging pathway, incorporating modern modalities and overseen by pituitary tumor centers of excellence (PTCOE). This has the potential to enable more patients with acromegaly to benefit from definitive treatment interventions whilst preserving normal gland function.

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P86

Key predictors of quality of life in patients with acromegaly

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Background
Despite current efforts in trying to accurately identify determinants of impaired quality of life (QoL) in acromegalic patients, studies on this topic are still conflicting and more research is needed in order to improve the well-being of these patients.
Methods
We conducted a cross-sectional study, administering two standardized questionnaires (AcroQol and EuroQol-5D) to 38 acromegalic patients and examined the results alongside data from their medical records.
Results
The study group was composed of 57.9% women and 42.1% men, with a mean age at diagnosis of 44.16±13.95 years. Most of the patients (84.2%) underwent surgical treatment, 57.89% received medical treatment (dopamine agonists, somatostatin analogues, pegvisomant or a combination of these), and 52.63% radiation therapy. Out of 38 patients, 11(28.95%) were cured, 5 (13.16%) had active uncontrolled disease, and 22(57.89%) were in biological remission with current medical therapy. The average value of the AcroQoL score was 69%, range 17.05-97.73%. The median value of visual EuroQol was 80%. The most impaired domain of the EuroQol-5D questionnaire was pain/discomfort, 59.46% patients describing moderate pain, closely followed by mobility, 54.05% presenting walking difficulties. The presence of arterial hypertension was associated with decreased Qol. The AcroQoL score was negatively correlated with the postoperative IGF1 levels (ρ=-0.428, P=0.029). Patients without medical therapy presented higher AcroQoL scores than patients who currently needed treatment (79.23±6.13% vs 64.85±18.54%, P=0.042). The use of radiation therapy was associated with lower global AcroQol scores (60.51±17.8% vs 78.47±18.2%, P=0.04). Patients free of disease showed statistically significantly higher AcroQoL global and subdomain scores as well as EuroQoL-personal and mental care scores compared to those who were not cured.
Conclusions
Early diagnosis, expeditious biochemical control without continuous therapy and management of comorbidities could improve Qol in acromegalic patients.

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P87

Pituitary apoplexy: a retrospective study of 71 cases from a single center

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Background and objective
The purpose of this study was to retrospectively analyse the clinical, imaging and hormonal features, as well as the therapeutic outcomes in a series of consecutive patients presenting with pituitary apoplexy (PA).
Design
We retrospectively reviewed 71 case-records of patients with PA admitted during 2019 in a single tertiary endocrinology center.
Results
71 patients (40 men, 31women) were included, 56.3% of them presenting typical symptoms of PA (subgroup 1), 43.7% with a-/oligosymptomatic tumor haemorrhage on imaging (subgroup 2). The most common presenting symptoms in subgroups 1 and 2 were headache (85% vs 9.7 %), visual abnormalities (77.5% vs 45.2%) and digestive symptoms (30% vs 3.2%, respectively). At diagnosis, hormonal deficiency was observed in 27 (38%) patients. Neurosurgical intervention was recommended (after evaluation by multidisciplinary team) in 41 patients (58%), 24 of them with classical PA. 75.6% of operated cases and 88.8% of cases managed conservatively presented tumor remnant. Vision improvement was obtained in 64.5% of the operated and 82% of conservatively managed cases. 61% of all cases required chronic hormonal replacement therapy (more frequently in the surgical group).
Conclusion
Complex management of PA frequently leads to visual improvement but longstanding hypopituitarism.

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P88

Macroprolactin: Do we need to repeat its measurement?

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Macroprolactinaemia, a common phenomenon variably expressed in different assays, influences interpretation of prolactin results, as recognised since 1978. The degree of macroprolactinaemia manifest over time is less well described. We examined how macroprolactin status (based on polyethylene glycol(PEG) precipitation prolactin % recovery) varied over serial measurements in hyperprolactinaemic individuals.
Methods
All serum total prolactin results(measured using Roche-Cobas-8000-analysers) were extracted from the laboratory-information system for the period 1January 2011 to 1April 2021, along with relevant patient demographic/test data. Of these, samples with a macroprolactin(% recovery) screening test performed (on samples with prolactin >700 iu/l) were included in the main analysis.
Results
2782 macroprolactin checks were performed during the study period(12.5% of all prolactin tests) in 1810 individuals (median age = 35 (IQR:25-47, range = 16-93) years; male = 599, female = 2183). Of these, 465 patients had more than one macroprolactin test(totalling 1437 samples tested). 141 tests were macroprolactin screen positive($<60\%$ recovery) in 94 patients. Only 19 patients (18 female) had at least one result above + one below the 60% screening cut-off. Of these, 10 patients had results around cut-off borderline, 3 had clearly different results, 6 appeared to be errors based on other previous/later/confirmatory results. In terms of clinical details, 6 were on antidepressants/antipsychotics, 4 had prolactinoma, 1 was pregnant, 2 on OCP, 1 on levothyroxine.
Conclusion
In this study, very few patients appeared to change macroprolactin status (between positive/negative) based on the PEG%recovery cut-off. Of the 19 that did, the majority were on antipsychotic/antidepressant medication or had a prolactinoma; only three appeared to have clear deviation in the %recovery. This suggests that once macroprolactin status is determined, it is unhelpful to repeat, except where there is clinical discordance between result vs patient's condition, or a new prolactinoma diagnosis/significant change to medication/prolactin level.

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P89

Desmopressin prescription safety in adult inpatients: Experience from a quality improvement project

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Background
Cranial Diabetes Insipidus (CDI) or Arginine-Vasopressin Deficiency (AVP-D) is a potentially life-threatening condition requiring treatment with desmopressin. Omission or delay in desmopressin can result in serious patient harm.
Aims
Evaluation of desmopressin prescription/administration practice and implementation of an action plan to improve patient safety.
Methods
Retrospective review of electronic case notes of patients with CDI/AVP-D admitted to Sheffield Teaching Hospitals between 2018-2021 was performed. The outcomes were defined as: total number of missed and delayed doses, time to prescription and administration from admission, and incidence of dysnatraemias.
Results
Total 102 admissions from 46 patients were identified with median [IQR] age of 60.7 [38.5-70.8] years (females = 55.8%). 38% of the admissions were via emergency department (ED). Total number of missed and delayed doses were 132/1315 (10.0%) and 139/1283 (10.9%) respectively. 33% of admissions had ≥ 1 missed doses while ≥ 1 doses were delayed in 54% of admissions. Reason was documented for 43.2% of missed and 15.8% of delayed doses. Most common reasons were medication unavailability, patient's inability to take medication, and clinical reasons to omit dose. Median [IQR] prescription and administration time from admission was 5.6 [2.7-10.7] and 15.1 [8.7-27.0] h, respectively. The incidence of hypernatraemia was 7.6% and hyponatraemia was 30.4%. ED rates of desmopressin prescription were low at 5%.
Based on these findings following steps have been implemented:
1. Desmopressin is listed and stocked as critical drug in all areas.
2. Development of local registry.
3. Electronic notes and prescription alerts with reminders to contact endocrinology.
4. Qualitative staff surveys to determine knowledge baseline.
5. Development of tailored education package.

Conclusion
Desmopressin prescription and administration delays are common and pose patient safety risk. Point of ED was found to have the lowest rate of prescription and education package is planned. Re-audit is required to evaluate these interventions.

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P90

Type 2 diabetes mellitus and the risk of parkinson's disease; a systematic review and meta-analysis

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Background
An estimated 462 million individuals are affected by type 2 diabetes mellitus (T2DM), corresponding to 6.28% of the world's population. Many epidemiological studies have indicated that T2DM may be a risk factor for neurodegenerative diseases, including Parkinson's disease (PD). Whilst research suggests there are common molecular mechanisms underlying the conditions, studies investigating the epidemiological association have revealed conflicting results. In this review, we aim to investigate the exposure-risk relationship between T2DM and PD, as well as the effects of T2DM on the risk of developing PD.
Method
A systematic review and meta-analysis of 17 observational studies ($n = 32{,}551{,}133$) was undertaken by searching 3 databases for peer-reviewed articles that included subjects with T2DM and PD vs patients without T2DM and a diagnosis of PD. Outcomes assessed included overall risk of developing PD in T2DM patients, risk of PD in patients with T2DM stratified by sex, and age, effects of T2DM complications on risk of PD, the effect of T2DM exposure duration on the risk of PD and the association between T2DM and motor progression of PD.
Results
The overall association between T2DM and PD was deemed significant logOR = 0.47 [95% CI; 0.26, 0.67]. The odds of developing PD were higher in participants with T2DM complications compared to T2DM patients without complications (logOR = 0.50 [95% CI; 0.28, 0.71]). T2DM was also associated with more severe motor decline. The odds of PD were not significantly influenced by age, sex, or diabetes duration.

Conclusions
Overall, participants with T2DM were at an increased risk of developing PD compared to those without T2DM. The odds of developing PD were even higher in participants with T2DM complications. With the established association between the two conditions, further research should prioritise identifying the underlying mechanism and exploring potential of repurposing anti-diabetic medications as disease-modifying treatments for PD.

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P91

A novel AIP deletion emphasising the variable phenotype of AIP-related pituitary neuroendocrine tumours

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A 16-year-old female presented with secondary amenorrhoea. Menarche was age 14 years and periods were less frequent over the preceding 12 months. There was no galactorrhoea, headache or visual field disturbance and no known family history of pituitary disease, tall stature or infertility. There were no clinical signs of Cushing's disease or acromegaly and visual fields were full to confrontation. Height was 160 cm. Investigations showed a prolactin of 2,452 mIU/l (RR 102-496). Insulin like growth factor-1 and random growth hormone were measured at 39.6 nmol/l (RR 16.8-70.9) and 0.5 ng/ml respectively. Magnetic resonance imaging of the pituitary demonstrated a 7.8 mm T2 hyperintense pituitary lesion located centrally within the gland which enhanced post gadolinium. A diagnosis of microprolactinoma was made and cabergoline was titrated to 750 micrograms once weekly with prolactin normalising at 3 months follow-up (358 mIU/l). Pituitary magnetic resonance imaging at 4 years follow-up showed the prolactinoma had decreased to 3.0 mm in diameter with less conspicuous contrast enhancement and T2 hyperintensity. Due to age of onset, germline testing was undertaken with the R217 panel including genes associated with pituitary tumours, which revealed a deletion c.442_444del (p.Leu148del) located in exon 3 of the aryl hydrocarbon receptor interacting protein gene (*AIP*). The amino acid change causes an in-frame deletion affecting a highly conserved residue likely disrupting the FKBP-like domain. Functional testing for this variant has been initiated. *In silico* protein modelling suggests this has a deleterious impact on protein folding and inter-strand bonding which will impair the AIP protein core. VarSome classifies this as variant of uncertain significance based on protein length changing (ACMG PM4) and it is not found within the gnomAD database (ACMG PM2). Genetic screening of family members is being pursued to determine if it is a *de novo* variant.

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P92

A functioning gonadotroph macroadenoma presenting with features of OHSS and sustained remission 4-years after TSS

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It is well established that the majority of the immunohistochemically confirmed gonadotroph adenomas are hormonally silent, accounting almost 64% of all clinically nonfunctioning pituitary adenomas. Whereas clinically functioning gonadotroph adenomas (FGA) are very rare and the exact prevalence is not known. We present the case of a FGA in a premenopausal. A 31-year-old female presented in the ED with oligomenorrhea for 11 months, abdominal pain and distention over the preceding 6 months with gradually increased intensity. She had attained menarche at 12 years with regular menses until 12 months before presentation. She denied headaches and visual disturbances. Examination revealed distended abdomen and biochemistry showed high concentration of oestradiol (2718nmol/l) with FSH: 10IU and LH: $<$1.0IU. Prolactin was 835mIU/l while TSH, fT4, cortisol, IGF-1 and somatotropin were unremarkable. A transvaginal ultrasound scan showed significantly enlarged ovaries bilaterally with multiple cysts. Contrast enhanced pituitary MRI demonstrated a sellar-suprasellar macroadenoma (13x21x16mm), minimally abutting the adjacent left cavernous sinus without significant invasion and chiasmal compression. Subsequently, the patient had transsphenoidal surgery (TSS) with transient postoperative diabetes insipidus. Postoperatively, immunohistochemistry showed strong immunoreactivity with FSH and pan-α-subunit along with weaker focal staining for LH and strongly positive for SF1. Ki67 proliferation index was 1-2%. MRI imaging and hormone profile over the next 4 years following surgery continued to reveal radiological and biochemical remission. FGAs are a heterogenous group of rare neoplasms which in females manifest with ovarian hyperstimulation syndrome (OHSS), hyperoestrogenaemia and normal or mildly elevated FSH. Most of the reported FGAs in premenopausal women are macroadenomas, in keeping with our case. Long-term data on the outcome of patients with FGAs after surgery, with or without combined radiotherapy are very sparse. Our case provides useful evidence of sustained remission 4 years after TSS in a patient with a FGA treated in comprehensive multidisciplinary pituitary service.

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P93

The clinical course of pituitary metastases: illustrations from clinical cases

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Pituitary metastases are reportedly uncommon. Here we report two cases illustrating metastases responding to systemic anticancer therapy (SACT). A 49-year-old woman with metastatic renal cell carcinoma treated with combination ipilimumab and nivolumab immunotherapy was referred for hypocortisolaemia (morning cortisol 74 nmol/l). Biochemical screening revealed an adrenocorticotropic hormone of 16ng/l (0-46), thyroid-stimulating-hormone 0.1mU/l (0.55-4.78), free thyroxine 7 pmol/l (10.0-22.0) and prolactin 1400mu/l. Immunotherapy-induced hypophysitis was suspected and treated with hydrocortisone and levothyroxine. There was no visual field defect or symptoms of polyuria/polydipsia. Pituitary imaging demonstrated a 1.5 x 1.6 x 1.3 cm suprasellar lesion initially suspected to be a non-functioning macroadenoma. Follow-up imaging (6 months) showed a reduction in size of the pituitary lesion, which coincided with an interval response of her underlying metastatic disease. Subsequent scans revealed complete resolution of the pituitary lesion. A 72-year-old man was referred following the incidental finding of liver lesions on an abdominopelvic computed tomography scan (CT) undertaken for lower abdominal symptoms. Histopathology was consistent with a neuroendocrine neoplasm (CEA and calcitonin staining). A further staging CT showed a calcified irregular mass in the left thyroid, multiple bone lesions and a pituitary mass. Serum calcitonin was markedly elevated (16149.00ng/l [0.00-8.40]) confirming the diagnosis of medullary thyroid carcinoma. Subsequent pituitary magnetic resonance imaging (MRI) confirmed a 1.8x2.8x2.7 cm suprasellar mass eroding the sphenoid bone (clear of the optic chiasm) which progressively increased in size (2-month period), consistent with pituitary metastases. The patient was clinically eupituitary with normal biochemistry. He underwent palliative radiotherapy to the spine and was commenced on Cabozantinib, which led to a reduction in volume of the suprasellar mass on follow-up MRI scans. Metastases should be considered for pituitary lesions in patients with underlying cancer, despite seemingly being rare. Loco-regional treatments (especially for compressive symptoms) and SACT remain the mainstay of treatment.

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P94

Effectiveness of Dopamine Agonists in managing Non-Functioning Pituitary Adenomas- a United Kingdom single centre retrospective review

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Background
While dopamine agonists (DAs) are used for managing residual/recurrent non-functioning pituitary adenomas (NFPAs), guidance on patient selection, drug dosing, follow-up imaging and response criteria is lacking.
Methods
Retrospective review of NFPAs treated with DAs at a U.K single centre. 14 patients on Cabergoline (November 2011-2022) were identified. Radiological response was based on 2 follow-up (FU) scans or imaging at 12 months. Tumour shrinkage defined as $>$ 20% reduction in volume; tumour stabilisation was defined as 0-20% reduction in volume; tumour growth was defined as any increase in volume. 3 patients were excluded (2-prolactinomas, 1-insufficient data).
Results
In a total 11 patients (mean age 67.73 years; median age 65.5 $\pm$ 23.5 years) (45.5% females). Cabergoline was commenced pre surgery, due to inoperability or post-surgery and radiotherapy. At time of submission, 8 had repeat scans (1 awaiting 1st scan, 1 excluded as DA stopped due to intolerance, 1 couldn't tolerate MRI). Variable time to 1st FU scan (3 – 13 months) with 50% of 1st FU scans in 6 months.
50% of patients demonstrated either tumour shrinkage (25%) or stabilisation (25%), while tumour growth despite DA therapy was observed in 50% of patients.

Patient number	Time to 1st FU scan (months)	Cabergoline dosage (mg) and frequency	Results
1	12	250, OW	Shrinkage
2	8	500, twice weekly	Shrinkage
4	11	500, 3x a week	Stable
6	11	500, OW	Increase
7	6	250, OW	Increase
8	6	250, twice weekly	Stable
10	4	250, twice weekly	Increase
11	3	250, OD	Increase

Conclusion
We report a limited role of DA therapy in preventing tumour growth within a small cohort. Further multicentre studies are warranted for guiding more selective use of DA in management of NFPA.

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P95

Pituitary apoplexy with a twist

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Introduction
Multiple myeloma (MM) is a haematological disorder characterised by an aberrant rise in monoclonal paraprotein. Intrasellar plasmacytomas can be infrequent MM manifestations. They are challenging to diagnose and frequently mimic pituitary adenomas; however rarely present with pituitary apoplexy. We describe a patient with pituitary apoplexy-like symptoms, subsequently diagnosed with MM, whose intrasellar mass entirely resolved after chemotherapy.
Case report
A 54-year-old female presented with headache and visual disturbance to the emergency department. Her CT head showed a pituitary lesion with haemorrhage. She was managed as pituitary apoplexy, with IV Hydrocortisone at the presentation, followed by oral hydrocortisone replacement. Her MRI head identified a pituitary mass reported as a macroadenoma, distorting chiasm and optic nerves despite the normal visual fields assessment. Hypertension and renal impairment were noted with anaemia (Hb 72 g/l, creatinine 149 umol/l, and eGFR 35 mL/min/1.73 m2). Subsequently, MM screening revealed significantly high kappa free light chains ($>$ 6000 mg/l). Following a haematology review, she had a bone marrow biopsy that showed 80% plasma cells, and a whole-body MRI reported multiple lytic lesions consistent with MM. The pituitary MDT agreed this might be a pituitary plasmacytoma and suggested considering lumbar puncture, but the haematology MDT recommended reassessing after chemotherapy. Following the first cycle of Daratumumab-VTD (Dara-VTD), a contrast pituitary MRI revealed complete remission of the pituitary plasmacytoma. She completed four cycles of Dara-VTD with an excellent response to treatment and has completed autologous stem cell transplant under haematology care. She remains on a small dose of hydrocortisone replacement with otherwise normal pituitary function.
Discussion
Pituitary plasmacytomas can present with pituitary apoplexy. Despite their challenging diagnosis, they are usually responsive to chemotherapy treatment.

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P96

A first report of pituitary Neuro-Endocrine-Tumour in a young patient with Coffin-Siris syndrome. Is there a link between the ARID1B c.6157dup gene and pituitary tumourigenesis?

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A 19-year-old gentleman, with Coffin-Siris-Syndrome(CSS)(ARID1B:c.6157dup gene-mutation), was referred to our endocrinology clinic, with rapid weight-gain and recent onset of Type-2-Diabetes. He was of short stature, he had central-adiposity, facial plethora, proximal myopathy and gynaecomastia. Endocrine testing revealed ACTH:61ng/l, Cortisol:772nmol/l, Total-Testosterone:2.8nmol/l, FSH:6.3U/l, LH:2.2U/l, Prolactin:87mU/l, IGF-1:61ug/l, TSH:0.18mU/l, T4:10.3 pmol/l, HbA1C:84mmol/mol. Overnight-Dexamethasone-Suppression-Test(ONDST) showed a cortisol of 907nmol/l, a Low-Dose-Dexamethasone-Suppression-Test cortisol was 708nmol/l and 24-h Urine-Free-Cortisol(UFC) was 1383.5nmol/l/24hrs. Pituitary-Magnetic-Resonance-Imaging(MRI) showed a 2.6cm pituitary-macroadenoma with suprasellar-extension, in contact with the optic-chiasm, lack of sphenoid-sinus pneumatisation and dysgenesis of the Corpus-Callosum. Z-score was -4.9 on Dual-Energy-X-ray-Absorptiometry(-DEXA) scan. Access to the sella, for transsphenoidal pituitary-surgery, was achieved via drilling though a thick layer of sphenoid-bone, which was complicated by significant haemorrhage and an intra-operative ischaemic-cardiac-event. Post-operatively cortisol-levels were 56 and 60nmol/l, ODST-Cortisol $<$28nmol/l, 24hr-UFC was 36nmol/l/24hrs and late salivary-cortisol levels were 41.5/1.2($<$2.6nmol/l). Pituitary histology showed a corticotroph adenoma/Pituitary-Neuroendocrine-Tumour(PitNET) with some very atypical features[ACTH, Steroidogenic-Factor-1(SF-1) and Neuronal-nuclear-antigen(-NeuN) expression and mutant BRAF]. This is the first case to demonstrate Cushing's disease in a patient with CSS. Endocrine disorders associated with CSS, include pituitary hypoplasia, Growth-Hormone(GH) deficiency, idiopathic short stature, hyperinsulinism, obesity and cryptorchidism. CSS is a rare (200 cases world-wide), autosomal-dominant, usually de-novo, genetic syndrome characterised by intellectual disability, aplasia/hypoplasia of the fifth finger/toe, coarse facial features, and multiple anatomical abnormalities. "AT-Rich-Interactive-Domain-1B"(ARID1B)-gene mutation, the one that our patient had, is the commonest. ARID1B encodes a protein in the "SWItch/Sucrose Non-Fermentable"(SWI/SNF) complex, thought to act as a tumour suppressor. Somatic ARID1B-gene variants are involved in breast cancer, neuroblastoma and diffuse large B-cell lymphoma. In recent years, our knowledge on pituitary tumourigenesis has exponentially expanded(germline/somatic mutations and epigenetic-mechanisms). ARID1B:c.6157dup gene's potential role in pituitary tumourigenesis remains to be elucidated.

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P97

"The changing colours" –cabergoline induced raynauds phenomenon- a rare clinical presentation

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Introduction
Prevalence of prolactinoma is approximately 10/100,000 (men) and 30/100,000 (women) and dopamine agonists remain pharmacological treatment of choice. Cabergoline, an effective dopamine agonist, is preferred due to better tolerability withhigher efficacy in lowering prolactin and reducing tumour size in comparison with bromocriptine. Digital vasospasm, known adverse effect of Bromocriptineis mediated by activation of α1 adrenergic receptors. It's rarely reported with Cabergoline. We describe a case of cabergoline induced Raynaud's phenomenon in a woman with microprolactinoma necessitating medication stoppage.
Case
A 34-year-old non-smoker referred to Endocrine clinic with incidental high prolactin (1140Mu/l) during assessment of sub-fertility. Rest of pituitary hormone profile being unremarkable, subsequent pituitary MRI confirmed pituitary micro-adenoma (5x3mm) and started on Cabergoline 250 mg twice/week and then reduced to weekly. Prolactin levels normalised on Cabergoline. 2-years following initiation of treatment, (during the pandemic) shenoticed gradual onset of numbness with pins and needles, discolouration of second and third toes of her feet that turned yellow/white in cold weather. She reported it to us 2 years later

with nocomplaints with hands. Foot warmers and putting feet in warm water relieved her symptoms. No other clinical findings or risk factors were identified. Rheumatology work up with autoimmune screen (ANA, ENA, antidsDNA, ANCA, anti-Yo, anti-Hu and anti-Ri antibodies) were negative. Clinical diagnosis was Raynaud's phenomenon secondary to Cabergoline with symptoms resolving 1-2 months after stopping Cabergoline. Currently 15-months post cessation of drug no symptoms have recurred with serum prolactin levels 683 mu/l (query secondary to Sertraline) and stable size of microadenoma. On literature review, our case developed Raynaud's at the minimal dose of 250 mg weekly.
Conclusion
Raynaud's phenomenon a rare side effect of Cabergoline that normally comes on within 5-10 years post treatment should be taken into consideration with co-existent autoimmune conditions when clinical presentation merits.

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P98

Use of metoclopramide to induce lactation in a post-partum female with panhypopituitarism

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Lactation is under the control of the anterior and posterior pituitary via prolactin and oxytocin release. A number of galactogogues, including dopamine antagonists, have been described and used with success in lactation induction. To date, there are no reports in the literature of their use in patients with panhypopituitarism. We present the case of a forty-year-old female known to endocrinology services with a background of anterior panhypopituitarism and AVP deficiency associated with a hypoplastic pituitary. At age forty, she underwent in-vitro fertilisation and delivered a pre-term baby boy at 30 + 1/40 gestation. The patient expressed wishes to breast-feed post-partum. Metoclopramide 10mg TDS was commenced which was continued during the breast-feeding period. This was well-tolerated with neither maternal side effects nor adverse neonatal outcomes. The patient expressed 40ml/three hours breastmilk on average with a maximum of one supplemental feed required per day. One week after breastfeeding was stopped, the patient suffered a seizure secondary to acute hyponatraemia, serum sodium 112mmol/l, urine sodium 84mmol/l, serum osmolality 239mmol/kg, urine osmolality 371mmol/kg, clinically euvolaemic. Oral fluid intake had been increased during the breastfeeding period and, after stopping breastfeeding one week prior to her seizure, she had not resumed pre-breastfeeding levels of fluid intake. This resulted in additional free fluid absorption while on regular Desmopressin and a positive fluid balance with subsequent hyponatraemia. She recovered well with no further seizure episodes. There are few randomised control trials with small sample sizes studying Domperidone and Metoclopramide in mothers of preterm babies with insufficient milk supply. Their use for lactation induction in this cohort remains 'off-label'. However, there are no reports of adverse neonatal outcomes secondary to the use of pharmaceutical galactogogues. Further studies are required in women with panhypopituitarism to establish safety and efficacy.

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P99

Spinal epidural lipomatosis: A rare complication of Cushing's disease

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Background
Cushing's syndrome is rare (1.8-3.2 cases/million population)1, with Cushing's disease (CD) accounting > 70%. We seek to highlight a rare complication, spinal epidural lipomatosis (SEL), rare cause of spinal compression (prevalence-2.5%2), commonly related to exogenous steroid use with 3 reported cases secondary to CD3,4,5.
Case
36-years old man, background asthma and alcohol excess presented with palpitations. He appeared cushingoid with moon-face, facial plethora, central adiposity and purple abdominal striae and referred to Endocrinology.
Investigations
Unsuppressed cortisol 466nmol/l post overnight dexamethasone suppression test. Raised 24h urinary cortisol concentration (928nmol/day). Low dose dexamethasone suppression test confirmed ACTH dependent CD (Unsuppressed ACTH: 190ng/l) with normal pituitary hormonal profile, MRI pituitary, and CT adrenal. Inferior Petrosal Sinus Sampling (IPSS) revealed central source with left-sided gradient. During investigation & treatment initiation (block and replace therapy: metyrapone 250 mg TDS and dexamethasone 0.25 mg BD.), patient presented with bilateral lower-limb weakness over 4-5 weeks without bowel/bladder symptoms, leading to being wheel chair bound. Examination demonstrated thoracic myelopathy with grade 3/5 power, hyper-reflexia, bilateral clonus and reduced sensations below T10-11 level but preserved perianal sensation. MRI spine demonstrated diffuse excessive epidural fatty tissue posteriorly over thoracic cord, spondylodiscitis (T11-T12) with generalised narrowing of thecal dimension, old superior end plate compression fracture at T11 and significant cord compression in thoracic spine. Diagnosis was paraparesis secondary to SEL. Spinal MDT suggested conservative management with optimization of CD, weight-bearing exercises and DLSO brace. Trans-sphenoidal complete hypophysectomy led to post-operative pan hypopituitarism and commencement on Desmopressin 50 mg BD, Hydrocortisone 20 mg/10 mg and thyroxine 50 mg OD.
Conclusion
SEL a manifestation of metabolic syndrome secondary to CD has significant morbidity and necessitates early diagnosis and treatment. This highlights necessary awareness regarding myelopathy with thoracic compression fractures related to SEL, which may require conservative or surgical management.

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P100

Ipilimumab associated hypophysitis and painless thyroiditis: case report

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Introduction
Ipilimumab is an efficient medication used for the management of melanoma. However, it has been associated with endocrine dysfunctions such as hypophysitis, thyroid disorders (hypo- or hyperthyroidism), and adrenal insufficiency.
Case report
We report the case of a 65-year-old male diagnosed with melanoma (Clark V). In 2022, he was operated and received treatment with ipilimumab 3 mg/kg. Three weeks after the first administration, he presented in the Emergency Department with hypotension, nausea, extreme tiredness. Further investigation revealed a low cortisol level of 0.2 mg/dl and ACTH below 1.5 pg/ml. Based on the findings, the patient was diagnosed with adrenal insufficiency secondary to immunotherapy-associated hypophysitis, and treatment with IV glucocorticoids was immediately started, with rapid improvement of the symptomatology. The thyroid tests showed a TSH level of 0.7 mUI/ml, slightly increased ft4 levels of 2.04 ng/dl, positive ATPO, and antithyroglobulin antibodies. However, he had no signs of hyperthyroidism, and anti TSH receptor antibodies (TRAb) level came 0.8 UI/l (N < 1.7), so silent thyroiditis was assumed. The other tests showed both low testosterone and GH levels, no optic chiasm compression and normal MRI of the pituitary. Upon discharge, he was prescribed continued replacement therapy with glucocorticoids and beta-blockers in case of increased heart rate.
Conclusion
Endocrine dysfunctions can occur at varying points during treatment with ipilimumab, so monitoring and early detection are essential in these cases.

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P101

Severe hyponatremia in a 46-year-old female with pituitary stalk duplication and empty sella internal medicine, endocrine department

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Introduction
pituitary duplication is a rare congenital malformation. It has been mainly reported in the pediatric and neonatal population with few reported cases in the adult population. In this case we will be discussing the presentation of an adult female patient with pituitary stalk duplication and empty Sella causing hyponatremia.
Case Presentation
A 46-year-old female presented with severe euvolemic hyponatremia. Urine analysis showed high urine osmolality and urinary sodium concentration with low

serum osmolality. Chest x-ray was normal. Further history revealed the history of amenorrhea. On physical examination, the patient had underdeveloped secondary sexual characteristics. Laboratory tests showed low FSH, LH and estradiol. Prolactin was moderately elevated. Morning cortisol was low, ACTH was within lower normal range, ACTH dynamic test was suboptimal and IGF-1 was low. MRI imaging showed enlarged bony Sella with duplication of pituitary stalk.
Conclusion
Severe hyponatremia was due to secondary adrenal insufficiency with primary empty sella syndrome (PES) PES is usually asymptomatic and mostly diagnosed as an incidental radiological finding. Severe hyponatremia as the presenting manifestation of empty sella syndrome is rare. The pathogenesis of hyponatremia in patients with adrenal insufficiency is mainly attributed to an increase in ADH secretion. ADH is produced together with corticotropin-releasing hormone (CRH) by the paraventricular nuclei of the hypothalamus to activate the synthesis and release of ACTH from the pituitary gland.

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P102

Macroprolactinoma management during pregnancy

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Case
This 23-year-old lady initially presented in 2013 with headaches, galactorrhoea and secondary amenorrhoea. Visual fields were normal to confrontation. Prolactin levels were elevated at 3028miu/l. MRI pituitary revealed a 14x13x15mm adenoma pushing the pituitary stalk posteriorly, and compressing the left side of the optic chiasm.
Initial Management
Cabergoline was commenced (250mg twice weekly), with good clinical response. Galactorrhoea ceased and her menstrual periods returned. Prolactin levels reduced to within the normal range (277miu/l). Repeat MRI pituitary following six months of treatment (April 2014) revealed reduction in size of the previous macroadenoma (9x8x10mm).
Clinical Course
In December 2018, this lady became pregnant and she stopped taking Cabergoline at the time of a positive pregnancy test. Visual fields were monitored throughout pregnancy with nil concerns. Following delivery, she recommenced Cabergoline. Repeat MRI Pituitary in June 2022, whilst continuing Cabergoline, revealed further interval reduction in the left sided adenoma (7x8x9mm), with no optic nerve compression or cavernous sinus invasion. She became pregnant again in October 2022 and stopped Cabergoline. At 16 weeks pregnant, severe left sided headaches commenced. Initially managed with analgesia (paracetamol and dihydrocodeine), but at 22 weeks inpatient admission was required due to persistent debilitating headaches. She was unable to complete visual field assessment due to vasomotor symptoms in her left eye. MRI Pituitary repeated as an inpatient, highlighted an increase in size of the left sided pituitary adenoma (8x12x11mm), with left sided cavernous sinus involvement. Cabergoline was recommenced due to symptomatic trigeminal irritation and headaches much improved with this therapy. This was successfully continued throughout pregnancy and post-partum, as this lady did not plan to breastfeed.
Conclusion
This case highlights Macroprolactinoma management challenges during pregnancy. Following an initially uncomplicated first pregnancy, re-initiation of dopamine agonist therapy was required during her second pregnancy.

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P103

ACTH as a tumour marker in Cushing Disease following surgery

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Silent corticotroph adenomas are a distinctive subgroup of nonfunctioning pituitary tumours without biochemical or clinical evidence of Cushing's disease. They are diagnosed after surgery by positive immunostaining for ACTH. They are usually macroadenomas with more aggressive behaviour. On rare occasions, they transform into active Cushing's disease, with elevated serum ACTH levels. I report a case of a 44 years old lady I first examined in the postoperative neurosurgical unit on the third day following a second transsphenoidal intervention for a pituitary macroadenoma. Two years before (Oct 2020), she was diagnosed with a pituitary macroadenoma symptomatic with a visual field defect. A first transsphenoidal resection was performed with complete recovery of her visual field. The three months control MRI described a tumoral rest (7/6/4 mm). She gained hypopituitarism on the gonadotropic and thyrotropic axis, and replacement therapy was started without requiring hydrocortisone replacement. Immunohistochemistry revealed positive staining for ACTH and Ki67 of 12%. Subsequent MRI shows a gradual increase of the tumoral rest. On February 2022, the patient complained of accelerated vision loss. The MRI shows a sellar tumour with a suprasellar extension of 25/20/27 mm. The hormonal sampling shows high ACTH (x2 UNL) with high normal cortisol. Suppression tests on the corticotrophic axes were not performed, and the patient was addressed for a second surgery. Following the second surgery, she fully recovered her vision and was discharged with hydrocortisone substitution therapy until testing the corticotrophic axis could give reliable results. The immunohistochemistry shows Ki 67 - of 12% and positive p 53 with a nuclear index of 70%. Three months following surgery, her cortisol levels were undetectable while on hydrocortisone substitution treatment with a slowly increasing trend for ACTH to 25 pg/ml (nr 7-63). An MRI showed a suprachiasmatic tumoral rest; the patient was referred for radiotherapy.

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P104

Ectopic posterior pituitary in an adult with stalk interruption hypogonadotrophic hypogonadism and hyperprolactinaemia

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Ectopic posterior pituitary is a rare congenital pituitary anatomical defect of complex inheritance resulting in heterogeneous clinical and radiological phenotypes. Presentation is primarily in paediatric patients with growth and development effects. We present a rare adult presentation patient. A 33 year old male presented with low libido and paucity of facial hair. Previous medical history was limited to a left undescended testis. He took no regular medications, anabolics or recreational substances. Examination confirmed weight 112.7 kg, BMI 36, normal secondary sexual characteristics with testicular volume 25 ml right and 20 ml left. Basal endocrine investigations at 09:00 h: cortisol 528 nmol/l, ACTH 71.5 ng/l, fT4 10.3 pmol/l, fT3 6.4 pmol/l, TSH 4.03 mU/l, testosterone 5.0 nmol/l, free testosterone 151 pmol/l, bioavailable testosterone 3.3 nmol/l, FSH 2.2 IU/l, LH 1.7 IU/l, prolactin 812 mU/l, IGF-1 13 nmol/l, plasma osmolality 291 mmol/kg and urine osmolality 836 mmol/l (post 8 h water deprivation). Dynamic endocrine testing: insulin tolerance test confirmed normal cortisol and growth hormone responses. MRI pituitary demonstrated a hyperintense lesion along the pituitary stalk consistent with ectopic posterior pituitary. Further investigations: plasma AFP 5 kU/l, HCG $<$1.0 IU/l and CSF AFP $<$0.5 kU/l, ACE 18 U/L. Treatment with cabergoline 0.25 mg once weekly for 6 months normalised prolactin (219 mU/l) with minimal effect on testosterone (7.9 nmol/l, free testosterone 220 pmol/l and bioavailable testosterone 5.39 nmol/l) with no symptomatic improvement. A GnRH test suggested an impaired gonadotrophin response. Treatment with testosterone supplements resulted in alleviation of his symptoms.

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P105

Arginine vasopressin deficiency (central diabetes insipidus) in a case of suprasellar germinoma: Is it reversible? - Case report

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Background
Arginine Vasopressin Deficiency [AVP-D] can occur as consequence of any abnormality or injury at one or more of the sites involved in the Antidiuretic hormone [ADH] secretion. AVP-D is one of the presenting features of suprasellar lesions with panhypopituitrism. The natural course of the disease differs based on the underlying aetiology. It is likely to be transient post-operatively. Idiopathic DI is usually permanent however DI can be reversible with infiltrative diseases.
Case Presentation
A 29-year-old gentleman who was diagnosed with suprasellar germinoma affecting the optic pathway. He presented initially with change in his vision. Further investigations confirmed a suprasellar mass with panhypopituitarism. He Underwent frontotemporal craniotomy for open biopsy. Histology reported germ cell tumour in keeping with germinoma. Diuresis came to the medical attention within 24 hrs postoperatively that was associated with hypernatremia. The patient reported that he used to drink around 5 Liters of water daily even before the

procedure. He was started on regular Desmopressin 100 mg PO twice per day because of persistent polyuria. Oncology review concluded Suprasellar Germinoma, with no metastasis. The patient was started on chemotherapy and received Radiotherapy as well. Six weeks postoperatively and while on chemotherapy the dose of desmopressin was reduced down to 50 mg PO nightly then switched to desmopressin nasal spray 10 mg/inh 1 puff at night.
Discussion
Clinical assessment is always the key during the long-term management of central DI. The dose of desmopressin should be reviewed and changed based on the degree of polyuria The need for clinical indicators to help define the course of the disease is crucial. As the case with other pituitary hormones deficiency, it is important to reassess the recovery of the AVP axis after treating the underlying cause using a valid clinical tool.

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P106

A case report of relapse of non-Hodgkin lymphoma presented with diabetes insipidus

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Introduction
There are many causes of central diabetes insipidus including trauma, drugs, metastatic tumor, lymphoma, leukemia, inflammation, virus infection and gene mutation. They're very few cases in England reported as pituitary involvement of NHL [no-Hodgkin lymphoma] Approximately about 31 cases were reported in the literature as NHL of the pituitary as in Pub medicine, however in these series of cases the most common presentation among them was central hypothyroidism followed by adrenal insufficiency and diabetes insipidus subsequently. Learning points

- Relapse of NHL presenting as diabetes insipidus is rare presentation and sudden onset of cranial diabetes insipidus in patient with complete remission should raise the suspicious of the relapse.
- Although tissue diagnosis is the gold standard for the diagnosis but the images and clinical presentation is acceptable when the tissue diagnosis is not amenable.
- As in all other malignance's the treatment rely on the prognosis and the quality of life.

Case report
71 years old lady with previous history of non-Hodgkin lymphoma of spine under remission for many years, presented with features of diabetes insipidus. Subsequent investigation confirmed diabetes insipidus. Her blood test didn't show hypopituitarism however prolactin was elevated because of stalk pressure effect. Treated with close monitoring, IV dextrose 5% and desmopressin subcutaneously 1mg three times /day with aiming of urine output <200 ml/h. After 72 h of treatment her sodium dropped to <150 and her urine output approximately was 150ml/h. On the fifth day her sodium was around 135 and she became more alert and started to eat and drink. MRI pituitary with contrast revealed hypothalamic lesion approximately 9mm highly suspicious of no-Hodgkin lymphoma. She has been discussed in both Neuro-oncology MDT and Hematology MDT and both decided for supportive care given the outcome likely poor and no further step needed.

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P231

Analyses of the effects of adrenomedullin on the gonadotrophin-releasing hormone pulse generator and luteinising hormone pulses

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The pulse mode of gonadotrophin-releasing hormone (GnRH) release from the hypothalamus and following luteinising hormone (LH) pulses from the pituitary induce follicular development in female animals. Kisspeptin neurons in the hypothalamic arcuate nucleus (ARC) are suggested to be the GnRH pulse generator. Adrenomedullin (AM) is a secretory peptide expressed in various tissues, including the hypothalamic paraventricular nucleus, but its functions in the central regulation of reproduction remain unclear. We previously reported that an injection of AM into the lateral ventricle (LV) suppressed LH pulses in ovariectomised and estradiol-treated female rats without affecting the number of kisspeptin neurons in the ARC. In the present study, we aimed to analyse the effect of AM on GnRH pulse generator activity and LH pulses using goats, whose activity of the GnRH pulse generator can be monitored *in vivo*. AM (0 or 5 nmol) was injected into the LV of ovariectomised Shiba goats while recording the multiple unit activity (MUA) in the ARC area and taking blood samples serially for 2 h of pre- and post-injection. And then, plasma LH concentrations were measured by radioimmunoassay to detect LH pulses. AM administration did not change the frequency of MUA volleys (pre vs post). On the other hand, AM decreased the rate of change of mean and baseline LH concentrations. These results indicated the suppressive effect of AM on pulsatile LH secretion in ruminants as with rodents. It is also suggested that the suppressive effect is not mediated by ARC kisspeptin neurons, the GnRH pulse generator.

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P232

The relationship between serum oxytocin and measures of quality of life in hypopituitary patients – a cross sectional case control study

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Introduction
Patients with hypopituitarism often report poor quality of life (QoL) despite adequate hormonal replacement therapy. Oxytocin, a peptide hormone produced in the hypothalamus and released by the posterior pituitary, has been known for its role in social and emotional behaviour. Our aim was to investigate the relationship between oxytocin and QoL domains in patients with hypopituitarism under optimal hormonal replacement therapy.
Methods
Patients with a previous diagnosis of hypopituitarism with optimal replacement therapy and subjects with no evidence of a pituitary disease attending the out-patient clinic were recruited between 2016 and 2018. The research protocol included fasting blood tests to assess oxytocin levels. The QoL was evaluated using valid instruments such as the Short Form Survey (SF-36), Questions on Life Satisfaction-Hypopituitarism (QLS-H), UCLA Loneliness Scale, and Hospital Anxiety and Depression Scale.
Results
Data were available for 30 patients [19 females, 11 males, ages 20-80 [mean 56 yrs)] and 16 controls [9 females, 7 males, ages 30-73 (mean 54 yrs). Comparison of baseline characteristics of participants between the groups showed no differences for age, gender, BMI or oxytocin levels (10.65 vs. 11.44, $P=.58$). Patients had significantly lower (worse) scores for the domain Pain ($P=.024$) measured by the SF-36, and Sexual Arousal measured by QLS-H ($P<0.01$) compared to patients. Across both groups we found a moderate correlation between oxytocin and Initiative/Drive domain, measured by QLS-H (.345, $P=.03$).
Conclusion
In our cohort of subjects we observed a linear relationship between serum oxytocin and initiative/drive domain measured by QLS-H. Our study was statistically underpowered to detect a difference for serum oxytocin, however, a trend towards a lower serum oxytocin was observed in patients compared to controls.

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P233

Characterisation of the Impact of Joint Pain on Patients with Acromegaly

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Acromegaly is caused by excessive growth hormone (GH) and insulin-like growth factor (IGF-1) secretion. Arthropathy is a leading cause of morbidity and impaired quality of life in acromegalic patients, often persisting despite therapeutic interventions and biochemical control. This cross-sectional study aimed to characterise the extent and impact of arthropathy in terms of pain and functional impairment. Validated questionnaires, including DASH (Disabilities of the Arm, Shoulder and Hand), Oswestry Disability Index, KOOS (Knee Injury and Osteoarthritis Outcome Score) and FFI (Foot Function Index) were completed by 85 patients (45 women; median age 58) with biochemically controlled and uncontrolled acromegaly. Seven patients were excluded due to missing data. An Annotated Human Figure Diagram and Numerical Rating Scale were used to identify painful anatomical sites and assess the severity of joint pain, respectively. Patients with biochemically uncontrolled disease (defined as GH >1 mg/l or raised IGF-1 levels) were compared to patients with biochemically controlled disease. In the preceding 3 months, 90.1% of acromegalic patients reported joint, neck or back pain lasting >6 weeks. The knee was most commonly affected (63.4%), followed by the lower back (53.5%) and hands/fingers (46.5%). Symmetrical arthropathy was observed in the majority of affected joints, with the exception of the groin and wrist. The median number of painful joints reported was five. The knee was most frequently reported as the most painful joint (29.8%), followed by the lower back (19.3%). Patients with uncontrolled acromegaly showed no statistically significant difference in pain scores compared to patients with biochemically controlled acromegaly across all domains. Clinical arthropathy is widely prevalent among patients with acromegaly, with the knee, lower back and hand/fingers most commonly affected. In our study, biochemical control of acromegaly did not significantly impact on the severity of arthropathy in terms of pain and functional limitation.

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P234

The utility of routine fasting gut hormone assessment in asymptomatic individuals with Multiple Endocrine Neoplasia Type 1 (MEN1)

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Background
Secretory pancreatic neuroendocrine tumours (PanNET) are common in MEN1. The MEN1 Clinical Practice guideline (Thakker, 2012) recommends annual assessment of fasting gut hormones (FGH) with annual pancreatic imaging for routine NET surveillance in MEN1.
Study aim
To determine whether FGH (gastrin, glucagon, somatostatin, pancreatic polypeptide, VIP, insulin, chromogranin-A) in a cohort of asymptomatic individuals with a genetic diagnosis of MEN1, over a 5 year period, changed patient management.
Study design
Single centre retrospective case series. Inclusion criteria: individuals with MEN1 undergoing routine surveillance, including those with non-functioning PanNET and those with previously resected PanNET. Exclusion criteria: individuals with symptoms suggestive of a functioning PanNET (hypoglycaemia, profuse diarrhoea, significant acid-reflux) and those on somatostatin analogue therapy (SSA).
Study participants
43/54 people with MEN1 met the inclusion criteria (26M, 17F, age range 22-84 year). 11 were excluded (3 due to symptoms; 8 due to SSA therapy). 169 FGH panels were analysed.
Results
94/169 (56%) FGH panels contained 1 or more abnormal result. Chromogranin A was most frequently abnormal (62/169 panels; 37%), followed by glucagon (28%) and gastrin (20%). Abnormal VIP and somatostatin were uncommon (1% and 0.6%, respectively). 22/169 (13%) panels contained a result more than 3 times the upper limit of normal (ULN); 9 (5%) had a result more than 10 times ULN. Over 5 years, 142 pancreatic MRI scans were performed where paired FGH were available. 89/142 MRIs were reported as normal. 53/89 (60%) were paired with a completely normal FGH panel. Taken in isolation, the FGH results did not change patient management across the series.
Conclusions
FGHs are frequently abnormal in asymptomatic people with MEN1 undergoing routine surveillance, with doubtful clinical significance. Taken in isolation, these do not alter management however, the FGH trends over time can be useful when interpreted in the context of serial radiological findings.

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P235

Short chain fatty acid ameliorates hypothalamic apoptosis in a rat model of polycystic ovarian syndrome via modulation of gamma-aminobutyric acid

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Background of Study
Polycystic ovarian syndrome (PCOS) is an endocrine disorder, contributing to increased neurodegenerative disorders including hypothalamic disturbance. Short chain fatty acid (SCFA) has been reported to regulate metabolic health. However, its therapeutic nature in hypothalamic dysfunction, especially in PCOS individuals is unknown. This study hypothesized that SCFA reverses hypothalamic injury and its related abnormalities in experimentally induced PCOS rat model, possibly by modulating GABA.
Materials and Methods
Eight week old female Wister rats were divided into four groups ($n=5$), namely control, PCOS, acetate-treated and PCOS + acetate-treated. PCOS was induced by administering 1 mg/kg body weight of letrozole for 21 days. After PCOS confirmation, the animals were treated with 200 mg/kg of acetate for 6 weeks.
Results
PCOS rats were characterized with insulin resistance, leptin resistance, increased plasma testosterone as well as degenerated ovarian follicles, there was also a significant increase in plasma and hypothalamic triglyceride levels, triglyceride glucose index, inflammatory biomarkers (SDF-1 and NF-kB) and hypothalamic caspase 6, plasma LH, an increase in plasma adiponectin, GnRH, FSH, and hypothalamic HIF-1α and NrF2 as well as severe apoptosis and inflammasome expression. These were accompanied by decreased level of GABA and the alterations were reversed when treated with SCFA, acetate.
Conclusion
Collectively, the present results suggests the therapeutic impact of SCFA on hypothalamic apoptosis and its related comorbidity in PCOS via modulation of GABA. The study therefore provides a clinical relevance in the management of hypothalamic disorder especially in PCOS individuals.
Keywords
Acetate; Apoptosis; GABA; Hypothalamus; Insulin resistance; PCOS.
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P236

Desmopressin prescribing in Arginine Vasopressin (AVP) Deficiency at University Hospitals of Leicester: a further case for a name change from Diabetes Insipidus

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Background
Cranial diabetes insipidus (DI) is characterised by the inability to produce ADH (antidiuretic hormone) also known as AVP (arginine vasopressin) resulting in uncontrolled diuresis. Desmopressin is a synthetic form of AVP used to treat this. Treatment errors can lead to dehydration and hypernatremia which can be life-threatening. In view of recent literature suggesting current concerns with Desmopressin administration worldwide, Diabetes Insipidus is currently undergoing a proposed name change to Arginine Vasopressin (AVP) deficiency.
Methodology
We audited the standards set in the "Society for Endocrinology clinical guidance: Inpatient management for cranial diabetes insipidus". We reviewed all admissions October 2020 - November 2022 where Desmopressin was prescribed with a diagnosis of AVP deficiency (DI).
Results
There were 35 admissions of patients with AVP deficiency (DI). An absence of a 'DI/AVP deficiency' alert on the patient electronic system was noted in 27 (77%) patients. An error in Desmopressin prescription was noted in 22 admissions (63%) , with multiple errors in some admissions resulting in a total of 28 errors in total. In 4/35 of admissions the Desmopressin was omitted appropriately. The cause of Desmopressin delay in patients whom it was inappropriate to omit Desmopressin can be see in **Table 1.**

Desmopressin cause of delay	N/31 (%)
Not prescribed on time	10 (32)
Unavailable	14 (45)
Unclear cause	2 (6.5)

Conclusion
Our audit has shown the time from admission to administration of Desmopressin in patients in AVP deficiency is inadequate. A significant proportion of errors were due to drug unavailability and lack of timely prescription. Going forward, we hope to reduce Desmopressin administration delays by increased drug availability, use of patient safety electronic alerts, education and that increased healthcare professional awareness of this condition by the use of the new name AVP deficiency.

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P237

A post-operative fluid restriction protocol to reduce the incidence of delayed hyponatraemia following trans-sphenoidal pituitary surgery

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Delayed hyponatraemia(DH) is a well-known complication following trans-sphenoidal pituitary surgery (TSS), varying in incidence from 9–36% and occurs between post-operative days(POD) 4 to 14. Various studies have demonstrated that post-operative fluid restriction after TSS reduces the incidence of DH.
Objective
to assess whether a fluid restriction protocol from POD5 to POD14 following TSS reduces the incidence of post-operative DH in comparison to our historical cohort.
Methods
Prospective study, with fluid restriction to $\leq$1.5 liters/day from post-operative days 5 to 14 among patients who underwent TSS for pituitary tumours from 1 August 2021 to 30 April 2023. The proportion who developed DH was compared between the prospective cohort and our retrospective cohort of patients who underwent TSS and were managed by standard protocol [$n=100$, 1 November 2017 -31 December 2019].
Results
We recruited 80 subjects(45 males and 35 females) over 20 months in the prospective study, which included the summer of two years [temperature~106°F]. Seventy-three(91%) were macroadenomas and 60% were invasive, including 35 functioning tumours(44%) -26 acromegaly and 9 Cushing's disease. The pre-operative pituitary hormonal deficiencies included secondary hypogonadism-69%, secondary hypothyroidism-51% and secondary hypocortisolism-35%. Twelve subjects(15%) developed transient post-operative diabetes-insipidus. Eleven subjects(13.7%) developed delayed hyponatraemia(DH) between POD4 -14. Nine subjects were non-compliant with fluid restriction, but none required hospital readmission. Sixty-six subjects(82.5%) were compliant with fluid restriction, among them only 2(3%) developed DH vs. 9(64%) non-compliant subjects($P<0.005$). The proportion with post-operative DH reduced significantly from 36% with standard post-operative management in our retrospective cohort to 13.7% with a post-operative fluid restriction protocol.
Conclusions
Post-operative fluid restriction is a simple and cost-effective method to avoid delayed hyponatraemia in patients undergoing TSS for pituitary tumours. Moderate fluid restriction is possible even in tropical countries like India.

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P238

Is the cannulated prolactin an useful test in evaluation of hyperprolactinemia?

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Background
Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic-pituitary axis. It is difficult to differentiate between stress induced hyperprolactinemia and true hyperprolactinaemia and may result in patients having unnecessary imaging.
Methods
We have collected data for 46 patients who had a cannulated prolactin test between January 2017 and June 2023 in the Royal United Hospital of Bath (RUH). After cannula insertion, prolactin was measured at 0, 30, 60 and 90 minutes.
Results
Prior to testing: 45 patients had raised prolactin. 1 patient had a normal prolactin. After cannulated prolactin testing: 67% results normal, no further action required 33% (13 patients) abnormal test suggestive of prolactinoma. Therefore, only 33% of patients had MRI pituitary: 12 were reported and 1 was pending. Of the 12 that had an MRI:

- 2 identified pituitary pathology and were started on cabergoline
- 10 no pituitary pathology identified:
  1. 1 was within 6 months of pregnancy so was followed up with biochemistry that settled.
  2. 1 without pituitary pathology present but symptomatic was started on cabergoline (nadir prolactin on test 1.4 x ULN)

We have reviewed the costs for a cannulated prolactin test and an MRI pituitary in the NHS: Cost of completing a cannulated prolactin test (staff/blood test/equipment) £76.11 Cost of MRI £500 Total cost if all patients had an MRI: £23,000 Total cost of all patients having cannulated prolactin: £3,501.06 Total cost of cannulated prolactin tests completed + MRI for those with positive tests: £10,001.06 Savings to the Trust by completing cannulated prolactin prior to MRI: £12,998.94.
Conclusion
Cannulated prolactin is a very good cost-effective test which saved us £13000 in unnecessary MRI's. We have saved 33 clinic consultations as patients with normal results get sent letters, no endocrine appointments.

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P239

An aggressive prolactinoma with orbital involvement and excellent response to treatment with temozolamide. A case report and systematic literature review

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A proportion of prolactinomas exhibit aggressive features (including invasiveness, relevant growth despite adequate dopamine agonist treatment, and recurrence potential) and few may exhibit metastasizing potential (carcinomas). We present an uncommon case of intra-orbital spread from a large infiltrative prolactinoma, with excellent response to temozolomide and a systematic review of the literature. A 55y.o male patient presented with generalized weakness and hyponatraemia. Further investigations revealed hypopituitarism (cortisol: 24nmol/l, TSH: 1.01mIU/l, fT4 9.0nmol/l, testo 0.4nmol/l) and markedly elevated prolactin (PRL: 23937mU/l). A contrast enhanced MRI pituitary demonstrated a 27x16x16mm neoplasm, extending into the right Meckel's cave encroaching the internal carotid artery. The neoplasm was slightly compressing the optic chiasm. Initial management included Cabergoline 0.25mg BW, hydrocortisone 10mg BD and thyroxine 50mg OD. After 2 months the patient developed pituitary apoplexy which required transphenoidal surgery (TSS). Histology showed Pit-1 positive pituitary adenoma with extensive haemorrhagic necrosis and few positive PRL cells. Ki67 was 8-9%. Postoperatively PRL reduced to 1577mU/l, but despite high cabergoline doses (1mg OD), PRL continued to rise to 30707mU/l. Progression of the residual soft tissue and extension into the right orbit via the right superior and inferior orbital fissures was confirmed on MRI imaging. Treatment with temozolomide (TMZ) 390 mg OD for 5 days every 28 days for 12 cycles was trialed after discussion in the pituitary MDM without significant side-effects. Cabergoline was decreased to 0.5mg BW and after 10 cycles of TMZ biochemical remission (PRL: 411mU/l) was achieved with remarkable radiological improvement. Prolactinomas are the most common functioning pituitary neoplasms with the majority being responsive to medical treatment. However, up to 15% of cases are resistant and locally invasive and depict an aggressive behavior. This case demonstrates the efficacy and safety of TMZ post-TSS for aggressive PRLoma management and need for multidisciplinary approach to managing complex PRLoma cases.

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P240

Psychiatric side effects of cabergoline treatment of hyperprolactinaemia: risk factors and prevalence of patient counselling and monitoring

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Background
There is increasing evidence that dopamine agonists used to treat hyperprolactinaemia may cause psychiatric side effects. Male patients have been identified to be at increased risk. This study aimed to establish the incidence of cabergoline-induced psychiatric side effects, potential risk factors for their development and to determine the prevalence of counselling and monitoring for these side effects.
Methods
A retrospective cohort study, conducted at a single centre, of patients with hyperprolactinaemia who received an outpatient cabergoline prescription between January 2018 and December 2022. Data were collected for patients who did and did not develop psychiatric side effects, including cabergoline dose and duration, sex hormones and prolactin, counselling, and monitoring.
Results
257 patients were included (61 males, 196 females). 8.6% ($n=22$) developed psychiatric side effects secondary to cabergoline, with mood disorders being the most common. Incidence of these side effects was similar between men and women. There was no difference in baseline prolactin between groups. However, baseline hypogonadotrophic hypogonadism was associated with an increased risk of developing psychiatric side effects (OR = 8.22; CI = 1.62 to 150.1; $P=0.04$). Over the five-year study period, 47.5% of patients ($n=122$) were counselled about psychiatric side effects prior to cabergoline initiation, with enquiry into these at least once during follow-up in 48.6% of patients ($n=125$). The prevalence of both counselling and monitoring for these side effects increased year-on-year from 2018 to 2021.
Conclusions
Patients with baseline hypogonadotrophic hypogonadism may be at increased risk of developing psychiatric side effects secondary to cabergoline treatment of hyperprolactinaemia, but this requires further research. A consistent approach to counselling and monitoring is needed. Future studies should explore and validate effective, practicable tools for screening and monitoring.

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P241

Assessing healthcare professionals' knowledge on Cranial Diabetes Insipidus (CDI) and Recognition of the Proposed New Name of Arginine Vasopressin Deficiency(AVPD)

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Background
Cranial Diabetes insipidus (CDI) is a rare condition but is potentially life-threatening if there is a delay or omission of desmopressin. Recent patient safety alerts highlighted the need to raise awareness to avoid mortality and morbidity. The baseline knowledge of the health care professional (HCPs) is very important to avoid deleterious outcomes.
Aim
Qualitative survey to determine the baseline knowledge and awareness of proposed name change for CDI in HCPs.
Methods
A set of 10 simple questions on CDI were designed to assess the baseline knowledge of HCPs working in A & E and hospital wards in Sheffield Teaching Hospitals NHS Foundation Trust. 50 surveys were performed. Questions assessed knowledge of definitions, clinical presentation, treatment, and awareness of the proposed new name AVPD. A pilot questionnaire was tested on endocrine nurse specialists to assess the questionnaire for general suitability.
Results
A total of 50 health care professionals (HCP) ;14 junior doctors, 12 middle grade doctors, 22 nurses, 1 advanced clinical practitioner and 1 physician associate responded to the questionnaire. Overall correct answers achieved was 60%.. A total of 62% of HCPs were aware of the origin of cranial Diabetes insipidus. Only 34% were aware of the term AVP deficiency. Only 14 % recognized that Desmopressin was a critical drug, and should be available in an oral preparation on all wards. 42% of HCPs were aware of possible complications.. Interestingly, only 12% of HCPs correctly mentioned all the available preparations of Desmopressin.
Conclusion
Despite an overall score of 60%, the baseline knowledge in some critical areas in terms of consequences of CDI, Desmopressin as a critical drug and the available preparations was below average. It was notable that the proposed new name of AVPD was only recognized by 34 %. These data support the needs for an updated educational package to all HCPs.

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P242

Uncontrolled primary hypothyroidism causing pituitary hyperplasia and mimicking pituitary adenoma

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Pituitary hyperplasia secondary to primary hypothyroidism (PHPH) is a consequence of long term untreated or uncontrolled primary hypothyroidism. The proliferation of thyrotrophs in the pituitary gland, due to the lack of negative feedback on the hypothalamus from low circulating thyroid hormone levels, causes elevated thyroid stimulating hormone (TSH) levels. Hyperprolactinaemia can also be present due to the stimulatory effect of TSH on lactotrophs. Pituitary hyperplasia causes enlargement of the pituitary gland, and pituitary imaging with Magnetic Resonance Imaging (MRI) may not always reliably differentiate between pituitary adenoma and hyperplasia.
Case report
A 23-year-old lady, diagnosed with primary hypothyroidism at age 7. Thyroid function tests (TFTs) showed persistently elevated TSH levels. No hypothyroid symptoms reported other than irregular menses and constipation. No reported issues with compliance from patient. No history of glandular fever, coeliac screen was negative. Alpha subunit measurement was normal. Assay interference was excluded. Pituitary profile bloods were within range other than mild hyperprolactinaemia. Dynamic Pituitary MRI reported a bulky pituitary gland, measuring 16 x 11 x 13 mm, with convex upper border protruding into the suprasellar cistern. Regional Pituitary MDT discussion reported physiological hyperplasia, likely due to poorly controlled primary hypothyroidism. Further imaging following good adherence to treatment reported pituitary size reduction.
Conclusion
Pituitary hyperplasia in prolonged, poorly controlled hypothyroidism is a common finding. The importance of biochemical evaluation cannot be dismissed in favour of pituitary imaging; hyperplasia can be misdiagnosed as pituitary adenoma and where there is visual compromise due to hyperplasia, unnecessary surgery may be performed. Hyperplasia can be reversed with levothyroxine replacement and good adherence to replacement. Correct evaluation of patients with robust history taking and biochemical investigations lessens the possibility of patients undergoing unwarranted surgical interventions.

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P243

A rare case of phaeochromocytoma secondary to Phosphatase and Tensin Homolog (PTEN) mutation

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A 65-year-old female with PTEN Hamartoma Tumour Syndrome, Follicular thyroid carcinoma, and Endometrial Carcinoma, presented at a tertiary centre due to an asymptomatic adrenal lesion. Previous genetic testing for phaeochromocytoma and paraganglioma in 2020 showed no pathogenic variants in multiple genes (FH, MAX, MEN1, SDHx, SDHAF2, TMEM127, VHL, RET gene). Recent imaging revealed a 9 cm left supra-renal lesion that had been gradually increasing in size since 2010. Plasma normetanephrines were significantly elevated. A biopsy of the left adrenal mass from 2011 (performed outside our centre) was re-examined and showed a granular, oncocytic cytoplasm, positive for chromogranin and negative for cytokeratinin. The features were compatible with phaeochromocytoma. The patient underwent alpha-blockade and subsequent laparoscopic left adrenalectomy. Paragangliomas and phaeochromocytomas are rare neuroendocrine tumours that originate from cells of the autonomic nervous system. They typically develop in the adrenal glands (phaeochromocytoma) or parasympathetic ganglia in the head, neck, or abdomen (paraganglioma). Paragangliomas and phaeochromocytomas can occur sporadically or be hereditary due to genetic mutations. PTEN (phosphatase and tensin homolog), a tumour suppressor gene, regulates cell growth, division, and death. Mutations in the PTEN gene lead to PTEN hamartoma tumour syndrome. This increases the risk of developing various tumours, but very rarely paragangliomas and phaeochromocytomas. PTEN mutations are not known to be associated with

paragangliomas and phaeochromocytomas in humans, but have shown to be associated in PTEN knockout mouse models. We do not routinely screen for PTEN mutations in patients who present with paragangliomas and phaeochromocytomas. Hereditary paragangliomas and phaeochromocytomas have been linked to several genetic mutations. Individuals with PTEN mutations have an increased risk of developing multiple malignancies. This case demonstrates a rare case of phaeochromocytoma secondary to PTEN mutation.

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P244

Co-occurrence of neurofibromatosis type 1 and pituitary rathke cleft cyst

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Introduction
The most common sellar and suprasellar lesions are pituitary adenomas, craniopharyngiomas and benign cysts. Rathke's cleft cyst (RCC) is a benign developmental sellar or suprasellar cystic lesion, which is rarely symptomatic.
Case History
We present the case history of 21-year-old woman with a suprasellar RCC, causing early optic chiasmal compression and associated with hyperprolactinemia. Past medical history included neurofibromatosis type 1 (NF1), optic glioma and right-sided cerebellar cystic lesions. There was bilateral ptosis, learning difficulties and precocious puberty. Our patient presented with sudden onset of headache and left-sided visual blurring. There was no history of galactorrhoea and periods were regular. Visual fields were normal and there was no papilledema. Cafe-au-lait spots were noted on the trunk. Pituitary hormone profile revealed elevated prolactin 1191mu/l (normal range, 0-450), TSH 1.89mu/l (0.30-5.50), FSH 3.6u/l, LH 4.6u/l and somatomedin C 22.4nmol/l (13.4-62.1). Short synacthen test was normal. Visual fields and ocular coherence tomography was normal. MRI pituitary revealed an enlarged pituitary gland measuring 1.3 x 1.2 x 1.1 cm. There was suprasellar extension and in the superior portion of the gland there was a 6 mm diameter rounded hypo-enhancing lesion causing early optic chiasmal compression. Our patient was reviewed by the pituitary surgeon who felt that surgical intervention was not needed. We initiated cabergoline (500mg once weekly) and this caused the prolactin levels to normalise. Repeat MRI pituitary scan did not reveal any interval change in size or appearance of the well-defined superiorly located pituitary lesion with suprasellar extension. As in the previous MRI, there was early optic chiasm compression.
Conclusion
It is important to consider RCC in the differential diagnosis of sellar and suprasellar cystic lesions. RCC may occur with pituitary adenomas but an association with NF1 has not been previously reported.

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P245

A challenging case of recurrent cushings disease

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A 45-year-old female developed clinical and biochemical recurrent Cushings' Disease 2.5 years after transsphenoidal hypophysectomy for 2cm pituitary macroadenoma. Past medical history included Type 2 Diabetes mellitus, asthma, hypertension, grade 3 obesity, dyslipidaemia, depression and sleep apnoea. MRI showed residual pituitary tissue with left sphenoid sinus extension. MDT advised repeat transphenoidal surgery over radiotherapy due to presence of a clearly visible surgical target. Neurosurgery was initially delayed at patient request. She commenced metyrapone, titrated to cortisol levels but this was poorly tolerated. Whilst awaiting neurosurgery, she developed pituitary apoplexy with right sixth nerve palsy and superior quadrantanopia. MRI showed reduced tumor volume but she became progressively hypercortisolaemic. MDT discussion felt redo transphenoidal surgery no longer appropriate but unfortunately, the patient declined radiotherapy. Over the next 5 years, her metabolic control deteriorated, managed with intensive insulin regime, GLP-1 agonist and SGLT2 inhibitor, anti-hypertensives, statin, Levothyroxine for central hypothyroidism, prophylactic Rivaroxaban for thromboembolic risk and intermittent Metyrapone. Despite this she developed worsening alopecia, arthralgia, myopathy and NAFLD and became wheelchair dependent. Options of pituitary radiotherapy, bilateral surgical adrenalectomy or ablation were discussed. Bilateral surgical adrenalectomy was accepted by the patient but delayed due to Covid-19 pandemic. Whilst awaiting adrenalectomy she developed worsening headaches and superior quadrantanopia. Repeat MRI showed increase size of pituitary adenoma with supraseller extension. She commenced Pasireotide after MDT discussion but attended A/E with worsening headache, visual field defect and ongoing cushingoid symptoms after 3 doses. Repeat MRI scan showed no significant tumour growth or apoplexy and MDT recommended Osilodrostat, which the patient is awaiting.
Conclusion
This challenging case highlights the alternative options of managing resistant hypercortisolaemia in an individualized approach and the difficulty explaining complex treatment options with patients.

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P246

Assessing growth hormone replacement practice in patients with hypopituitarism in queen elizabeth hospital birmingham

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Background
In the UK, adults with growth hormone deficiency (GHD) are treated with recombinant Growth Hormone (GH) therapy according to NICE guidelines (TA64). Provided that patients show an initial improvement in their quality-of-life score, assessed using the Quality-of-Life Assessment of GHD in Adults (QoL-AGHDA) questionnaire, they can continue with their GH treatment long-term. However, in clinical practice, many patients are observed to discontinue GH replacement on their own accord.
Aim
To identify common reasons for discontinuing GH treatment among patients and propose measures to support planned discontinuation of treatment.
Methods
This service evaluation was conducted in Queen Elizabeth Hospital Birmingham. Data regarding patient demographics, details of GH treatment and metabolic long-term outcomes including cerebrovascular accident, type 2 diabetes mellitus, fragility fractures, myocardial infarction and mortality following GH discontinuation was collected. The reasons for GH discontinuation were analysed among patients who discontinued treatment on their own vs under clinician guidance. The incidence of long-term metabolic outcomes was compared between the 2 groups.
Results
A total of 106 patients were included. 36.8% ($n=39$) of patients discontinued GH treatment on their own accord. Among patients who discontinued GH replacement on their own, 41% ($n=16$) did not specify a reason. The patient guided treatment discontinuation group was not observed to be at increased risk of adverse metabolic outcomes compared to patients who discontinued GH treatment under clinician advice.
Recommendations
Patients should be encouraged to consult their clinician if they consider discontinuing GH treatment. Dedicated endocrine nurse support should be available to assess the appropriateness of treatment discontinuation based on patients' individual circumstances. Clear clinical protocols to facilitate the process of GH discontinuation is necessary.
Conclusion
A significant number of patients on GH replacement undergo unplanned discontinuation of treatment. It is important to establish clear clinical protocols to support and guide treatment discontinuation.

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P247

Primary ileal carcinoid presenting with metastatic ovarian tumours and florid carcinoid syndrome: a multidisciplinary care challenge

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Introduction
Ovarian metastasis from neuroendocrine tumours is rare with < 80 reported cases. We describe a case of bilateral ovarian metastases from a primary ileal carcinoid

tumour managed with somatostatin receptor agonist (SSA) therapy and surgery.
Case report
A 68-year-old lady presented with abdominal pain, distension, and episodic facial flushing. Echocardiography done to investigate left bundle branch block showed severe tricuspid regurgitation (TR) with preserved left ventricular function. Carcinoid heart disease due to carcinoid syndrome was suspected and confirmed with elevated urinary 24 h 5-HIAA excretion (310 umol/l). Chromogranin A was 377 mg/L. A diagnosis of probable primary ovarian carcinoid syndrome was made. Other causes of TR were excluded. Pelvic ultrasound showed a right ovarian mass of 5.6 cm. Serum CA-125 was 67 U/mL. CT scan showed bilateral adnexal masses, ascites, and a calcific small bowel mesenteric deposit without hepatic lesions. A multidisciplinary team involving endocrinology, gynaecologic oncology, cardiology, and anaesthesiology were involved in management. SSA therapy with Octreotide was initiated (100 mg TDS) pre-operatively and an octreotide infusion at 50-100 mg/h was used to minimise the risk of intraoperative carcinoid crisis. Staging laparotomy with bilateral salpingo-oophorectomy, ileal resection and anastomosis and removal of peritoneal disease was performed to complete cytoreduction. There were no enlarged retroperitoneal nodes. Characteristic findings included dense sclerosing fibrosis of peritoneal and retroperitoneal tissues. Histopathology showed a well-differentiated neuroendocrine tumour. Bilateral ovarian tumours, the absence of other teratomatous elements and presence of a well-differentiated NET in the ileal mesentery favoured a primary ileal tumour with ovarian metastases. Facial flushing resolved postoperatively.
Conclusion
A thorough history and clinical evaluation are critical in the diagnosis and management of unusual presentations of neuroendocrine tumours. A multidisciplinary team approach is critical to optimizing patient outcome and in anticipating and managing critical events such as carcinoid crisis.

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P248

Hypophysitis: a case report on how multidisciplinary approach aids the diagnosis and management of a rare pituitary disease with nonspecific presentations

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Introduction
Hypophysitis is the inflammation of the pituitary gland, characterised by hypopituitarism and pituitary enlargement. It can occur as primary (commonly lymphocytic, granulomatous or xanthomatous) or secondary to systemic disease, immunotherapy or sella-based pathologies.
Case presentation
A 30-year-old female was admitted to hospital with headache, fatigue, low mood and blurred vision, 3 months after having an emergency Caesarean section. Her initial bloods showed cortisol level <28 nmol/l, TSH <0.05mIU/l (0.3-5.5mIU/l), fT3-7.3 pmol/l (3.1-6.8 pmol/l), fT4-15.3 pmol/l (12-22 pmol/l), sodium 151mmol/l (133-146mmol/l). On further history taking, she complained of polyuria and polydipsia. Pituitary screen reported as ACTH <5pg/mL(10-60pg/mL), prolactin-2934mIU/l (102-496mIU/l), LH <0.5IU/l, FSH <0.5IU/l, oestradiol <50 pmol/l, IGF1 21.3nmol/l (10.2-40.7nmol/l). MRI showed avidly enhancing thickening of the pituitary infundibulum and absence of the posterior pituitary bright spot suggesting hypophysitis. Serum/urine osmolality and a water deprivation test were suggestive of cranial diabetes Insipidus. Blood tests, a Bone scan and a CT scan of the chest/abdomen showed no evidence of systemic causes of hypophysitis. Her case was discussed in the regional pituitary MDT and she was diagnosed with post-partum hypophysitis, partial hypopituitarism and cranial diabetes Insipidus. She was discharged with oral replacement dose hydrocortisone and desmopressin with plans to observe her carefully in the outpatient clinic. One month later, during follow-up, she reported worsening symptoms. Repeat MRI scan showed increasing size of the enhancing pituitary lesion involving the optic chiasm, hypothalamus and pituitary infundibulum. She was reviewed by ophthalmology and her case was rediscussed in the pituitary MDT and where her diagnosis of hypophysitis remained unchanged. She responded well to high-dose prednisolone, an oestrogen patch and levothyroxine to treat secondary hypogonadism and hypothyroidism.
Conclusion
Hypophysitis is a rare disease with non-specific clinical, pathological and radiological presentations. MDT approach is the key in diagnosis and management of hypophysitis patients.

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P249

Beyond the run: Loperamide's toll on the pituitary gland

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A 76-year-old lady with a background of Crohn's disease (ileostomy in 1991) was referred to endocrinology in March 2022. Her 9-am cortisol level was <50 nmol/l, with a sodium of 130 mmol/l. These were done as she reported tiredness, lethargy and dizziness since November 2021. She had also lost 7 lb of weight. No evidence of hyperpigmentation. She had then been empirically started on hydrocortisone (10 mg-morning, 5 mg-afternoon and 5 mg-evening) pending evaluation of her pituitary function. It was initially believed that the chronic use of steroids in the past (for her Crohn's) may have caused the adrenal insufficiency. Anterior pituitary profile done at 9-am showed a random GH of 0.9 μg/l, IGF-1 of 18.7 nmol/l, TSH of 2.1 mIU/l, FT4 of 8.6 pmol/l, normal prolactin, FSH of 0.3 IU/l, LH <0.3 IU/l, cortisol <50 nmol/l, and ACTH <5 ng/l, with a normal MRI pituitary. Based on these tests, she was labelled as idiopathic hypopituitarism, and the hydrocortisone was continued (the dose subsequently altered to 5 mg TDS following a cortisol day curve). Levothyroxine was added. In the clinic, reconciliation of her medications revealed her to be on codeine since 2003 and loperamide (structurally similar to opioids) since 1998-both prescribed to control her stoma output. Since many years, she had been on 120 mg/day of codeine (equating to a daily dose of 12 mg of morphine), and 16 mg/day of loperamide. She was asymptomatic, with her only issues being stoma-related. ≥16 mg/day of loperamide has been shown to suppress ACTH. Opioids suppress the release of the GnRH and CRH. In the absence of a structural pituitary abnormality, it was postulated that the hypopituitarism was secondary to chronic usage of loperamide, exacerbated by chronic codeine use.

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P250

Hypophysitis secondary to monoclonal antibody treatment

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Background
Immunotherapy has become one of the standard interventions to treat various malignancies and auto-immune conditions with favourable responses to the treatment. However, the immune related adverse events of these medications are diverse which may include a variety of endocrinopathies, like Hypo cortisol, Hypophysitis, hypo and hyperthyroid states.
Case Report
A 62 year old female with a background of Metastatic Malignant Melanoma on Combination Immunotherapy with Ipilimumab and Nivolumab (completed Immunotherapy First Cycle in June 2022, second cycle in 3rd Week of July 2022) attended routine phlebotomy clinic in end of July 2022 when she was found to be unwell. Patient had been muddled and extremely lethargic for 2 weeks, and also had complaints of anorexia, generalised fatigue and body pain for the same duration. Blood investigations revealed a low cortisol level of 102 and an in appropriately Low paired ACTH of < 5, low TSH (0.10) and T4 (10.8). The patient was immediately commenced on Hydrocortisone, treated with fluids. MRI of the pituitary revealed that the pituitary gland is not enlarged and enhances uniformly. The pituitary stalk is central with no abnormal enhancement. Patient improved clinically with the treatment and was discharged with Oral Hydrocortisone, and Hydrocortisone Emergency kit with a follow-up in the endocrine clinic, when patient was initiated on Fludrocortisone to manage her symptoms.
Conclusion
Immunotherapy related Endocrinopathies are being seen increasingly in clinical practise. It is seen most commonly in the first few months after initiating the treatment, and it is important for the clinicians involved in the patient care to monitor the patients receiving treatment closely with appropriate laboratory investigations which may include thyroid function tests, early morning cortisol levels along with regular follow-up after initiation of immunotherapy to promptly recognise any possible immunotherapy mediated endocrinopathies while patients are on Ipilimumab and Nivolumab.

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P251

Severe arginine vasopressin resistance (nephrogenic diabetes insipidus) secondary to lithium requiring intensive care admission

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Arginine vasopressin resistance (AVP-R) (previously termed nephrogenic diabetes insipidus) is well known to be associated with lithium treatment. However, cases are usually mild and patients can almost always compensate for their polyuria with excessive fluid intake. We present the case of a moribund patient who required intensive care admission secondary to AVP-R, developing hypernatraemia to 183mmol/l and serum osmolality of 394mmol/kg. A 68 year old gentleman, on lithium treatment for bipolar disorder, presented with an acute kidney injury and lithium toxicity. At this point he was compos mentis, and after being treated with intravenous fluids, his renal function and lithium levels improved. However, his sodium level rose, and, in the subsequent days, he significantly deteriorated, suffering from polyuria and polydispia. His GCS dropped as low as 8, and at this point his condition rapidly worsened, developing worsening hypernatraemia with a sodium of 183 and serum osmolality of 394mmol/kg. The diagnosis of lithium induced AVP-R was recognised upon discussion with endocrinology, and his intravenous fluid regime intensified, with rapid administration of 5% dextrose. He was transferred to intensive care immediately, and administered desmopressin intravenously, requiring doses up to 3micrograms. At its greatest, his fluid intake and urine output exceeded 6L over 24 h. His condition gradually improved over the next few days, with careful management of his fluid balance, titration of desmopressin and reduction in serum sodium to normal. His cognitive state returned to baseline and, after a short period of rehabilitation and monitoring, was discharged home on 100micrograms TDS of oral desmopressin with psychiatric follow up for initiation of an alternative mood stabiliser. From a review of the literature, there have been very few documented cases of AVP-R secondary to lithium as severe as this.

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P252

A rare presentation of cushing's disease with aortic dissection- a case report

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Key words- Cushing' Disease, Aortic Dissection

Background

Cushing's syndrome is a rare endocrine disorder. It is frequently presented with obesity, type 2 diabetes, or hypertension with an increased cardiovascular risk. The association of Cushing's syndrome with aortic dissection is rare. We report a young man who presented with hypertensive emergency and aortic dissection. He was later found to have Cushing's disease.

Case Report

A 42-year-old male presented to the GP with stage 3 hypertension and was started on antihypertensive. Two months later, he presented with severe chest pain and noted to have differential blood pressure on arms. The CT angiogram showed Type A dissection of the Ascending aorta. He underwent urgent surgical repair of the dissection. As he had Cushingoid features, he was referred to Endocrinology. His BMI was 29.2 kg/m2 and had typical features of Cushing's Syndrome. He had a non-suppressed overnight dexamethasone suppression test (Cortisol 91 nmol/l), high 24-h urine cortisol (368 nmol/24h), and a non-suppressed low dose of Dexamethasone suppression test (cortisol 196 nmol/l). The ACTH measurement of 52ng/l confirmed ACTH dependant Cushing's. MRI pituitary showed a microadenoma measuring 6mm, confirming the diagnosis of Cushing's disease. He was diagnosed with osteoporosis. His glucose tolerance test was normal. He is awaiting further management.

Conclusion

Aortic dissection is a rare cardiovascular manifestation of Cushing's syndrome with high mortality. A high index of suspicion for secondary hypertension in a young person with high blood pressure is required. Early detection of Cushing's syndrome is the key to reduce the cardiovascular and metabolic risks associated with the disease.

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P253

Young male presented with primary hyperparathyroidism secondary to Multiple Endocrine Neoplasia type 1 syndrome

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MEN1 is a rare hereditary tumor syndrome characterized by a predisposition to a multitude of endocrine neoplasms primarily of parathyroid, enteropancreatic, and anterior pituitary origin and non endocrine tumor. Here we will discuss a case of 36 yrs. old male who was referred for high calcium on routine blood test. Subsequent investigations confirmed primary hyperparathyroidism. His serum calcium level was 2.71, PTH 7.5 Pmol/l, and vitamin D 57.4 nmol/l on presentation and was referred to geneticist He is a smoker and his mother was diagnosed with metastatic bronchial carcinoid tumor. Clinically, he was asymptomatic. PMH: includes hypertension which was controlled with amlodipine and Ramipril. Clinical examination was unremarkable with BP 140/80 mmhg. Follow up blood test after one year showed IGF 1 30.5 nmol/l, FSH 5.4 iU/l, LH 2.0 iU/l, testosterone 6.3 nmol/l, SHBG 15 nmol/l, prolactin 390 mU/l, Adjusted calcium 3.03 mmol/l, PTH 6.6 Pmol/l, Phosphate 0.89 mmol/l, and EGFR $>$90 ml/min. Subsequently genetic was advised by geneticist which showed MEN1: Presence of familial pathologic variant in MEN1 c.76G$>$T. Full surveillance of MEN1 was advised in genetic clinic. Subsequently MRI pancreas, abdomen, and thorax showed Couple of small foci of DWI high signal within pancreatic tail. Pancreatic protocol CT +- Endoscopic ultrasound was suggested which showed within pancreatic tail there was approximately 1-1.2 cm enhancing lesion—appearances were consistent with small neuroendocrine tumour. MRI pituitary showed no pituitary gland lesion. Further biochemical tests including gut hormone profile and octreotide scan is still waiting. This case illustrates the importance of screening for MEN1 in young patient with hypercalcemia related to primary hyperparathyroidism with positive family history of MEN1 related tumors. Early surveillance with regular biochemical test and imaging can help early diagnosis of MEN1 related tumor and reduce morbidity/mortality.

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P254

Oral contraceptive pill (yasmin®) can partially suppress ACTH secretion in addison's disease

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Background

ACTH concentrations remain typically elevated in patients with Addison's disease. We present a case of an extremely potent oral contraceptive pill (OCP) induced increase in total cortisol resulting in inhibition of ACTH secretion that was normalized on OCP withdrawal.

Case Presentation

A 20-year old female was diagnosed with Addison's disease [cortisol 1.59 μg/dl, ACTH$>$500 pg/ml (0-65)] and started on hydrocortisone. Few months later an OCP (Yasmin®) was added. She still felt unwell, so further tests were performed. Her cortisol day curve (hydrocortisone 15 mg (8 am) + 10 mg (15.00)) showed several cortisol concentrations above upper assay detection limit [e.g. cortisol 8:00 (pre-dose) 3.0 μg/dl, 10:00$>$63,44 μg/dl] with low ACTH concentrations [e.g. ACTH 8:00 (pre-dose) 24.1 pg/ml; 10:00 - 3.8 pg/ml]. Even 5 mg hydrocortisone induced a massive increase in cortisol [cortisol pre-dose: 1.7 μg/dl, post-dose 30min. $>$63.44 μg/dl, 60min. $>$63.44 μg/dl]. CRH test showed stimulation of ACTH far below concentrations observed in Addison's disease, suggestive of partial hypothalamic suppression of CRH release: ACTH -15min. 42.4 pg/ml, 0min. 44.5 pg/ml, 15min. 63.3 pg/ml, 30min. 87.3 pg/ml, 60min. 76.3 pg/ml, 90min. 58.0 pg/ml, cortisol concentrations $<$2.5 mg/dl at all time-points. Withdrawal of an OCP resulted in normalisation of ACTH secretion with ACTH concentrations typical for patients with Addison's disease on hydrocortisone replacement: e.g. cortisol 8.00 $<$0.054 [ug/dl], ACTH 924.7 [pg/ml], cortisol 10:00 7.3 μg/dl, ACTH 10:00 181.6 pg/ml.

Conclusions

Effects on an OCP on total cortisol concentrations are often underestimated, as an OCP-induced increase in total cortisol can inhibit CRH and ACTH release even in patients with Addison's disease. An assessment of an adrenocorticotropic axis may be invalidated if a patient is taking an oral contraceptive pill.

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P255

A "never" event case of hyponatraemia

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An NHS Patient Safety Alert in 2016 warned "Risk of severe harm or death when desmopressin (DDAVP) is omitted or delayed in patients with cranial diabetes insipidus". Endocrinologists added "It (DDAVP) needs to be continued in all situations with the assistance of endocrine teams".

Case report

A 63 year old male was referred with a sodium of 116 mmol/l following a re-do hip replacement 2 weeks earlier. A progressive decline in sodium levels from normal had occurred over the post-operative period. Cushing's disease diagnosed by us 20 years earlier was treated with radiotherapy (37.5 Gy in 15 fractions) following failed pituitary surgery. ACTH had decreased but remained elevated. Moderately severe diabetes insipidus (urine volumes 6.8-9.7 L/24h) was also confirmed. Follow-up was elsewhere. Examination found him to be unwell, confused and hypotensive receiving intravenous antibiotics and DDAVP 100 mg bd orally. The impression formed was one of profound worsening hyponatraemia due to (1) Remnant endogenous SIADH secondary to stress/infection superimposed on diabetes insipidus (2) Secondary hypoadrenalism secondary to previous pituitary radiotherapy with impaired free water clearance (3) A combination of (1) and (2). Investigations prior to treatment (at 17:00h) confirmed sodium 115 mmol/l and cortisol 100 nmol/l. An add on (09:00h same day) cortisol was 93 nmol/l. DDAVP was stopped and administration of intravenous normal saline/hydrocortisone normalised sodium over 64 h with symptomatic improvement. Case review led to: a plan to identify DDAVP treated patients and to provide them with a DDAVP card; hospital pharmacists to inform the endocrine team of DDAVP treated patients on admission; and education for clinical staff on the DDAVP patient safety alert. This case confirms the need for early endocrine input to patients with cranial diabetes insipidus and that DDAVP should be continued in most, but not all, patients.

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P256

Acromegaly with normal phenotype?

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Introduction

More than 95% of cases of Acromegaly are caused by pituitary adenomas that present with insidious onset of symptoms due to local mass effects or due to excess of GH/IGF-1. It is often diagnosed late and results in high morbidity and mortality.

Case

We present a case of a woman in her fifties with atypical presentation of acromegaly with a left sided headache for 2 years with no associated visual symptoms and fatigue. She only had a past medical history of type 2 diabetes and hypertension. On examination, she had a short stature with normal facial features, no gross phenotypical abnormalities s and her visual fields on confrontation were unremarkable.

Investigations

MRI scan of the pituitary gland showed a 1cm enhancing nodule in the left lateral aspect of pituitary gland consistent with a pituitary adenoma. Her anterior pituitary screen were within normal range other than an isolated raised IGF-1 49.7 nmol/l which, along with the MRI findings, raised the suspicion of possible Acromegaly. He OGTT was diagnostic at 60 min non suppression of GH levels as well.

Management and Discussion

This patient was referred for trans sphenoidal surgery (TSS) under neurosurgery as her pituitary lesion was a surgical target. TSS has been the definite treatment of choice in this cohort of patients. We recognize that the mainstay of treatment for pituitary adenomas can be either pituitary surgery, medical therapy for residual disease or radiotherapy. All these decisions must be undertaken under an MDT setting to achieve better outcomes. This patient highlights the importance of exercising a high degree of suspicion for early detection of Acromegaly which can sometimes present with vague symptoms. Over all benefit would be better long term outcomes of this high risk group of patients with active disease.

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P257

A complex case of Acromegaly, resistant to treatment & discovered during pregnancy; A regional, collaborative approach

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Background

Acromegaly is a rare Endocrine condition caused by excessive secretion of growth hormone; in 2022, there were approximately 3500 people with a known diagnosis in the UK. Patients with Acromegaly can achieve successful remission of the disease with medical therapy, pituitary surgery and radiotherapy (sometimes a single treatment, sometimes combination). However, these treatment options have associated risks, including side effects, late effects of radiotherapy and poor surgical outcomes. To further complicate matters, Acromegaly can be resistant to these treatment options, increasing the risk of increased morbidity and mortality.

Case Study Subject

We present a case of Acromegaly in a 24 year old female, during her first pregnancy. She initially presented in A&E (Derby) with severe headaches in December 2019, along with disturbed vision in her right eye and partial ptosis; interestingly she had also noticed an increase in her shoe size over several months, which prompted investigation and led to a diagnosis of Acromegaly. This complex case was managed during the highly challenging time of Covid19, through a collaborative approach of multiregional centres (Derby, Nottingham, Sheffield, Oxford), whilst the majority of care was provided by her local hospitals (Derby and Nottingham). We will review the evidence for best practice and the processes used to achieve reduction of growth hormone and IGF1 levels, remission of Acromegaly and reduced risk factors to mother and child (resulting in a successful birth and improved prognosis).

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P357

An endocrine cause of diabetes remission

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29 year old African lady with a background of PCOS and type 2 diabetes, who was under the care of preconception clinic, presented to A&E with sudden onset headache associated with spontaneous closure of right eyelid. CT brain was suggestive of pituitary fossa lesion and pituitary MRI revealed pituitary necrosis. She was diagnosed with pituitary apoplexy and was commenced on appropriate hormone replacement. Examination revealed right complete third nerve palsy and reduced visual acuity in the right eye. BMI was 22.5 kg/m2 and there was no other focal neurological deficit. Blood tests revealed a random cortisol of 1548 nmol/l, free T3 was 2.3 pmol/l, free T4 was 832 pmol/l, TSH was 2.8 mIU/l and prolactin of 36 mU/l. Beta HCG was undetectable. The patient was transferred to a neurosurgical centre and had transsphenoidal surgery of the pituitary gland. Diabetes medications were discontinued on discharge. HbA1C done at 3, 6 and 12 months post the episode had levels <40 mmol/mol off diabetes medications and suggestive of remission. The patient was investigated in an endocrine clinic (3 years prior to the episode) for PCOS and had random cortisol checked as part of the work up panel. This was found to be 1,500 ng/l. She did not attend subsequent appointments to investigate this and was discharged. She was consistently seen in diabetes clinics and treatment was intensified to aid preconception with mixed insulin. Histology revealed a corticotroph adenoma, suggesting undiagnosed Cushing's disease. The apoplexy resulted in resolution of Cushing's disease causing diabetes remission.

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P358

Copy number variation (CNV) in self-limited delayed puberty (SLDP)

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Self-limited delayed puberty (SLDP) is characterized by an onset of puberty that is more than 2-2.5 standard deviations later than the population mean age and is often familial with strong genetic determinants. The reproductive axis is regulated by gonadotropin-releasing hormone (GnRH), which plays a crucial role in

initiating puberty and maintaining fertility through its pulsatile secretion. Disruption in GnRH neuron development or hypothalamic function can lead to delayed puberty (DP). UK Biobank data has identified negative health outcomes associated with SLDP including early menopause/andropause and cognitive and psychosocial disabilities. Consequently, there has been extensive research to investigate genes affecting the hypothalamic-pituitary-gonadal (HPG) axis that might be implicated in the pathogenesis of DP by our group and others which has identified sequence variation contributing to the aetiology of SLDP. However, factors beyond nucleotide variations, such as epigenetic changes and CNVs can also lead to pubertal timing disorders. Moreover, CNVs are seen in multiple individuals ($n=92$) from the Deciphering Developmental Disorders study (https://www.deciphergenomics.org) with a phenotype including DP (HP:0000823). We performed whole genome sequencing on 49 probands with SLDP and subsequently, analysed the data for CNV. The data was initially called, annotated, filtered then partitioned for classification of CNVs using a command-line tool that implements the American College of Medical Genetics and Genomics (ACMG) guidelines to evaluate the pathogenicity of germline duplications and deletions. Using an unbiased candidate gene approach, we identified several deletions that affected 60 known/predicted dosage sensitive genes combined with functional enrichment analysis. This revealed potential molecular pathways involved in the pathogenesis of SLDP, including histone acetylation, and neural plate development. This study highlights the role of CNVs in SLDP and expands our understanding of the biological processes involved in this condition, shedding light on the complex mechanisms underlying DP.

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P359

Prescription profile of narrow therapeutic index medications used in pediatric endocrinology

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Introduction
According to the FDA, narrow therapeutic index (NTI) medications are those in which small differences in dosage orblood concentration can lead to serious therapeutic failures and/or adverse reactions that can endanger the patient's life or result inpersistent or significant disability or incapacity. A literature not have studies about used this medication use in endocrinology pediatric population. OBJECTIVE: Establish the prescription profile of narrow therapeutic index medications used in pediatric endocrinology in patients included General Health System of Colombia between January 1st and December 31st, 2021.
Materials & Methods
Descriptive cross-sectional study. Convenience sampling collect data from the dispensing database of a pharmaceutical manager in Colombia for patients under 18 years old who received narrow therapeutic index medications included in the DrugBankdatabase between January 1st and December 31st, 2021. This research was classified as a no-risk investigation approval from CEISH with the code 0405-2022. Regarding the analysis plan, univariate analysis was performed for qualitative variables, which were described using measures of absolute and relative frequency.
Results
For the period between January 1st, 2021, and December 31st, 2021, medications were dispensed to 777,924 pediatric patients of 24,053 received narrow therapeutic index medications, prevalence of 3.09%. Regarding the ATC category for endocrinology, 13.86% ($n=$ 3480) used thyroid therapy, 0.17% ($n=$ 43) other gynecologicals, 0.04% ($n=9$) endocrine therapy and 0.02% ($n=4$) lipid modifying agents. Regarding the molecules, out of the 254 medications registered in DrugBank, 56 medications were dispensed to the pediatric population, of which 5 are used in endocrinology. The most commonly dispensed medication was Levothyroxine, accounting for 14.5% ($n=3480$) of the patients, followed by 0.2% ($n=43$) Cabergoline, 0,03% ($n=9$) Tamoxifen, 0.02% ($n=4$) Lomitapide and 0.01% ($n=1$) Bicalutamide
Conclusion
Out of 254 narrow therapeutic index medications registered worldwide, 5 are used in endocrinology and were dispensed to the pediatric population.

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P360

A 3D neurosteroids atlas of mouse brian using mass spectrometry imaging

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Neurosteroids are synthesized locally within the central nervous system and play essential roles in modulating neuronal activity and various brain functions. They can have a wide range of effects, including anxiolytic, sedative, analgesic, and neuroprotective actions. Understanding their distribution in the brain and how they interact with neurotransmitter systems is of significant interest to researchers studying brain function and related disorders. We aim to construct a 3D atlas of a panel of neurosteroids to uncover the complex network of functions of neurosteroids in the mouse brain. Mass spectrometry imaging (MSI) is a powerful bioimaging tool that combines mass spectrometry with spatial information to three-dimensional maps of the distribution of molecules within a sample with direct histopathological correlation. Matrix assisted laser desorption ionisation (MALDI)-MSI was used to create distribution maps of neurosteroids, with 100 and 150 μm spatial resolution, from brains of 56-days-old male and female C57BL/6 mice. Serial sagittal 10μm cryostat brain sections were collected at around 200 μm intervals across the right hemisphere from cortex to midline. On-tissue chemical derivatisation with Girard-T reagent was applied to enhance the signal sensitivity of detection of neurosteroids containing keto functional groups. MSI data were collected on Bruker-12T-SolariX-Fourier-transform–ion-cyclotron-resonance (FT-ICR)-MS. Estrone, androstenedione, 7aOH-DHEA, progesterone, 17aOH-Progesterone/11-deoxycorticosterone, 11-dehydrocorticosterone and corticosterone were detected in brains from both sexes, mainly localised in cortex, hippocampus and cerebellums. Z-Stacking of sequential MSI plates allow generation of 3D models. Future work includes MSI data alignment and co-registration with the 20 Allen Mouse Brain Reference Atlas. This will be made publicly available via interactive webpages to allow precise anatomical annotations to search and visualise concentrations of individual neurosteroids in different areas of the mouse brain.

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P361

Unusual presentation of suprasellar lesion with adrenal crisis/pan-hypopituitarism but raised tsh

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A 44 years old lady with history of suspected psychogenic polydipsia (2021), presented with acute on chronic abdomen pain. She complained of lethargy, intermittent vomiting, abdomen pain, weight loss (four stones) over last six months associated with confusion and visual hallucination since two weeks. She mentioned feeling always thirsty and drinks around 4-5 litres of water per day. Her blood pressure was 87/61 mmHg, heart rate 74/min and U&Es were normal (serum sodium 140 mmol/l, potassium 3.7 mmol/l, urea 3.0 mmol/l and creatinine 76 umol/l). The CT abdomen was normal but the CT head showed new supra-sellar lesion (20x 14 mm) involving optic chiasm, pituitary stalk. The pituitary work up showed very low cortisol at 43 nmol/l, suppressed gonadal axis, with raised TSH at 9.19 mu/l, low FT4 of 5.0 pmol/l and raised prolactin at 3459 miu/l. She was started on injection hydrocortisone 100 mg qds and tab levothyroxine 100 mg was started after three days. The MRI head confirmed bright supra-sellar lesion (19x18x10 mm) inseparable from optic chiasm and pituitary stalk. After two days of receiving hydrocortisone injection she had clinical (had polyuria) and biochemical evidence of diabetes insipidus (serum osmolality 308 mosmol/kg, serum sodium 149 mmol/l, urine osmolality 287 mosmol/kg) hence tablet desmopressin 100 mg twice daily was started, following which polyuria resolved and serum sodium level improved.
Conclusion
- A high index of suspicion is required to identify adrenal crisis
- Patients with adrenal crisis along with diabetes insipidus may not have hyponatremia.
- Steroid replacement could unmask central diabetes insipidus, hence close input output monitoring and daily U&Es needed.
- Raised TSH and low FT4 in context of supra-sellar lesion, should still be considered as central hypothyroidism, as the raised TSH likely reflects the biologically inactive form.

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P362

Pituitary adenomas- a retrospective review of a health board's experience

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Background
Pituitary adenomas are broadly classified based on size (microadenomas and macroadenomas) and functionality. While their management has established national and international guidelines based on these two classifications, we aim to evaluate the same in a post-pandemic era, when health care resources are already stretched and have a significant backlog to deal with.
Aim
To carry out a retrospective analysis of all pituitary adenomas diagnosed in the Aneurin Bevan University Health Board (ABUHB) area with a catchment population of 600, 000 between January 2021 to June 2023.
Method
In a retrospective observational study all Pituitary adenomas diagnosed during this between Jan 2021 – June 2023 were identified for detailed analysis from a database of all MRI scans of Pituitary performed over the same period.
Results
A total of 79 MRI pituitary scans were done during the period established above, identifying 56 patients with pituitary adenomas. 29 of these 56 patients were found to have new pituitary adenomas, and were reviewed in-depth via case notes, as the other 27 already had established management prior to the pandemic.
The Incidence of Pituitary tumours within the Gwent area is 0.5/100,000 population.

Microadenomas	8/29
Macroadenomas	21/29
Referred to Regional Pituitary MDT	12/29
Average Duration from referral to evaluation by MDT	23.4 days
Hormonal Dysfunction-	24/29
1. Prolactinomas	13
2. Secondary Hyperthyroidism	8
3. Hypogonadism	2
4. Acromegaly	1

Conclusion
Our findings indicate a growing incidence rate of Pituitary adenomas in the last decade, due to the increased percentage of Incidentalomas identified with the rising volume of requests for Brain and Pituitary imaging and the impact of the delayed tests from the effect of the recent Covid Pandemic. Our study also demonstrates that referrals to the Regional Pituitary MDT were appropriate.

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P363

Hindering the progression of cardiac fibrosis in acromegaly – the role of somatostatin receptor ligands

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Introduction
Acromegaly links to cardiomyopathy and potential cardiac failure, if untreated. Mechanisms involved in acromegalic cardiomyopathy are incompletely understood. We investigated the effects of growth hormone (GH) excess and somatostatin receptor ligands (SRLs) on cardiac fibrosis using an acromegalic mouse model with pituitary-specific deletion of the Aip gene coding aryl hydrocarbon receptor interacting protein ($Aip^{Flox/Flox}$;$Hesx1^{Cre/+}$), causing early-onset acromegaly characterised by GH-secreting tumours, greater body weight, and elevated IGF-1 levels.
Materials and Methods
Heart samples were collected from pituitary-specific *Aip* knockout (KO, $Aip^{Flox/Flox}$;$Hesx1^{Cre/+}$) and littermate control (WT) mice at 3, 6, 9, 12, and 15 months ($n=54$). Another group of KO animals received monthly subcutaneous injections from age 3-month of either long-acting octreotide (30μg/g body weight; $n=6$), pasireotide (60μg/g; $n=7$), or vehicle control ($n=6$). Cardiac interstitial and perivascular fibrosis were assessed by picrosirius red staining and QuPath scoring.
Results
Heart fibrosis, both interstitial and perivascular, was significantly higher in KO mice compared to age-matched control. The extent of interstitial cardiac fibrosis in KO mice was gradually increasing and reached statistical significance from as early as 3-months-old (mean ± SEM: KO 1.73 ± 0.46% vs. WT 0.19 ± 0.09%, $P<0.01$). Perivascular fibrosis in KO mice started increasing at 3-months-old and reached significance at 6-months-old (KO 4.28 ± 0.34% vs. WT 1.07 ± 0.09% ($P=0.01$). These significant differences persisted at 15-months-old in both groups. In SRL-treated KO animals, octreotide significantly reduced interstitial fibrosis compared to the control group (1.73 ± 0.16% vs. 0.99 ± 0.25, $P=0.04$), and revealed a trend in reducing perivascular fibrosis ($P=0.08$), while pasireotide did not reduce fibrosis.
Conclusion
Acromegalic mice showed progressive intracardiac fibrosis over time. Direct effect of SRLs on cardiac tissue, probably through somatostatin receptor 2, as well as hormonal effects on GH/IGF-1 play a role in the treatment effects on the heart. Octreotide represents a promising approach in delaying interstitial and perivascular fibrosis.

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P364

Audit of compliance with NICE TA64 on prescribing growth hormone treatment in adults at the queen elizabeth hospital, birmingham

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Adult growth hormone deficiency (AGHD) is a metabolic syndrome characterised by osteoporosis, increased visceral fat, adverse lipid profiles, decreased muscle mass and reduced energy levels. As such, it is associated with reduced quality of life (QoL) and increased mortality from cardiovascular disease. Synthetic growth hormone (GH) can be given to replace natural GH; however, treatment is costly at around £3350 per patient per year and could cause side effects including myalgia, fluid retention and carpal tunnel syndrome. NICE therefore limits its use to strict criteria outlined in the technology appraisal TA64. To commence treatment, patients must meet three criteria: have a severe GH deficiency (ITT < 3ng/ml or similar test), be treated for co-existing pituitary hormone deficiencies, and if > 25 years have an impaired QoL (QoL-AGHDA score ≥ 11). The guideline further states that treatment must be stopped in patients > 25 years after 9 months if there is an insufficient QoL improvement (< 7 points QoL-AGHDA). This audit aimed to assess compliance with NICE TA64 at the Queen Elizabeth Hospital, Birmingham between January 2017-December 2021 and identify areas for improvement. Data was collected retrospectively using the trusts electronic records system. Of the 74 patients started on GH, 96% met the criteria for initiating GH. This was likely driven by the need for external verification of the criteria for drug funding. Of patients > 25 years of age ($n=47$), compliance with the re-assessment of QoL following a 9-month GH trial was low, with 68% completing the questionnaire but only 32% completing it within 9 months. Although COVID-19 could have caused disruptions, improvement is needed to prevent potential side effects and costs associated with unwarranted medication. There could be scope for the questionnaire to be completed during face-to-face follow up clinics rather than emailed questionnaires (particularly in patients with reduced access to technology).

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P365

Suboptimal treatment of acromegaly potentially leading to onset and progression of B cell lymphoma

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Acromegaly is a rare endocrine disorder mostly caused by a growth hormone (GH)-secreting pituitary adenoma. The aim of treatment is to normalize GH/IGF1 levels to limit disease burden. Growth hormone hypersecretion is associated with an increased cancer risk; cases of Acromegaly complicated by lymphoma have

been reported. We share a clinical case characterized by suboptimal treatment, potentially leading to advancing orbital lymphoma. This 49-year-old man was diagnosed with Acromegaly secondary to a pituitary macroadenoma in 2018. He was treated with Octreotide LAR and Cabergoline as the tumour was initially deemed unresectable. GH hypersecretion was seemingly controlled with averaged normal IGF1. The patient retained physical signs of Acromegaly and developed progressive cardiometabolic complications. Interestingly, a concomitant but unclear diagnosis of orbitopathy was made. In 2018 an MRI scan showed diffuse soft tissue infiltration involving both orbits however this was not followed up. At our department, in 2022, the patient underwent a pituitary and orbit MRI, showing a pituitary macroadenoma extending into the right cavernous sinus, and progression of disease in the left orbit, threatening the optic nerve. A colonoscopy and echocardiogram identified a benign tubular adenoma and left ventricular hypertrophy, respectively. Following MDT discussion, pituitary surgery and orbital biopsy were performed. Histology confirmed a somatotroph adenoma. The orbital biopsy was highly suggestive of B cell lymphoma; a total body CT was unremarkable apart from a left adrenal incidentaloma. Adrenal biochemistry and MEN screen were normal. This is an intriguing case where potentially curative treatment was delayed which may have led to progressive cardiometabolic complications and malignancy. A growing collection of case reports have reported an association between Acromegaly and Lymphoma, especially with the B cell subtype. This clinical case highlights the importance of prompt treatment and supports a link between Acromegaly and B cell lymphoma.

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P366

MGMT and MSH2 immunohistochemistry status identifies a pituitary tumour subgroup with excellent progression free survival response to temozolomide: a single centre case series

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Temozolomide has an established role as first line chemotherapy for aggressive pituitary adenoma and carcinoma. There are mixed reports whether the MGMT (methylguanine methyltransferase) and mismatch repair protein (MSH2/6) status of a tumour, assessed by immunohistochemistry (IHC) can predict response to temozolomide. This is the first series to assess combined MGMT and MSH2 status. We analysed a retrospective case series of patients treated with temozolomide at our tertiary pituitary service (2009-2022). We assessed the radiological (RECIST) response to temozolomide treatment and correlated it with the MGMT and MSH2 immunohistochemistry.

Results

22 patients treated were included in the study. 73% of patients (16/22) had a good radiological response to temozolomide (1 complete response, 14 partial response, 1 stable disease). The remaining 6 patients had progressive disease, 5/6 now deceased. Immunohistochemistry (IHC) MGMT and MSH2 status demonstrates that 10/22 patients were MGMT positive, 16/22 patients were MSH2 positive. Analysis of the subgroup who are MGMT negative and MSH2 positive showed 100% (11/11) good radiological response. Conversely the remaining 11 patients with other IHC profiles show a significantly worse response rate 45% (5/11) (Fisher exact test $P=0.0053$). The progression free survival analysis (Kaplan-Meier plot) shows significantly better survival for the MGMT negative MSH2 positive group ($P<0.001$).

	MGMT Negative (<10% IHC)	MGMT Positive (≥10% IHC)	Total
MSH2 Positive (>50%)	100% response (11/11)	40% response (2/5)	16
MSH2 Negative (≤50%)	0% response (0/1)	60% response (3/5)	6
Total	12	10	22

Conclusion

The case series identifies a pituitary IHC subgroup (MGMT negative, MSH2 positive) expected to show a favourable response to temozolomide. This finding will assist treatment sequencing and timing decisions. Unfavourable IHC profiles may, in future, be offered alternative combination treatments. We recommend that aggressive pituitary tumours have prospective histopathological assessment of MGMT and MSH2/6.

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P367

Multisystem Langerhans cell histiocytosis presenting in adulthood. Don't forget the mouth!

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Background

Langerhans cell histiocytosis (LCH) is an uncommon myeloproliferative disorder characterised by inflammatory lesions and accumulation of histiocytes leading to the destruction of affected tissues. LCH has a variable presentation and can occur as a single indolent lesion or can affect multiple organs such as the pituitary gland, bones, CNS, liver, lungs, lymph nodes, spleen, skin, heart and gastrointestinal tract. LCH of the pituitary gland most commonly presents with arginine vasopressin deficiency (AVP-D).

Case presentation

A 61 year old lady presented to dermatology in 2017 with two vulval lesions which were excised. Histology confirmed LCH. 16 months later she presented to endocrinology with an 8 month history of thirst and polydipsia. Her water deprivation test was consistent with AVP-D and pituitary MRI showed thickened pituitary stalk. Desmopressin was commenced. On recommendations of the specialist histiocytosis centre, oral mucosa and teeth were carefully examined. A history of intermittent oral ulcerations affecting the mouth floor, tongue and gingiva was elicited. Oral mucosa biopsy confirmed LCH leading to a diagnosis of multisystem disease. FDG PETCT revealed avid foci within the iliac bone and cervical lymph nodes progressing to multiple bone sites during follow up. She was managed with Prednisolone, Mercaptopurine and Methotrexate, the latter stopped after a severe chest infection. In 2020 she developed secondary hypogonadism and osteopenia. Attempted taper of medications in 2022 was unsuccessful leading to disease relapse.

Discussion

Multisystem LCH in adults is rare. There is no consensus on the optimal treatment and most of our understanding and management is derived from paediatric literature. Our case illustrates the course of the disease over a six year period and the importance of thorough oral examination that can reveal multisystem involvement necessitating systemic therapy. LCH should be considered in patients presenting with AVP-D with a history of recurrent oral or vulval ulceration.

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P368

Every blood clot has story to tell

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35-year lady with BMI of 43 was admitted to local hospital after acute shortness of breath. History of Right calf pain and swelling was evident which raised suspicion of VTE with high likelihood of Pulmonary Embolism. Subsequent CT Pulmonary Angiogram confirmed the same with origin of clot from her leg DVT. She had successfully thrombolysis in intensive care as per hospital protocol. Her high body mass index was thought to be risk factor for blood clots. Her periods were regular and Inpatient pregnancy test was negative. Covid swab was negative. Routine biochemistry revealed persistent high sodium level. In patient blood glucose levels were normal. She was discharged home after intravenous fluids, analgesics and advised to continue Rivaroxaban for 6 months. OP follow up sought by patient herself due to persistent nocturia and polydipsia. Her main concern was Diabetes. Detailed history revealed frequent headache episodes and disturbed sleep due to nocturia. Her serum sodium level was consistently above 160 with total urine output ranging from 8-9 litres. Fasting urine osmolality revealed her inability to concentrate urine with strong suspicion of Central Diabetes Insipidus. We started her on oral Desmopressin, the dose of which was titrated upwards on follow up visits. Rest of anterior pituitary hormonal profile was satisfactory. MRI pituitary scan was consistent with lymphocytic infundibular neurohypophysitis.

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P369

The Natural History of Clinically Non-functioning Pituitary Macro-adenomas (NFPAs) managed conservatively

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Transsphenoidal surgery is the first-line treatment for non-functioning pituitary macroadenomas (NFPAs) causing pressure symptoms. However, the approach to asymptomatic NFPAs is unclear due to the limited data on their natural progression. This study retrospectively analysed data from patients with NFPAs who underwent conservative management for at least six months. The study screened 175 individuals treated at the National Neurosurgery/Pituitary Centre at Beaumont Hospital between 2010 and 2020. Following screening, 90 patients met the inclusion criteria, encompassing a minimum of six months of conservative management, diagnosis of NFPA exceeding 1cm in size, and adequate follow-up. The mean age of the included patients was 56 years (range 15-85 years), 56% were male, and the median follow-up period was 44 months (interquartile range (IQR) 23-84 months). The median tumour volume was 2422 mm3(IQR 1121-4032 mm3). Meaningful progression was defined as an adenoma volume increase of 20% or more and/or visual field deterioration on formal examination. Two independent Neuro-radiologists blinded to patients' symptoms confirmed true radiological progression. Forty patients (44%) demonstrated progression, with 21% representing visual field deterioration alone, 13% exhibiting radiological progression alone, and 10% presenting with both. The median time to radiological progression was 18.5 months (IQR 12-34 months). 19/90 (21%) underwent surgical resection, while the remaining 71 patients were managed conservatively and regularly monitored. Statistical analysis showed no association between tumour progression and age, gender, baseline tumour size, baseline pituitary status, baseline visual fields or extra pituitary extension. In conclusion, the findings show that approximately half of all conservatively managed NFPAs will progress at a median time of less than two years. The study did not identify any predictors of tumour enlargement, in keeping with prior published studies. This information is useful when counselling the patient regarding the merits of surgical vs conservative approaches to NFPAs.

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P370

A retrospective review of new hyperprolactinaemia referrals undergoing MRI pituitary

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Hyperprolactinaemia is a common referral reason from primary and secondary care for contrast-enhanced pituitary magnetic resonance imaging (MRI). This retrospective study at University Hospitals of North Midlands, Stoke-on-Trent reviewed the records of new patients referred for pituitary MRI between 1 June 2021 and 31 May 2023 with hyperprolactinaemia as indication. 71 patients were identified. 82% of the cohort were women. Age ranged between 18-87 years; the majority were between 21-40 years (66%). 22 requests were from primary care, remaining 49 from hospital clinics. Indications for prolactin testing included menstrual irregularities (35%), infertility (22%), headache (18%), erectile dysfunction (14%), galactorrhoea (13%), antipsychotic monitoring (6%), and incidental finding (4%). 18 patients (25%) had a first prolactin of <500; 42 patients (58%) had a prolactin of 501-1000; 10 patients (14%) had 1001-5000 and 2 patients (3%) had >5000. 15 patients met the laboratory screening criteria for macroprolactin. 38 patients (54%) had repeat prolactin. 24/38 (63%) had normal repeat prolactin. Among the 24 patients with normal repeat prolactin, 23 (96%) had a normal pituitary gland, and one had a 2.5mm incidental pituitary cyst. 12 patients (17%) had pituitary adenoma (mean prolactin: 4,163); 7 (10%) macroadenoma and 5 (7%) microadenoma. Of these 12 patients, seven were treated as prolactinoma and received cabergoline (mean prolactin: 6,479). Cabergoline reduced prolactin in five patients, mean prolactin reducing to 480. In one patient, prolactin increased from 597 to 796 and one is awaiting post treatment prolactin. Two patients showed a reduction in adenoma size, two had a stable appearance and the remaining three are awaiting follow-up scans. Our data suggests that repeat prolactin testing can potentially reduce pituitary MRI requests for transient hyperprolactinaemia. Such requests add to the significant burden on radiology services. However, in those with persistently elevated prolactin, pituitary MRI is crucial for further evaluation and management.

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P371

GnRH neuronal disruption and hypotestosteronemia in COVID-19

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Loss of gonadotropin-releasing hormone (GnRH) and cognitive deficits have recently been demonstrated by our group in conditions including Down syndrome and Alzhiemer's disease. In some patients with COVID-19, olfactory and cognitive alterations persist, and persistent hypotestosteronemia in SARS-CoV-2-infected men could be a consequence of deficient GnRH. To understand whether neuroinvasion of GnRH system by SARS-CoV-2 could explain some post-COVID symptoms and thus result in accelerated or exacerbated cognitive decline, we assessed the hormonal profile of patients with COVID-19 and targets of SARS-CoV-2 infection in post-mortem brains and human fetal tissue. Our data demonstrates that persistent hypotestosteronemia in men could result from hypothalamic disruption, favouring post-COVID neurological or cognitive symptoms, and that change in body weight and testosterone levels were inversely correlated. Infection of multifunctional glia, called tanycytes, and olfactory sensory neurons, highlighted at least two viable neuroinvasion routes. Moreover, in all patient brains studied, GnRH neurons themselves were dying, resulting in reduction of GnRH expression. Human fetal GnRH neurons, as well as the fetal olfactory and vomeronasal epithelia from which GnRH neurons arise, appeared susceptible to infection. Thus, putative GnRH neuron and tanycyte dysfunction following SARS-CoV-2 neuronivasion could be responsible for resulting reproductive, metabolic and cognitive health consequences in long-COVID and could result in an increased risk of neurodevelopmental and neurodegenerative pathologies over time in all patients.

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P372

An unusual case of Myeloma masquerading as SIADH

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Introduction
Hyponatremia from SIADH secondary to undiagnosed Myelomas are extremely rare and we present one such case.
Clinical case
63 year old woman with background of MGUS under regular haematology review/ILD/NAFLD/IHD presented with severe constipation on top of weakness, weight loss and tingling in the peripheral extremities. She was euvolemic on admission with Serum Sodium 124mmol/l, Potassium 4.3 mmol/l, Urea 3.1 mmol/l, Creatinine 53 micromol/l & eGFR >90 and normal Sodium 2 months before admission. 9 am cortisol $>$ 400 nmol/l & TFTs normal. Plasma osmolality 265 mOsm/kg, Urine sodium 138 mmol & urine osmolality 631 mOsm/kg consistent

with SIADH. Pseudohyponatremia excluded using Direct ISE. CTTAP showed stable but advanced ILD but no malignancy and CT/MRI Brain/Pituitary unremarkable. Symptoms worsened after fluid restriction, so Tolvaptan 15 mg OD started. Diarrhoea replaced constipation along with ascending distal sensorimotor symptoms & Autonomic neuropathy/Postural Hypotension. Investigated in depth by Neurology with LP showing oligoclonal bands, nerve Biopsy showing possible Vasculitic neuropathy, with mildly positive MPO antibody, normal CRP and VEGF levels & TTR gene negative. PET showed some increased activity in the left femur, liver & spleen. Neurology started her on Methylprednisolone with minimal improvement in symptoms, while Sodium levels hovered around 131 on 15 mg of Tolvaptan daily. IgG/FreeKappa raised but MGUS deemed stable by Haematology, however we pushed for Bone Marrow biopsy, as SIADH remained unexplained. BM biopsy suggested IgG Kappa myeloma and Haematology added Lenalidomide, alongside the Prednisolone which Neurology had continued for her Vasculitic/paraproteinemic neuropathy. Sodium levels maintained above 135 mmol/l on Lenalidomide, patient fully mobile back to baseline and completely off Tolvaptan.

Discussion

Literature evidence for Myelomas as a cause of SIADH is very limited, apart from the odd case report and possible mechanisms include effect of IL-6 on AVP.

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P373

A case of mild autonomous cortisol secretion (MACS) to full-blown Cushing Disease

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A 44 years old lady was reviewed by endocrinology team in January 2020 for weight gain, increased fat deposition around the neck, constant fatigue and decreased libido. She denied usage of exogenous steroids. She was normal BMI, normotensive and did not display signs of Cushing's syndrome in first visit. Although overnight dexamethasone suppression was failed to suppress: cortisol of 141 nmol/l and ACTH 78 ng/l, Low dose dexamethasone suppression test (LDSST) was adequately suppressed with cortisol was 38nmol/l. The diagnosis of mild autonomous cortisol secretion (MACS) was made and regularly following up for cardiovascular risks. Unfortunately, she defaulted follow-up. She presented with worsening of fatigue, 15 kg weight gain and easy bruising skin one year later. She had purple striae in abdomen, increase dorso-cervical fat pad and proximal myopathy on examination. Her BMI was 36.8 kg/m2. She was diabetic with Hb A1c of 70 mmol/mol, hypertensive and sustained osteoporotic rib fracture. BMD reported osteopenia Potassium was normal with random cortisol 971 nmol/l. 24 h Urinary cortisol was $>$ 1396. LDDST showed cortisol of 607 nmol/l with ACTH 290 ng/l. Pituitary profile showed secondary hypogonadism with low FSH, LH and oestradiol. Formal visual field reported as normal. MRI pituitary demonstrated 20x15mm adenoma with no chiasmatic compression. Metyropone was initiated and it was discussed in pituitary MDT. Transphenoidal hypophysectomy was performed. Histology confirmed corticotroph adenoma positive for ACTH and TPIT with Ki67 1-2%. Subsequently she developed panhypopituitism which requiring full pituitary hormone replacement. However, glycaemic control and quality of life have improved dramatically post operation. In conclusion, diagnosis of Cushing syndrome is always challenging as there is no single test or scan is absolutely sensitive and specific. Management of MACS should be individualised with close monitoring of cardiovascular risks and progression of Cushing syndrome

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P374

A case of pituitary apoplexy on long term cabergoline for prolactinoma

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Pituitary apoplexy is an uncommon, but well recognised clinical syndrome, which usually results from ischaemic or haemorrhagic necrosis of pituitary gland, which is frequently precipitated by an existing pituitary adenoma. Early diagnosis of this condition is essential as prompt management may be life and vision saving. We are highlighting a case of Pituitary apoplexy on long term Cabergoline for Prolactinoma.

Case report

A 62 year old lady presented to emergency department with history of sudden onset of severe headache after waking up in the morning. She also mentioned about multiple episode of vomiting and photophobia. Her past medical history includes stem cell transplant for Leukaemia, CKD stage 3, Macroprolactinoma which was diagnosed in 2015 and treated with Cabergoline. Her neurological examination was grossly normal apart from left sided temporal hemianopia. She underwent a CT scan of head which showed enlargement of the known pituitary adenoma which suspicion of haemorrhage within it. She was started on IV hydrocortisone. Her pituitary hormonal profile was done. Formal visual field study showed evidence of bi-temporal (L$>$R) hemianopia. She had a dedicated pituitary MRI which confirmed the evidence of haemorrhage within the adenoma. Her case was discussed urgently with neurosurgical team and was treated conservatively. She underwent daily visual field study which significantly improved over next few days. Her Cabergoline was continued. Her recovery was uneventful and was discharged with appropriate medical follow up with pituitary MDT.

Discussion and learning point

1. The role of dopamine agonist's treatment as precipitating factor is still questionable.
2. Role of thorough clinical examination is always the key to aid management. In this case findings of bedside visual field test were promptly addressed.
3. High index of suspicion, early management and interdisciplinary collaboration is the key to prevent serious complications.

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P399

Paltusotine maintains IGF-1, GH, and symptom control in patients with acromegaly switched from injected octreotide or lanreotide monotherapy: Topline results from PATHFNDR-1, a phase 3, randomized, double-blind, placebo-controlled, multicenter study

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Paltusotine is a once-daily, oral, selectively-targeted SST2 agonist in development for the treatment of acromegaly. PATHFNDR-1 (NCT04837040) enrolled patients with acromegaly who had an IGF-1 $\leq$1xULN on a stable ($>$12 weeks) dose of lanreotide or octreotide. Patients were randomized 1:1 to receive paltusotine 40 mg/day or placebo for 36 weeks. During the first 24 weeks, the paltusotine dose was titrated (range 20-60 mg) based on IGF-1 and tolerance. Dose changes were not permitted after week 24. IGF-1 was measured centrally using the iSYS immunoassay. Acromegaly symptoms were assessed using the Acromegaly Symptoms Diary (ASD), where higher scores represent greater symptom burden. 58 patients [(paltusotine $n=30$; placebo $n=28$), mean age 54.9 (SD 13.7) years, 55% female] were enrolled all of whom were controlled on octreotide (59%) or lanreotide (41%). The primary endpoint was achieved, with a significantly greater proportion of patients maintaining IGF-1 levels at $\leq$1.0xULN (mean of weeks 34 and 36) after switching from somatostatin receptor ligands (SRLs) to paltusotine compared to placebo (83% vs. 4%, $P<0.0001$). All three secondary endpoints were achieved. Paltusotine maintained mean IGF-1, GH and ASD scores significantly better than placebo [mean change from baseline in IGF-1: paltusotine $+0.04$ vs. $+0.8$xULN placebo, $P<0.0001$; proportion of patients who maintained GH <1.0 ng/ml (week 34) (paltusotine (87% vs. 28% placebo, $P=0.0003$) & mean change from baseline in ASD score (paltusotine -0.6 vs. $+4.6$ placebo, $P=0.02$)]. Paltusotine was well-tolerated with the most common AEs being consistent with either SRL therapy or acromegaly. One serious TEAE of acute cholecystitis was reported in a placebo patient. One placebo patient discontinued the study due to patient decision. There were no clinically significant changes in pituitary tumor size. In conclusion, once-daily, paltusotine treatment was significantly better than placebo at maintaining IGF-1, GH, and symptom control in patients switched from SRLs, and was well-tolerated.

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Nursing practice

P150

A service evaluation of the nurse-led adrenal incidentaloma clinic at University Hospital of Wales

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Background
In November 2017, a nurse-led Adrenal Incidentaloma (AI) clinic was launched at the University Hospital of Wales (UHW), Cardiff, based upon the 2016 European Society of Endocrinology AI management guidelines.
Objectives
To evaluate the effectiveness of a nurse-led clinic in managing AI patients at UHW.
Methods
Retrospective analysis of electronic records of patients seen in the nurse-led AI clinic over a 5-year period, December 2017-November 2022. The number of patients assessed, initial radiological scan characteristics, investigations ordered, management, waiting and discharge times, and final diagnoses were evaluated.
Results
316 patients with adrenal masses were assessed. The mean age was 64y, 43.7% male and 56.3% female. Referral routes: Most patients (39.9%) were referred by Primary Care. CT AP (29%) and CT TAP (24%) detected most lesions initially. Scan characteristics: 84.8% unilateral nodules, 11.4% bilateral nodules, 2.2% unilateral hyperplastic lesions and 1.6% bilateral hyperplastic lesions. 94.3% lesions were 1-4cm in size. Investigations ordered: 81% had Overnight Dexamethasone Suppression Test (ODST), 83% had urinary metanephrines measurement, 54% had an Aldosterone: Renin Ratio and 85% had at least one repeat imaging. 17% hormonal investigations and 4% repeat imaging requests were not completed by patients. Final diagnoses: made in 221 patients: 196/221 (88.7%) were non-functioning, 21/221 (9.5%) had Autonomous Cortisol Secretion, 2/221 (0.9%) Cushing's, 1/221 (0.45%) Conn's, 1/221 (0.45%) phaeochromocytoma. No adrenocortical carcinomas found. Patient flow: 219/316 (69.3%) AI patients have been discharged from the service, with discharged patients only attending a mean of 1.03 medical-doctor led clinics. Waiting times for clinic assessment have doubled from 103 days in 2017 to 232 days in 2022. Similar trends are seen in Discharge times.
Conclusions
A large proportion of AI patients can be effectively assessed and discharged through a nurse-led service, with majority of lesions found to be non-functioning and 69.3% having been discharged.

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P151

Growth hormone treatment in adults: A lifelong or time-limited therapy? A web-based survey of growth hormone prescribing practice in adults with growth hormone deficiency in the United Kingdom

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Introduction
In the UK, most adult patients with growth hormone deficiency (GHD) continue with growth hormone (GH) treatment indefinitely, even when they do not report any benefits from treatment. To date, the optimal duration of GH treatment in adults has not been established. We conducted a survey of UK endocrine clinicians between 01/06/2022 and 31/08/2022 to understand current practices regarding GH treatment discontinuation in adults with GHD.
Methods
Using an online platform Survey Monkey®, a web-based multiple-choice questionnaire was sent to the UK Society for Endocrinology membership. It consisted of 15 questions on demographics, number of patients receiving GH treatment and their current practice related to GH treatment discontinuation.
Results
102 endocrine clinicians completed the survey with majority from England ($n=91$, 89%). 65 respondents (33 endocrinologists and 32 specialist nurses) indicated active involvement in managing adult patients with GHD. 27.7% of the 65 clinicians ($n=18$) were routinely offering GH treatment discontinuation to adults receiving long-term GH therapy. Only 6% ($n=4$) used a clinical guideline/protocol to direct their practice of GH treatment discontinuation. 29.2% ($n=19$) supported that GH treatment discontinuation should be routinely offered to patients on long-term treatment with a further 60% ($n=39$) would consider treatment discontinuation for long-term users, whilst 9.2% ($n=6$) indicated that discontinuation should not be offered. During the period of GH treatment discontinuation, most clinicians monitor signs and symptoms (75.4%, $n=49$), measure IGF-1 levels (84.6%, $n=55$) and complete a quality of life assessment (89.2%, $n=58$).
Conclusions
This survey demonstrates that a significant number of clinicians would consider GH treatment discontinuation in adult patients with GHD who have been on long-term treatment. In the absence of clear evidence on the effects of GH treatment discontinuation in adults, more research is needed to guide the development of evidence-based recommendations that will inform clinical practice.

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P152

Outcomes of a self-reported knowledge survey on the management of adrenal insufficiency within a local accident and emergency Department

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Background
Evidence shows that in an emergency, prompt and appropriate treatment of patients with adrenal insufficiency (AI) significantly improves outcomes and mortality risk. However, patient feedback and evidence suggest shortfalls in care and treatment of AI due to lack of knowledge and understanding from clinical staff. The aim of this survey was to explore frontline nursing knowledge and understanding of AI, to identify gaps for future training purposes within a local NHS Emergency Department (ED).
Methods
A questionnaire consisting of 9 multiple choice and open-ended questions was distributed to 50 nurse members over two local ED Departments. Nursing staff skill-set ranged from 0-30 years' experience, at bands 4-8a. Questions focussed on self-reported knowledge, guidance, and their competence to identify and manage an AI patient. The questions asked participants to rank their knowledge from 1 (novice) to 5 (expert).
Results
Findings have shown that 51% ranked themselves as novice when identifying AI, as well as competence to treat (51%). Moreover, 30% participants reported lack of understanding of adrenal crisis (score of 1), with 71% scoring themselves 2 or below. 88% of participants were not aware of any AI guidance used within the department, 94% were not aware of the steroid 'sick day rules', and 80% were not aware how to advise patients on their steroid medication dose on discharge.
Conclusion
The survey has successfully identified gaps in knowledge and understanding of identifying and managing AI within an acute ED setting. It has highlighted areas needed for staff training and to improve knowledge and awareness to ensure that AI patients receive prompt and adequate medical care when presenting to ED. Future training will be specifically aimed at local ED staff with the aim to improve patient care. For comparison, the survey will be repeated post training to evaluate its success.

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P153

National steroid emergency card and delivery of education to specialties within NHS grampian on patients at risk of adrenal insufficiency and prevention of adrenal crisis

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Adrenal insufficiency is often under recognised which leads to adrenal crisis and death if not treated promptly. The NHS Improvement national patient safety alert (NatPSA) identified several actions an organisation needs to implement including introduction of the new steroid emergency card, identifying the patients at risk of adrenal insufficiency and those who require adrenal function assessment. This is also endorsed by Healthcare Improvement Scotland.

Aims
To educate and raise awareness and prevent Adrenal Crisis.
Method
Delivery of Educational sessions across NHS Grampian both online and in person to a variety of disciplines and specialties.
Outcome
Medical professionals prescribing glucocorticoids to provide steroid education and identify those who will require steroid emergency card or at risk of adrenal insufficiency 1a) Standard booklet on steroid sick day rule 1b) Ensuring patients have steroid emergency card if deemed at risk 1c) Identifying those at risk and for investigation of adrenal insufficiency This will ensure a large proportion of patients across NHS Grampian on long term steroids have equal access to steroid education, alerts on IT system and early recognition and treatment of adrenal crisis Delivery of Education to multiple speciality departments across NHS Grampian. Audience includes all disciplines within the healthcare team, predominantly targeting Consultants & all levels of the medical team, Specialist Nurses and those involved with patients who are currently and have previously been on treatment steroids. Teams Educated to date- Respiratory, Dermatology, Gastroenterology, Rheumatology, Oncology, Anaesthetic Department Advanced Nurse Practitioners & Pharmacists (Primary and Secondary Care) Education of these teams means improved patient's safety. Initiation and delivery of communication and support for these specialist teams by providing Multi-disciplinary team meetings and advice on pathways for Nurse led steroid clinics. There is also a dedicated Steroid Advice email. Specialist information and resources compiled for Grampian guidance

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P154

Improving collaboration between endocrine patient support groups and the society for endocrinology

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Background
Patient Support Groups (PSG) play a key role in the support, education, research and training for patients and clinicians alike, as well as providing invaluable input to key documents e.g. Defining the Future of Endocrinology (DfE), highlighting the importance of a closer working relationship with SfE.
About the PSG Network
Established in Sept 2021, the network includes representation from SfE affiliated PSG and a Nurse and Clinical committee representative. Meetings are held twice per year with the agenda driven by the PSG.
Hot Topics
- Support and collaboration between different PSG (importance highlighted by pandemic)
- Improving access and visibility
- Drug shortage information sharing
- GP collaboration/information sharing
- Research and Clinical Trials increased awareness
- Support to attend SfE events

PSG Activity
- PSG Facebook page and email set-up
- SfE formal affiliation of PSG (ratified and updated with the input of PSG representatives)
- PSG resources linked in the Resource Hub
- Active involvement in SfE projects e.g. ACC Service Improvement Project
- Travel and Project grants
- "How to guide" to access drug shortage information via the Specialist Pharmacist Service
- Working group formed to target GP collaboration
- Engagement with NICE and NIHR representatives
- PSG contribution to Nurse newsletter and presenting at key meetings i.e. BES
- Sharing expertise at PSG network meeting e.g. Patient Initiated Follow-up
- Feedback to Clinical and Nurse Committee

In development
- Poster for Clinical areas that includes the QR codes for SfE affiliated PSG and the Steroid Emergency Card
- Bitesize webinars -Sept 2023

Conclusion
The SfE PSG network provides a forum to share concerns and best practice in a collaborative and supportive environment. It has led to streamlining the PSG affiliation process, enabled improved engagement with PSG at Society events, the development of new tools for patient engagement/accessibility and essentially, a voice to the PSG.

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P155

An evaluation of the roles of adult and paediatric endocrine nurses in the UK

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Endocrine nursing practice has been changing, with the advent of more autonomous roles, involving nurse led clinics and independent prescribing, with more complex clinical case management. However, recent research highlights the emphasis on optimum patient care, but scope of practice is not always clear, leading to unequal balance in skills and capabilities, qualifications, and Agenda for Change (AfC) bandings. This study explored the remit, job components, and capabilities of adult and paediatric endocrine nurses in the UK, alongside an appreciation of work setting and organisational factors influencing role development and performance. The survey was sent via email through Society of Endocrinology nursing networks and through social media. 155 responded, with 49% of respondents working solely in adult endocrinology, 26% in paediatric endocrinology, and a mixture (25%) working in both. 37% of Endocrine Nurse Specialists (ENS) have achieved BSc degrees, 28% MSc, and 1% PhD/Doctorate level: over a quarter of respondents have completed MSc level Independent Prescribing qualifications. Clinical work is dominant, with 74% of ENSs undertaking dynamic function tests, where the majority (67%) are testing for adrenal insufficiency (AI), and 74% undertaking nurse led clinics (NLC). There is a wide range of focus within NLC, such as AI, Precocious Puberty, or Thyroid care, with most of the care focusing on detailed patient education. There is stark contrast in levels at which ENS are employed in relation to their AfC bandings, with only half working as Band 7, 40% as Band 6, 3% at Band 5 and 7% at Band 8. Advanced level practice is worthy of a Band 8 proficient level, which is evident in UK ENSs practice, although this data shows that ENSs at this level are wholly underrepresented. More focus is needed in organisational planning in line with competency frameworks, nurse management, and multidisciplinary teams.

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RET

P125

National Experience of the use of the highly selective RET tyrosine kinase inhibitor Selpercatinib in children with multiple endocrine neoplasia type 2 and advanced medullary thyroid cancer: updated experience

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Background and Demographics
Medullary thyroid carcinoma (MTC), in the context of Multiple Endocrine Neoplasia type 2 (MEN2), is caused by mutations in the RET proto-oncogene. For children with MEN2, both 2A and 2B subtypes, and advanced MTC, the RET tyrosine kinase (TK) pathway is a target for treatment with selpercatinib, a selective RET TK inhibitor (TKI). In the United Kingdom, 7 paediatric patients have been receiving named -patient, compassionate access treatment with selpercatinib for the management of advanced MTC, as primary systemic therapy after surgery. This updates our 2021 publication with an additional 48-month experience and an additional patient.
Results
7 MTC MEN2 (2A x2; 2B x 5) patients were reviewed; aged between age 9 and 17 years and with a male: female ratio of 4: 3. 6 remain taking selpercatinib. One patient demonstrated radiological and biochemical evidence of tumour progression within 23 months of continuous therapy, after an initial good response. The remaining 6 patients continue to demonstrate ongoing biochemical and radiological response. The average duration of therapy is 33 months (range 16 - 49). Pre-treatment calcitonin ranged between 146 - 36 000ng/l. Current calcitonin levels range between 1.6 - 176ng/l. All patients achieved a maximal reduction in tumour markers of $>90\%$. Overall, treatment was well tolerated. Two patients developed bilateral slipped capital femoral epiphyses (SCFE) requiring surgery. Another patient developed bowel lymphangiectasis responsive to dietary change. Two had intercurrent viral chest infections requiring hospital admission, oxygen and a temporary cessation of selpercatinib. One patient developed a prolonged QTc(F) which self-resolved without the need for dose modification.
Conclusions
Selpercatinib is deliverable, tolerable and efficacious at providing a period of disease control in a paediatric cohort. Further understanding of selpercatinib drug interactions and any causality between selpercatinib and SCFE for patients at known risk with MEN2, is required.

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P126

Characterising the natural history of Multiple Endocrine Neoplasia 2B caused by M918T RET pathogenic variants in children and young people

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Aim
We describe the natural history, treatment, and clinical outcomes of Multiple Endocrine Neoplasia type 2B (MEN2B) caused by the M918T RET pathogenic variant.
Methods
Retrospective case notes review of all young people <18 years presenting to a quaternary paediatric endocrinology referral centre in the UK between 2005-2023 who have MEN2B caused by the M918T pathogenic variant in the RET proto-oncogene.
Results
Twelve children (7F, 58.3%, median age at genetic diagnosis 3.5yrs, range 0.1-16) with a confirmed heterozygous c.2753T$>$C M918T RET pathogenic variant (de novo in 66.7% ($n=8$), maternally inherited in 25% ($n=3$), and of unknown inheritance in 8.3% ($n=1$)) were included. Eleven (91.7%) had gastrointestinal manifestations: constipation (83.3%, $n=10$), intestinal ganglioneuromatosis (50%, $n=6$), and gallstones (25%, $n=3$). Mucosal neuromas were found in 58.3% ($n=7$) and alacrima in 25% ($n=3$). Three children (25%) had clinically palpable disease. All had thyroidectomy with central lymphadenectomy (median age 4.5yrs, range 0.3-16); two had lateral neck dissections. Preoperative calcitonin was 85ng/l (range 23-7120) with an undetectable calcitonin achieved postoperatively in 33.3% ($n=4$). Medullary thyroid cancer was confirmed on histopathology in 91.7% ($n=11$); one child had c-cell hyperplasia. Four children (33.3%) had nodal involvement. One child had metastasis to surrounding mediastinal structures and received adjuvant EBRT. Three children had later biochemical and/or clinical recurrence requiring reoperation ($n=1$) and/or selpercatinib or vandetinib treatment ($n=3$, treated for a range of 1-3 years). No child developed a phaeochromocytoma during the study surveillance period. One child died of a respiratory arrest unrelated to thyroid pathology.
Conclusions
Early diagnosis and thyroidectomy are essential for children with M918T-associated MEN2B. Gastrointestinal manifestations are characteristic and should raise diagnostic suspicion of this rare disease. Selective RET tyrosine kinase inhibitors show therapeutic efficacy in progressive disease.

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P276

RET p.Val804Met: A study in genetic uncertainty

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Introduction
Pathogenic RET mutations cause Multiple Endocrine Neoplasia type 2 (MEN2) and sixty-one have been classified according to their penetrance of MTC. However, this distinct pattern of genotype-phenotype presentations is not always precisely predictable. P.Val804Met, the most frequent mutation in RET, is currently thought to confer a low lifetime risk with later onset of MTC.
Methodology
We present demographical, clinical, biochemical, genetic and histopathological data of three generations of patients from a family diagnosed with MEN2. The index case was a 7 year old girl who presented with advanced MTC with lymph node metastases, calcitonin of 3600 mg/l, CEA 204 ng/l and was found to have p.Val804Met RET mutation. Subsequent genetic testing identified twelve family members with the same mutation.
Results
Three generations of patients (3M, 9F, age ranges 1-72yrs) included two grandparents, three daughters and seven grandchildren. Biochemical assessment showed abnormal calcitonin in two grandparents, one of the daughters and two grandchildren. CEA levels were normal apart from index case. All patients underwent total thyroidectomies, five central and two lateral lymphadenectomies. Histology showed MTC with no LN involvement in two grandparents, MTC with LN involvement in one daughter and two grandchildren. One grandchild had microMTC and four C-cell hyperplasia. Additional pathology included papillary microcarcinoma and follicular cancer. Nine family members were cured (undetectable post-op calcitonin) but three have persistent disease with elevated calcitonin (3) and CEA (1), two of them receiving treatment with Selpercatinib. Analysis showed no second variant of RET mutation in blood and tumour DNA was negative for somatic RET, KRAS, HRAS and NRAS mutations in index case.
Conclusion
Our study showed that carriers of p.Val804Met have varying phenotypic presentation and not always a late onset or mild disease. Prophylactic thyroidectomy should be considered in these carriers if there is family history of early-onset MTC.

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P277

An unusual presentation of medullary thyroid cancer with proximal myopathy

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A 68-year-old gentleman presented with proximal myopathy in association with severe hypokalaemia (K+ 2.3mmol/l) and metabolic alkalosis. He had recently

been diagnosed with type 2 diabetes. His random cortisol was 1045nmol/l. His 24-h urinary free cortisol was 3536nmol/24 h, and midnight cortisol was 85nmol/l. On a low dose dexamethasone suppression test, his cortisol failed to suppress (cortisol 1195–983nmol/l, ACTH 275ng/l), consistent with ACTH-dependent Cushing's syndrome. He was commenced on a block and replace regime with metyrapone and prednisolone; eplerenone was started to manage his hypokalaemia. His MRI pituitary was unremarkable. CT imaging showed bulky adrenal glands and a 2cm left supraclavicular lymph node (low level uptake on FDG-PET). This was biopsied and histology demonstrated a well-differentiated neuroendocrine tumour with a Ki-67 proliferation index of 2%. Immunohistochemistry was positive for calcitonin, TTF1 and CEA. A significantly raised plasma calcitonin of >38,000ng/l confirmed a diagnosis of medullary thyroid cancer with ectopic ACTH secretion. A total thyroidectomy was not possible owing to significant mediastinal involvement and therefore a large open biopsy was undertaken instead. Molecular analysis confirmed the presence of a somatic RET mutation. He was commenced on a tyrosine kinase inhibitor (Cabozantinib) and despite a substantial fall in his plasma calcitonin, he was unable to tolerate maximal therapy due to progressive side effects. Ten months into treatment, the decision was made to switch to Selpercatinib with subsequent normalisation of plasma calcitonin (11ng/l) and all lesions decreased in size on CT. Furthermore, he was able to stop metyrapone and dynamic testing confirmed remission of his Cushing's syndrome. A new diagnosis of Cushing's syndrome may present in a variety of different ways. This case illustrates a rare presentation in association with medullary thyroid carcinoma that had an excellent response to tyrosine kinase inhibitors.

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P381

RET inhibitors in thyroid cancer: A single-institution experience

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Background
Mutations in the RET proto-oncogene occur in about 70% of medullary thyroid cancers (MTC) and is central in its pathogenesis. Two highly selective RET inhibitors, selpercatinib and pralsetinib, are FDA/EMA-approved in RET-altered thyroid cancers. We share our experience of these drugs in metastatic MTC.
Methods
Data were collected retrospectively from 19 patients commenced on selective RET inhibitors for MTC at our institution between November 2019 and December 2022.
Results
Of the 19 patients, 6 (32%) patients received pralsetinib and 13 (68%) patients received selpercatinib. 15 had received prior kinase inhibitors. All patients had distant metastatic disease. Median age was 58 (range 14-77) years and sex were evenly distributed. 15 (79%) of cases were sporadic and 4 (21%) had germline RET mutations. Median follow-up duration was 3 months. There were 3 deaths. Overall response rate (ORR) was 95%. The most common toxicities of all grades experienced by patients on pralsetinib were hypertension ($n=5$, 83%), infection ($n=4$, 67%), fatigue ($n=3$, 50%) and neutropenia ($n=3$, 50%). The most common toxicities in the selpercatinib group were hypertension ($n=5$, 38%), fatigue ($n=5$, 38%) and QTc prolongation ($n=5$, 38%). Of particular interest were 2 instances of grade 2 pneumonitis in the pralsetinib group and 1 case of grade 3 myocarditis in the selpercatinib group. The only grade 4 adverse event was a case of pulmonary emboli in the pralsetinib group. The majority of patients had dose interruptions ($n=14$, 74%). Dose reductions ($n=12$, 63%) due to toxicities were common, with hypertension, infections, and gastrointestinal disturbances as the most frequently reported. There were no permanent cessations due to toxicity.
Conclusion
Selective RET inhibitors represent a significant advancement in the treatment of MTC and although well-tolerated, clinicians ought to be vigilant to potentially serious complications such as pneumonitis or myocarditis.

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Reproductive Endocrinology

P107

Approach to male hypogonadism work up and treatment monitoring in secondary care

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Background
Male hypogonadism is a frequent reason for referrals to secondary care. Work up and approach to diagnosis and treatment varies among practicing physicians and proper work up and monitoring is crucial for safe and effective Testosterone replacement therapy (TRT).
Methods
Retrospective case reviews for all men who were prescribed TRT via secondary care endocrine unit between September 2021 and September 2022.
Results
127 patients received at least 1 prescription of TRT over 1 year time. All patients had documented signs and symptoms consistent with hypogonadism. On initial work up only 68% (56/82) had their total testosterone performed before 11 am and only 74% (62/84) had their levels repeated. Interestingly, Sex hormone binding globulins (SHBG) were checked in only 57% (51/89) of patients while there was no documentation of free testosterone measurement in 90% (81/90). Prostate specific antigen (PSA) measurements were documented in 77% (71/92) and only 68% (62/91) had this repeated 3-6 months after TRT initiation. Haematocrit (HcT) was checked in 84% (76/91) of patients prior to TRT initiation but only 65% (59/91) had their HcT rechecked 3-6 months later. Of the 13 patients with a haematocrit of 0.54% or higher, 2 patients had no action taken, 4 patients' TRT frequency was reduced, 3 patients' TRT was stopped of which 1 was referred to haematology. 14% (12/85) had anaemia before TRT initiation of which 2 had anaemia corrected with TRT after 1 year of therapy.
Conclusion
Biochemical work up for hypogonadism should be optimised to consider sampling conditions. Estimation of free testosterone/SHBG is helpful to unmask patients with functional hypogonadism. A standard approach to TRT induced erythrocytosis is necessary to ensure safe and effective provision of care.

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P108

A comprehensive transethnic metabolomic analysis in women with PCOS in the born in bradford (BiB) study

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Introduction
Polycystic ovary syndrome (PCOS) is the most prevalent endocrine and metabolic disorder of women of reproductive age. Comprehensive metabolic profiling of women with PCOS across different ethnicities will help in understanding the pathophysiology of this condition.
Methods
The Born in Bradford (BiB) study is a UK longitudinal birth cohort. Profiling of circulating lipids, fatty acids, and metabolites was done by a high-throughput targeted NMR platform (Nightingale Health© (Helsinki, Finland), providing quantitative information on 227 metabolomics. We obtained the PCOS case-control status using the ctv3 codes available as part of the dataset. We used the Mann-Whitney U-test to compare the metabolomics in the PCOS and control population.
Results
The study consisted of 10608 women in the Born in Bradford study with a median age of 28 (25-31) years. The predominant ethnic groups included 3979 participants (37%) with English, Welsh, Scottish, Northern Irish, or British ethnicity, 4250 Pakistani (40%), 405 Indian (3%), and 133 African ethnicities (1%). The study consisted of 276 women with PCOS and 10332 control. The metabolomics analysis showed that several metabolites in the pathways inflammation (Glycoprotein acetyls $P<0.0001$), Glycolysis related metabolites (Glycerol and Citrate $P<0.0001$), amino acids (Phenylalanine, Leucine, Isoleucine, $P=0.0003$), and Lipid pathways (Triglycerides in medium VLDL and Cholesterol esters in medium VLDL $P=0.0003$) were differentially expressed in cases with PCOS as compared to controls. Analysis restricted to women with south-Asian and white populations showed similar results.
Conclusion
The study identified differential expression of metabolites involved in inflammation, glycolysis, amino acid metabolism, and lipid pathways in women with PCOS with a similar association in the South Asian and white populations. These findings contribute to our understanding of PCOS pathophysiology and highlight potential targets for further investigation and therapeutic interventions.

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P109

Butyrate alleviates adipose mitochondrial dysfunction and inflammation in experimental model of polycystic ovarian syndrome by modulation of HIF-1α/MIF-dependent mechanism

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Impaired adipose tissue remodeling has been suggested as a pathophysiological driver of endocrinometabolic events in PCOS models, a condition that affects 6-21% of reproductive-aged women worldwide. Mitochondrial dysfunction, especially in the adipocyte plays a key role in adipose tissue inflammation that possibly aggravates endocrine/metabolic phenotypes in PCOS. Studies have reported Short-chain-fatty acids (SCFAs) as metabolic modulators that potentiate energy homeostasis. However, the impact of SCFAs, particularly butyrate, on mitochondrial dysfunction/inflammation in the adipocyte of PCOS individuals is unknown. The present study therefore hypothesized that butyrate would reverse adipose mitochondrial dysfunction/inflammation and endocrine/metabolic features in experimental PCOS rat model. Eight-week-old female Wistar rats were assigned into groups, $n=5$, namely control (CONT), sodium butyrate (SBUT), PCOS, and PCOS + SBUT. Polycystic ovarian syndrome (PCOS) was induced with Letrozole (1 mg/kg) for 21 days. After the confirmation of PCOS, the animals were treated with sodium butyrate (200 mg/kg) for six weeks uninterruptedly. The experimental PCOS animals expressed morphological alterations with multiple ovarian cysts and hormonal/metabolic changes characterized by hyperandrogenism, hypoestrogenism, elevated anti-Mullerian hormone and hyperinsulinemia/insulin resistance. In addition, animals also demonstrated decreased plasma triglyceride, adiponectin, and increased leptin, with corresponding decrease in adipose triglyceride, lipase, and increase in proinflammatory markers (NF-kB and TNF-α). A significant increase in adipose mitochondrial caspase-6, SDF-1, NF-kB, MDA, and decreased NrF2 and ATP synthase were also observed in experimental PCOS animals and these were immunohistochemically confirmed by severe expression of NLRP3 in the adipose tissue. These alterations were accompanied by altered adipose MIF and HIF-1α. Nevertheless, administration of butyrate alleviates these morphological, mitochondrial, biochemical, and immunohistochemical alterations in both ovary and adipose tissue of PCOS animals. The results suggest the ameliorative effect of SCFA, butyrate on adipose mitochondrial dysfunction and/or inflammation in PCOS by modulation of HIF-1α/MIF-dependent pathway.

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P110

Do all women with turner syndrome with 45, X/46, XY mosaic karyotype need early gonadectomy?: Experience from an adult tertiary care centre

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Introduction
Reports suggest the karyotype of up to 10% of women with Turner syndrome (TS) includes presence of a Y chromosome. Current guidelines recommend early gonadectomy given the potential risk of gonadoblastoma. However, the evidence basis for this practice is not strong. We aimed to assess pubertal development, clinical features, incidence of gonadoblastoma and long-term outcome including pregnancy in an adult-tertiary care TS clinic.
Methods
A quality improvement study (OUH 8477) was performed to retrospectively review consecutive data of patients (phenotypically female, without ambiguous genitalia) with 45,X, 46,XY mosaic karyotype.
Results
Y chromosome was identified in 12/168 (7.14%) using conventional cytogenetic analysis [median age 38 (range 17-65) years]. The median age of TS diagnosis was 13.5 (range 2-18) years. All had 45, X/46, XY mosaic karyotype with median percentage of XY cells of 43% (range 1%-91%). None of them had spontaneous puberty; median age of puberty induction 14 (12-18) years. Only 3/12 had pre-gonadectomy imaging available that showed bilateral 'streak' gonads. All except one (still pending gynaecology review) had bilateral gonadectomy [median age of surgery 15 (2-32) years], with 1/12 (8.33%) detected to have bilateral gonadoblastoma at the age of 20 years, presumed to be non-malignant with no recurrence during follow up. Out of 4 women who attempted pregnancy in-vitro-fertilization with donor eggs, 3 were successful including one twin pregnancy. During follow up, seven had bone density assessment, 2 women had osteoporosis (age of onset 41 years and 60 years) and one had osteopenia (age 28 years).
Conclusions
Prevalence of 45, X/46, XY karyotype in women with TS was similar to published studies. Non-functional gonads were universal requiring pubertal induction. Early bilateral gonadectomy was noted with low prevalence of gonadoblatoma.

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P111

Immunometric and functional measurement of endogenous vasoinhibin in human sera

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Circulating levels of the antiangiogenic protein vasoinhibin (16 kDa PRL), a fragment of prolactin, are of interest in vasoproliferative retinopathies, preeclampsia, and peripartum cardiomyopathy, but are unknown due to the lack of a quantitative assay. Here, human serum samples were investigated for the concentration and bioactivity of vasoinhibin using a novel enzyme-linked immunosorbent assay (ELISA) for human vasoinhibin employing an anti-vasoinhibin monoclonal antibody, a human umbilical vein endothelial cells (HUVEC) proliferation assay and a chick chorioallantoic membrane (CAM) angiogenesis assay. Serum samples from 17 pregnant women with and without preeclampsia and pregnancy induced hypertension demonstrated endogenous vasoinhibin concentrations in the range between 5 and 340 ng/ml. Vasoinhibin levels were significantly higher in preeclampsia serum compared to healthy pregnancy serum (mean 63.09 vs. 19.67 ng/ml, $P=0.0003$), as was the bioactivity of vasoinhibin determined by HUVEC proliferation (56.12 vs. 13.38 ng/ml, $P=<0.0001$). There was a correlation between the concentrations of vasoinhibin measured by ELISA and by HUVEC proliferation (Pearson r = 0.95, $P=<0.0001$). Healthy serum demonstrated a proangiogenic effect in the CAM assay ($P=<0.05$, compared to a PBS control), while serum from preeclamptic patients demonstrated an antiangiogenic action ($P=<0.05$ vs. PBS control), as did recombinant human vasoinhibin and a synthetic circular retro-inverse vasoinhibin analog (CRIVi45-51). The antiangiogenic effects in the CAM assay and the inhibition of HUVEC proliferation were abolished by the addition of the ELISA anti-vasoinhibin monoclonal antibody but not by mouse IgG. These results demonstrate the first quantitation of endogenous, bioactive vasoinhibin in human sera and its elevated levels and antiangiogenic activity in sera from women with preeclampsia. The development and implementation of a quantitative assay for vasoinhibin overcomes a long-standing barrier and opens the perspective to a thorough clinical verification of vasoinhibin as a relevant biomarker.

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P112

Are we over scanning women with turner syndrome who have the lowest risk of aortic dissection?

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Women with Turner Syndrome (TS) are at significantly increased risk of aortic dilation and dissection. However, predicting the risk of aortic dissection (AoD) is difficult with many women attending annual appointments with time, travel and parking costs and resource implications. We developed a risk-based pathway based on the international guidelines, enabling closer follow up for those with a greater risk and reduce the frequency of appointments for those at the least risk.
Methods
Women with TS ($n=168$) were divided into 2 pathways depending on risk factors for AoD, and subsequently split into 4 groups depending on aortic size index (ASI). The pathway then determined frequency of review and imaging. The main differences from the current international guidelines being that those with an ASI $<2.0\text{cm/m}^2$ and no risk factors are followed up by the endocrinology team and those with an ASI $\geq 2.5\text{cm/m}^2$ are referred directly to the aortic MDT.

Results
Over a 2-year prospective analysis, no patient changed pathway. Of the 11 patients in the highest risk groups: 7 had ascending aorta replacements, 1 is awaiting surgery, 1 had a low BMI therefore making her aorta proportionally larger, 1 had previously dissected her aorta whilst waiting surgery and 1 declined surgery. Following the implementation of our pathway, cardiology outpatient appointments have reduced from 168 to 93, saving 75 appointments and the trust nearly £8000 a year. There has been no increase in 'did not attend' appointments.
Conclusion
A risk-stratified streamlined aortic monitoring pathway safely allowed consolidation of resources to women perceived to be at the highest risk of AoD (excluding pregnancy), enabling diversion of resources to those most at risk of AoD and reducing travel and attendance times for patients.

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P113

Cord blood prolactin in the assessment of neonatal oxygenation at partition

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Introduction
Cord blood gases are measured following partition and are used as surrogate markers in the assessment of fetal oxygenation status at delivery and in identification of risk for neonatal encephalopathy. Low maternal prolactin levels were associated increased risk of respiratory distress syndrome. This study measured cord blood prolactin levels and correlated values with blood gases to examine possible value in assessment of fetal stress during delivery.
Methods
Cord blood samples ($n=73$) were collected following blood gases analysis, serum separated by centrifugation and stored at -20°C until further analysis. Prolactin levels were measured using DueSet ELSIA (R and D Systems, MN, USA). Samples diluted (1:400) prior to analysis.
Results
Cord blood prolactin levels ranged from 51 to 6108 mIU/l (median 2467 mIU/l). Blood gases parameters ranged from pH 7.14 to 7.49 (median 7.31), pO2 from <29 to 47 (median 33 mmHg), pCO2 from 24 to 77, (median 48 mmHg), and bicarbonate from 16 to 29 (median 23 mmol/l). None of the samples exhibited pH <7.0 which would correlate with adverse neonatal outcome. Prolactin levels were slightly negatively correlated with pH values but not significant, whereas no correlation was observed with pO2 nor with pCO2($P>0.8$). Prolactin levels slightly negatively correlated with bicarbonate ($P<0.06$). Maternal age at delivery ranged from 18 to 42 (median 27 years).
Discussion
The acidotic cord blood pH reflects the increased oxygen utilization and increased pCO2 elimination. Overall, there was poor correlation between cord blood prolactin levels and blood gases. However, there was slight difference in mean prolactin levels between samples with pH <7.27 and those with pH between 7.34 and 7.27. Additional studies are required to further elucidate the clinical utility of measuring cord blood prolactin.

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P114

Assessment of antenatal anxiety and depression in pregnant women with polycystic ovarian syndrome (PCOS)

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Background
Women with PCOS experience higher rates of depression and anxiety. There is a paucity of research relating to perinatal mental health in women with PCOS, as well as a lack of evidence-based guidelines for assessment and management of mental disorders specific to pregnant women with PCOS. Limited available evidence suggests PCOS is associated with a higher prevalence of perinatal mental health disorders. However, perinatal guidelines currently do not recognise PCOS as a risk factor for perinatal mental health disorders. International evidence based PCOS guidelines have highlighted the lack of research in this area. We aimed to prospectively assess mental health in pregnant women with PCOS.
Methods
Consenting pregnant women, with and without PCOS, were invited to participate. Standardised validated questionnaires were carried out including Generalised Anxiety Disorder Assessment (GAD-7), Patient Health Questionnaire (PHQ-9) and Edinburgh Postnatal Depression Scale (EPDS).
Results
To date, 107 women have been invited to participate. 64 responses include 43 with PCOS and 21 without PCOS. Interim analysis shows 47% of women with PCOS had a mental health diagnosis prior to pregnancy compared to 21% of women without PCOS. Pregnant women with PCOS had higher median anxiety scores (6, IQR 2-12) and depression scores (5, IQR 3-9) than women without PCOS (GAD7- 4, IQR 1-7, PHQ9- 3, IQR 1-8). Women with PCOS were more likely to experience moderate/severe anxiety (PCOS 35%, control 14%) and depression symptoms than women with PCOS (PCOS 21%, control 14%). Women with PCOS had higher median depression scores with EPDS (10, IQR 4-14) than women without PCOS (5, IQR 3-7, $P=0.02$).
Discussion
This study aims to assess prevalence of mental health disorders and highlight the need to screen for common perinatal mental disorders in women with PCOS. Interim analysis suggests higher prevalence of perinatal depression and anxiety in women with PCOS.

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P115

A case of neonatal hyperthroidism; associated with persistently elevated maternal thyroid rrceptor antibody (TRAb levels), post thyroidectomy for graves' disease. Mother was clinically euthyroid on thyroxine replacement

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30 yr/F, presented with C/O of palpitations, heat intolerance, significant unintentional weight loss with bulging of eyes and diplopia on extremes of vision. She had a background history of asthma, PCOS, obesity and difficulty in conceiving. OE, there was a smooth painless goiter. TFTs at diagnosis: TSH <0.05, T4 $=83$, T3 >30.8 and TSH receptor antibody level (TRAB) of 9.0. She developed skin reaction to both Carbimazole and PTU, hence treated with total thyroidectomy with lifelong thyroxine replacement. Subsequently she was reviewed 3 months after surgery, at that time she was 7 weeks pregnant and was started on levothyroxine 125mg od. She remained biochemically euthyroid throughout pregnancy but TRAb remained positive at 8.9, 4.8 and 4.4 at 13, 24 weeks and 28 weeks gestation respectively. She had an emergency C- section at 38 weeks due to fetal macrosomia. Baby had resuscitation for 6 mins and was taken to neonatal ITU, as he developed meconium aspiration syndrome and PPHN (persistent pulmonary hypertension of newborn) and neonatal thyrotoxicosis TFTs on day 1 showed low TSH level of <0.02, T3 5.8, T4 29.8 and TRAb was positive and he was started on carbimazole at 0.4mg/kg/day on day 8. He remained in hospital for 25 days when repeat bloods showed evidence of remission, hence Carbimazole was stopped. Repeat bloods after 1 week of discontinuing carbimazole showed biochemical evidence of hyperthyroidism and thus he was restarted on carbimazole 0.5 mg/kg/day (2.5 mg od) alongwith propranolol 250 mcg/kg every 8 h. 2 weeks later his TFTs still showed raised T4, hence carbimazole increased to 4 mg. Apart from on and off diarrhea, baby was thriving and gaining weight with no clinical evidence of hyperthroidism.
1 months later his TFTs were normalized and hence Carbimazole was stopped and repeat TFTs arranged in 2/7.

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P116

Patient and healthcare providers experience of access to menopause-related information and menopause-care provision across the UK: Results from a nationwide survey

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Menopause management guidelines advocate a personalised, evidence-based approach to menopause-care. This study explored the current landscape of menopause-care, from both patients' and healthcare-providers' perspectives, to better understand barriers to menopause-care across the UK.
Methods
A 25-question online patient-survey and a 23-question GP-survey was designed with individuals with lived-experience of menopause to understand access to and provision of menopause-care throughout the UK. The NIHR People-in-Research, VOICE websites, and menopause charities' social-media platforms were used to widen the survey's reach. The surveys were hosted on Qualtrics XM® and utilised convenience-sampling to gather nationwide experiences of menopause-care between September–December 2022.
Results
Patient-survey
Overall, 339 respondents aged 29-78 years across the UK participated. Collectively, NHS GPs provided 53.8% of menopause-related consultations. Almost half (48.4%) of patients experienced waiting-times of $\geq$12 months, and 23.4% $\geq$24 months. Appointment availability was the most frequent barrier to menopause-care (28.6%). 52% felt that insufficient information was provided to facilitate shared-decision making (SDM) and frequently resorted to additional resources. Social-media was most frequently utilised sources of information (18.4%; Facebook-7.2%; Instagram-7.2%; YouTube-2.6% and Twitter-1.3%) whilst official websites were used by only 12.9%.
GP-survey
Despite providing up to 100 menopause-related consultations per month, the majority of GP practices (84.6%) did not offer dedicated menopause services, and none of the GP-respondents ($n=18$) had receive additional training in menopause-care. 'Complex risk-interactions' and 'lack of consultation time' were cited as the greatest challenges (81.8%).
Conclusion
This nationwide survey reaffirms that GPs provide majority of menopause-related consultations. Time-limited consultations, complex risk-interactions of menopause treatments compounded by lack of menopause-specific training challenged provision of optimal menopause-care. The disparity in access to specialist menopause-services, gaps in information provision and impact on SDM were highlighted. These findings are important to guide relevant nationwide service improvements for menopause-care in line with the Government's Women's Health Strategy.

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P117

Management of PCOS – patient and clinician perspectives on quality of clinical care in the United Kingdom

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Background
Polycystic ovarian syndrome (PCOS) is the commonest endocrine condition affecting women of reproductive age, often adversely impacting their quality of life. Delayed diagnosis and poor patient experience are common themes reported by affected women. Several factors contribute to poor clinical care including the lack of specialised multi-disciplinary clinics and poor clinician familiarity with the varied health needs of affected women. We aimed to identify patient priorities, clinician perspectives, and barriers to effective clinical care by surveying both women with PCOS and relevant clinicians in the UK.
Methods
We conducted two web-based, anonymous quantitative surveys, one aimed at women self-reporting a diagnosis of PCOS and one for clinicians in primary and secondary care settings involved in PCOS care provision. Surveys were disseminated via social media. We reported using natural frequencies and percentages and assessed data distribution using Chi-squared test and one-way ANOVA tests.
Results
We received responses from 47 women with PCOS and 33 clinicians including GPs ($n=6$, 18.2%), Endocrinologists ($n=11$, 33.3%), and Gynaecologists ($n=15$, 45.5%). Most participating women ($n=34$, 75.6%) reported that conversations regarding psychosocial symptoms never took place despite 53.2% ($n=25$) self-reporting mental health concerns. Only ($n=1$, 3%) of participating clinicians agreed that mental health was always covered as part of the consultation. Only 8.5% ($n=4$) of participating women reported satisfaction with care in contrast to ($n=25$, 75.8%) of clinicians reporting that patients' priorities were always met in their care. Clinicians identified several barriers to providing optimal PCOS care including staff shortages (65.6%), time constraints in the clinic (59.4%), and lack of service availability (50%).
Conclusion
There is a systematic under-provision and appreciation of the health needs of women with PCOS in the UK. More clinician education and awareness are needed to optimise PCOS care provision, especially to offer holistic psychosocial and mental health support for affected women.

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P118

An audit of elevated serum testosterone in females with discrepant results

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Background
While investigating hyperandrogenism in women, local laboratory policy dictates adult females with a serum testosterone of >3.5 nmol/l should be confirmed with an alternative method to exclude interference by cross-reacting substances. Patients who were on testosterone replacement or had a previous result in the same year were excluded. We explore the biochemical investigation of discrepant testosterone in females.
Method
Retrospective audit over 1 year of testosterone requesting commencing April 2022. Testosterone was measured using Roche Cobas electrochemiluminescence immunoassay. Elevated female testosterone levels were confirmed with liquid chromatography tandem mass spectroscopy (LCMS). Results were reviewed independently by two individuals and discrepant results were further evaluated.
Results
An elevated testosterone was found in 1515 adult females (24.4% of total), with 89 (5.9%) sent for confirmation testing. Of these, 14 female patients with discrepant testosterone results were identified with a mean testosterone of 4.5 nmol/l (range 3.6-5.3) when measured with immunoassay, and 1.12 nmol/l (0.2-2.8) with an LCMS method (paired t-test $P<0.05$). Mean testosterone for females with non-discrepant results (and not on replacement therapy) was 4.4 nmol/l (immunoassay) and 4.2 nmol/l (LCMS) ($P=0.35$). Follow-up investigations consisted of repeat testosterone (50% of cases), SHBG (75%), DHEA-S (25%), Androstenedione (13%), and 17-OHP (6%). A review of the drug history showed Progesterone-only Pill was prescribed in 25%, Noresthisterone (13%), Depo-Provera (6%), HRT (6%), pregnancy (6%), and no findings (31%).
Conclusion
Elevated testosterone in females is not an unusually finding, however, this audit demonstrates the necessity of confirming elevated testosterone in females where the cause is unclear. Results show a wide variation in the follow up of patients with discordant testosterone results. Interference by Norethisterone in immunoassay testosterone is not a newly described phenomenon, however, clinicians should be aware of interferences in immunoassay to prevent unnecessary investigations into an analytical problem.

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P119

Investigating the therapeutic potential of HDAC inhibition on renal disorder in letrozole-induced polycystic ovarian Wistar rats

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Background
Polycystic ovarian syndrome (PCOS) is a multifactorial condition with metabolic-related complication, including chronic renal disorder, which is the leading cause of renal transplant globally. HDAC inhibitors (HDACi) have been suggested to protect renal function against biological assaults. Nonetheless, the current study investigated the restorative role of HDACi, butyrate in experimental PCOS-induced renal disorder.

Materials and methods
Female Wistar rats (8-week-old) were divided into four groups; control, letrozole (LET), butyrate-treated and LET + butyrate-treated groups. To induce PCOS, 1 mg/kg of letrozole was given (oral gavage) for 21 days. After confirmation of PCOS, 200 mg/kg of butyrate was administered for 6 weeks.
Results
Rats with PCOS revealed disruption in glucose homeostasis (hyperinsulinemia and impaired glucose tolerance and insulin resistance) and presented with the phenotypes of PCOS (hyperandrogenism, multiple ovarian cysts and elevated LH/FSH ratio). Increased plasma and renal triglycerides and inflammatory (TNF-α/SDF-1/NF-kB) markers was observed with elevated levels of TGFβ-1, renal lipid (MDA) and redox imbalance (GGT, Nrf2, HIF-1α). Interestingly, animals with PCOS reported a significant increase in body weight as well as renal mass. Whereas, heightened levels of renal function markers (urea, creatinine, urea/creatinine ratio and creatinine kinase) indicating renal dysfunction, which subsequently led to renal apoptosis (Caspase-6) with increased HDAC2 levels. Notwithstanding, administration of butyrate averted the alterations.
Conclusion
The present investigation demonstrates that PCOS is characterized with reno-metabolic dysfunction, which is accompanied by an elevated level of HDAC2 with corresponding reduction in anti-oxidant capacity and increased lipid peroxidation. Furthermore, the study in addition suggests that butyrate restores renal function in PCOS by suppressing HDAC2 activity.
Keywords: Butyrate, Caspase-6, HDAC2, Renal, PCOS.
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P120

48,XYYY – a rare case in our endocrinology clinic
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Introduction
48,XYYY is a rare condition where two extra Y chromosomes alter the neurological, skeletal and reproductive development of the affected individual. Clinical features are usually subtle and the diagnosis is not suspected until fertility issues arise. Here, were report an adult patient with 48,XYYY in the Endocrinology Clinic.
Case Report
A 24-year-old male was referred to UHL Endocrinology Clinic following infertility evaluation. Blood tests showed primary gonadal failure (raised LH & FSH with low testosterone). Sperm count showed azoospermia. He was referred for microTESE procedure to assist in sperm retrieval. Clinically; tall stature (184cm), high-arched palate, surgically corrected congenital club feet & joint contracture was noted. Ultrasonography showed small volume testes. Despite having normal libido, he described erectile dysfunction and reduced ejaculatory volume. He struggled with anger issues and needed speech therapy as a child. Karyotyping by conventional cryptogenic analysis and Fluorescent In-Situ Hybridisation (FISH) revealed pure 48,XYYY karyotype. One paternal uncle's family members were taller than average but were not screened for Y aneuploidy.
Discussion
Both 48,XYYY and Klinefelter syndrome (1:500 – 1:1000 males) share similar features of tall stature, joints deformity, long fingers and mental problems. However, 48,XYYY is extremely rare. In fact, only 15 cases have been reported. The few reported 48,XYYY cases share features of skeletal and joints deformity, mental development and reproductive issues. There have been a couple of reports of increased cancer risk with Y chromosome extraploidy but this is difficult to predict due to sparsity of cases. Prenatal diagnosis should be considered for these patients if they become reproductive. We recommend follow up to understand the phenotypic features of this very rare condition.
Learning points
48,XYYY should be considered as a differential diagnosis when evaluating cases of tall stature, developmental and reproductive issues. Low-threshold to evaluate for malignancy if clinically suspected.
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P121

Hypoglycaemia in pregnancy post-bariatric surgery: A case series
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Background
Bariatric surgery (BS) is a well-documented treatment targeting weight loss excess. There is little evidence of the impact of BS on antenatal glycaemic control. We present three cases of pregnancy post-BS, who experienced various degrees of hypoglycaemia during gestation.
Case presentations
Three women aged 25-, 26-, and 36-years-old, who were previously euglycaemic, presented to the joint antenatal clinic with a history of gastric bypass or gastric sleeve surgery. Pregnancy was achieved 3, 7 and 8 years post-BS, respectively. They were referred after the first trimester of pregnancy for postprandial hypoglycaemia, presenting with sweating, palpitations, dizziness and loss of consciousness. Oral glucose tolerance tests (OGTT) were carried out in the first and third cases, at a gestational age of 28 and 29 + 3 weeks respectively. Subsequently, both women experienced postprandial hypoglycaemia (blood glucose (BG) at 1hr: 2.3mmol/l and 2.6mmol/l, respectively). The women experienced variable degrees of hypoglycaemia during their pregnancies (lowest recorded BG 2.2mmol/l), which was especially pronounced in the first case secondary to co-existent hyperemesis gravidarum. The second case was advised for BG-monitoring and was not offered OGTT. No delivery was uneventful: the first was induced at 38 weeks and required intravenous glycaemic support during delivery. The second underwent emergency caesarean section (CS) at 39 weeks due to failure to progress, under oral glucose-supplementation. The third underwent elective CS at 38 weeks, with no glycaemic imbalance during delivery. All newborns were healthy but of low birth weight (15.7th, 13.7th and 13.7th centile, respectively). Post-delivery there has been significant improvement in hypoglycaemic episodes; only the first woman experienced two early morning episodes before discharge (BG 3.5 mmol/l).
Conclusions
A personal history of BS is associated with a more frequent hypoglycaemic episodes during pregnancy, which appears to be exaggerated in women subjected to OGTT. Glycaemic control appears to improve after delivery.
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P122

Rare case of a steroid cell tumour causing hirsutism in a young girl
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Steroid cell tumours are very rare ovarian sex cord tumours that account for only < 0.1% of ovarian tumours. We present an interesting case of a steroid cell tumour in a 17 year old girl referred with worsening hirsutism, weight gain of nearly 3 stones and oligomenorrhea over 2 years. Menarche with regular menstrual cycles was attained at the age of 13 followed by normal reproductive development. On examination, she had an elevated BMI of 33.7 and there was marked hirsutism with Ferriman-Gallwey score of 22. There was a strong family history of Polycystic Ovarian Syndrome and this was the presumed diagnosis until our clinic review. Investigations revealed Testosterone raised at 8.1nmol/l (NR < 2.7), Androstenedione of 58.8 nmol/l(NR- 0-9). The rest of her hormonal profile was unremarkable. MRI of adrenal and ovaries showed normal adrenals but revealed a right ovarian mass of 5.1 x 4.3 cm. She was urgently referred to the gynaecological team and her case was discussed in the teenage and young adult Gynaecological MDT where she was listed for a right sided laparoscopic salpingo- oophorectomy. Following surgery, histopathology of the ovarian mass confirmed Steroid cell tumour. Predictors of malignant behaviour namely size > 7 cm, older age, significant mitotic activity, necrosis, haemorrhage and nuclear atypia were negative. Post-operative blood tests results 6 weeks later, showed normalisation of serum testosterone and androstenedione levels at 2.1 and 8.1nmol/l respectively followed by spontaneous resumption of menstrual periods 2 months later; hirsutism has not yet shown response, however she is only 4 months post-surgery. She remains under review with monitoring of her hormonal profile.
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P123

Type 4 Perrault syndrome in males: Is there a reproductive phenotype?
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Introduction
Perrault syndrome (PS), a rare autosomal recessive condition mostly reported in females, is characterized by sensorineural hearing loss (SNHL), ovarian dysgenesis manifesting as primary amenorrhoea (PA), premature ovarian insufficiency (POI) and neurological manifestations but little is known about testicular function in males.
Case summary
A 34 year-old man was referred with progressively reduced libido, erectile dysfunction and intermittent testicular pain with previous normal libido and sexual function until the age of 17. He had no history of mumps, testicular trauma, chemo-radiotherapy or anabolic steroids use. He had bilateral cochlear implants and neonatal hypospadias repair. His sister has PS type-4 (OMIM# 615300), with a phenotype of POI requiring HRT. He harbours the same pathogenic compound heterozygous variants in LARS2: c.1565C>A [p.T522N] and c.351G>C [p.M117I]. He was well virilised (normal facial hair and frontal balding), but had small testes (3 and 10 ml – confirmed on sonography) and azoospermia but normal ejaculatory volume. Hormonal workup showed normal Leydig and Sertoli cell function with normal LH, FSH, AMH, Prolactin, Testosterone and free testosterone. Although he did not proceed to testicular biopsy, the likely clinical picture was a problem with spermatogenesis.' Management included psychosexual counselling, maximal doses of various phosphodiesterase inhibitors, intra-urethral alprostadil, intra-cavernous alprostadil and vacuum devices, but with only minimal benefit. This impacted adversely on his personal life and reinforced his psychological stress.
Conclusions
1. Our patient had an isolated defect of spermatogenesis, but exhibited no biochemical features of testosterone deficiency or of defective Leydig-Sertoli cell function despite a compelling clinical history. Thus, the cause of his profound sexual dysfunction has not been elucidated by us.
2. PS should be considered when SNHL is associated with infertility, testicular atrophy or a positive family history.
3. Earlier diagnosis in males may enable sperm freezing prior to progression to testicular atrophy.

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P124

Klinefelter syndrome in a resource-challenged setting: A case report

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Introduction
Klinefelter syndrome is the commonest sex chromosomal disorder in which the normal male karyotype 46XY, has at least one extra X chromosome. The commonest form is the 47XXY aneuploidy. It is characterized by hypergonatrophic hypogonadism, and associated with infertility and cardio-metabolic abnormalities. We report a case of a 36year old man who presented in our Endocrinology clinic in Ngeria.
Case Presentation
A 36year old man who presented with progressive bilateral breast enlargement with small penis of 21year duration. The enlargement in both breasts was of insidious onset, and increased progressively. No associated pain, no galactorrhea. He also noticed diminished size of his penis and testis, but the recent concern of his fiancée made him present at the hospital. There is positive history of decreased libido and erectile dysfunction. No previous testicular injury, and childhood and puberty were reported to be normal. He was not on any chronic medications. There was no family history of endocrine abnormalities. He first presented to the General Surgeon on account of the breast enlargement from where he was referred to the Endocrinologists. Examination revealed a young man with body mass index (BMI) of 33.8kg/m2. He had micropenis, with the testicles measuring 2mls each. No features of Chronic Liver Disease. Hormonal assay- Luteinizing hormone: 11.8(0-12)mIU/ml, Follicular stimulating Hormone: 18.3(0-12)mIU/ml, Testosterone: 1.3(3-10)ng/ml, Prolactin: 21.7(0-17)mg/ml. Blood glucose measurements were repeatedly elevated. Lipid profile also showed hyperlipidaemia. Scrotal scan confirmed small testicles bilaterally. Cytogenic analysis shows 47XXY karyotype. He had counselling done, and he was commenced on antidiabetics and anti-lipid management. He was referred for possible sperm retrieval and storage.
Conclusion
Many patients with Klinefelter's syndrome remain undiagnosed. Lack of awareness may result in delayed presentation, and may be associated with poor outcome.

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P258

Significant weight loss associated with GLP1 receptor agonist use in obese women with polycystic ovary syndrome- a retrospective cohort study

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Introduction
Women with polycystic ovary syndrome (PCOS) have a higher prevalence of obesity and weight gain. Obesity negatively impacts the fertility, mental wellbeing and long term health of women with PCOS. The 2023 international guidelines for the management of PCOS suggest that GLP1 receptor agonists could be considered, but highlight a lack of evidence for medical obesity treatment in women with PCOS. Previous studies showed that interventions which reduce weight by as little as 5% of total body weight have metabolic, reproductive and psychological benefits in women with PCOS.
Methods
We retrospectively collected data on 48 obese women with PCOS attending a specialist reproductive endocrinology clinic who were prescribed GLP1 agonist therapy. All women were provided with contraceptive advice. All women were also given dietary advice by clinicians, although access to specialist dietetic support was not routinely available.
Results
Mean age of women was 32.2 $\pm$ 7.5 years. Median duration of GLP1 agonist therapy was 12 (8-17) months. 94% of the women used semaglutide and 47% were also taking metformin. Average weight loss with GLP1 agonist therapy was 11.2 $\pm$ 8.5 kg ($P<0.0001$). Median % total body weight loss was 11% (IQR 4.8-14.7%). 77% of women lost more than 5% and 55% lost more than 10% of their total body weight. Mean systolic blood pressure reduced from 131 $\pm$ 12 mmHg to 123 $\pm$ 11 mmHg ($P=0.02$). Mean diastolic blood pressure remained unchanged 82 vs 81 mmHg ($\pm$7) mmHg. Mean HbA1C reduced from 41 to 35 mmol/mol ($P=0.047$). There was no significant change in lipid levels. Testosterone levels and gonadotropins were not routinely remeasured after treatment commenced.
Conclusions
GLP1 agonist use in women with PCOS was associated with significant weight loss, as well as reductions in systolic blood pressure and HbA1C.

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P259

Abstract withdrawn

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P260

Ovarian mitochondrial dysfunction in letrozole-induced PCOS rat model: Therapeutic role of HDAC2 inhibition

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Background
Androgen excess and metabolic abnormality largely contribute to the pathogenesis of PCOS, which primarily precipitates ovarian dysfunction and infertility in reproductive-age women. Impaired mitochondrial function and epigenetic alteration have been linked to the development of PCOS. However, the therapeutic potential of histone deacetylase (HDAC) inhibition on ovarian mitochondrial dysfunction is unclear, especially in PCOS is unclear. Herein, the present study hypothesized that HDAC2i reverses ovarian mitochondrial dysfunction in experimental PCOS rat model, possibly through modulation of mitofusin-2 (Mfn2).

Methods
Eight-week-old female Wistar rats were randomized into four groups ($n=5$). PCOS was induced by 1 mg/kg letrozole (p.o.), administered for 21 days. Thereafter, the rats were treated with acetate (200 mg/kg; p.o.) for six weeks.
Results
The PCOS rats demonstrated excess body weight gain and ovarian mass, abnormal metabolic indices, androgen excess, multiple ovarian cysts, elevated anti-mullerian hormone and leptin and decreased SHBG, adiponectin and 17-β estradiol with corresponding increase in plasma and ovarian triglyceride as well as TGFβ-1. Additionally, mitochondrial abnormality, including lipid peroxidation, depleted NrF2, inflammation (TNF-α and NF-kB), elevated caspase-6 and ATP synthase, decreased HIF-1α and Mfn2 as well as elevated level of ovarian HDAC2 were observed rats with PCOS. Treatment with acetate reversed the alterations.
Conclusion
The present results collectively suggest that HDAC inhibition by acetate ameliorate ovarian mitochondrial abnormality, a beneficial effect that is accompanied by mitofusin-2 with consequent normalization of reproductive/metabolic endocrine profile and ovarian function. Perhaps, the present data provide hope for PCOS individuals that suffer infertility.

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P261

Gonadectomy in people with a difference of sex development: Initial data from an I-DSD registry prospective quality improvement study

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Introduction
There is some variation in the practice of gonadectomy for individuals with Differences of Sex Development (DSD) worldwide. This quality improvement project aims to undertake continued surveillance of the occurrence of gonadectomy in suspected or confirmed cases of DSD.
Methods
Participating centres from the International-DSD Registry are sent a monthly email asking if a gonadectomy has been performed. A secondary survey is then sent for additional information on those individuals who have had a gonadectomy and who have provided informed consent for inclusion in the I-DSD Registry. This project will run until December 2025 and recruitment remains open for interested parties.
Results
During the first 6 months, a total of 56 gonadectomies have been reported from 15 (45%) countries. A median of 1 (0, 5) gonadectomy has been reported per centre. So far, 17/56 (51%) of the cases have been registered on the Registry with secondary surveys complete from 14 (82%) of these. Of these, median age was 2.3 years (2 days, 20 years). Eleven (79%) gonadectomies were bilateral. The most common underlying diagnoses were disorders of gonadal development in 5 (36%) , chromosomal DSD in 4 (29%) and disorders of androgen action in 3 (21). Indications for gonadectomy were for mitigation of tumour risk in 7 (50%), due to abnormal gonads in 3 (22%), to align with sex assignment in 2 (14%) and at parental request in 2 (14%). All individuals had been seen by a multidisciplinary team at a specialist centre prior to gonadectomy.
Conclusions
Prospective surveillance of rare procedures is possible via monthly email reporting. Such studies are essential to inform healthcare professionals regarding best practice in rare DSD conditions. Approximately 9 gonadectomies are reported per month in DSD specialist centres throughout the world. More data will be collected regarding the practices surrounding gonadectomy in these centres.

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P262

Sex affects Ca^{2+} channel expression of adult inguinal fat adipocytes and their Ca^{2+} response to oxytocin: Roles in mammogenesis and function?

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Inguinal subcutaneous fat, the site of murine mammary glands 4 and 5, is a suitable model of mammary white fat adipose tissue (WAT). WAT requires extracellular Ca^{2+} influx for differentiation and expansion; this primarily occurs via plasma membrane Ca^{2+} voltage-dependent channels (CaVs). Whereas the neuropeptide oxytocin can mobilise intracellular Ca^{2+} in WAT which has key roles in lactation. Our aim was to use a combination of molecular biology and calcium imaging to determine if post-pubescent differences exist in CaV expression and oxytocin Ca^{2+} responses between the sexes. We used qPCR on inguinal subcutaneous fat depots from pre (P14-30) and post-pubescent (>P140) male and female rats to explore their CaV expression profile. We measured cytosolic Ca^{2+} concentration, $[Ca^{2+}]_i$, in adipocytes isolated from inguinal fat pads of post-pubescent CD-1 mice (P32-84) with epifluorescent videomicroscopy. CaV expression was dependent on age and sex. A rank order of CaV1.2> CaV1.3>CaV3.1>CaV3.2 >Cav3.1 was observed in adult males but not females where the rank order was CaV3.1 = CaV1.2> CaV1.3>CaV3.1> CaV3.2. CaV3.1 expression was significantly larger in females compared to males; a difference not seen in pre-pubescent animals. No difference was seen in either diameter or basal $[Ca^{2+}]_i$ between adult male and female mouse inguinal adipocytes. However, we observed an association between sex and the adipocyte's ability to respond to oxytocin: 52% of males compared to 100 % of females. The type of Ca^{2+} response was also associated with sex where only 14% of male responders demonstrated oscillations compared to 32% of female cells. We show that changes in Ca^{2+} voltage-dependent channel expression patterns and Ca^{2+} mobilization occur during adipogenesis in inguinal subcutaneous fat. Consequently, CaV3.1 and oxytocin are potential pharmacological targets to modulate adipogenesis and lactation in the development and function of mammary glands respectively.

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P263

A case of high testosterone in an asymptomatic female patient

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Introduction
Testosterone <5nmol/l is commonly seen in conditions such as PCOS however when testosterone is >5nmol/l, concerns start to rise about more sinister causes. Here, we present a case of a female who was referred to clinic with testosterone > 5mmol/l
Case
A 32 year old presented to the GP with a heavier than usual menstrual period. For an unknown reason, the GP checked testosterone, which came back as 8.5nmol/l (0.5-2.6) and 10.3nmol/l on repeat testing. When taking the clinical historyin clinic, there were no signs or symptoms of hyperandrogenism and periods were regular. The patient took no regular medications including no contraception and denied over-the-counter/herbal remedies. Testosterone previously checked when the patient was 23 years old was 1.7nmol/Lessentially excluding androgen insensitivity. Testosterone was remeasured and was 9.4nmol/l. 17-OHP, androstenedione and DHEA-S were normal. A testosterone producing tumour was suspected. MRI of the ovaries and adrenals were urgently requested in which only polycystic ovaries and adenomyosis were seen. Given the lack of signs or symptoms of high testosterone or PCOS, assay interference was suspected so blood was sent to other laboratories for analysis. Whilst awaiting these results, a dexamethasone suppression test was arranged and testosterone fell from 8.5nmol/l to 4.7nmol/l. Our local laboratory uses a testosterone immunoassay. Testing on another immunoassay platform at another laboratory revealed a testosterone result of 13.3nmol/l (0.3-1.7). The same sample, when tested using liquid chromatography mass spectrometry gave a result of 1.9nmol/l (0.2-2.1) confirming assay interference. The patient denied contact with animals, although did eventually reveal taking a pro-collagen supplement containing biotin.
Learning point
Having an understanding of which assays are used in your local laboratory is essential when interpreting test results. When signs and symptoms do not match the results, think about assay interference.

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P264

Insights into dysregulation of luteinizing hormone receptor (LHR) signaling in granulosa lutein (GL) cells from women with polycystic ovary syndrome (PCOS)

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Polycystic ovary syndrome (PCOS) is a multifactorial, complex endocrine disorder affecting a significant proportion of the global population. Aberrant secretion and/or action of gonadotropins is implicated in PCOS, but, to date, we have only limited knowledge about the precise mechanisms involved. We therefore studied LHR expression, signalling and trafficking in GLCs from women with and without PCOS. GLCs from women with PCOS exhibited enhanced Gαs-cAMP signalling response to LH, without changes in receptor gene expression. Dose response studies revealed increased potency and efficacy of LH-induced cAMP in PCOS GLCs, indicating increased LHR sensitivity. We have previously demonstrated that LHR activation of cAMP signalling in HEK 293 cells requires receptor internalization to very early endosomes (VEEs), where Gs-cAMP signalling and recycling are tightly regulated by the adaptor protein APPL1. We have now shown that LH-mediated cAMP signalling in control GLC cultures is regulated by APPL1 in a similar manner and induces an LH-dependent increase in *CYP19* expression. However, in PCOS GLCs, inhibition of APPL1 dramatically reduces, rather than enhancing, LH-mediated cAMP levels, suggesting that APPL1 is driving this enhanced LHR activity, via altered phosphorylation of APPL1. Furthermore, pretreatment with insulin of GLCs from non-PCOS women mimics the 'switch' in APPL1-dependent regulation of LH-mediated cAMP signalling, while in PCOS samples, GLCs are resistant to insulin stimulation. We propose that insulin receptor (InsR), known to also be regulated by APPL1, underlies the enhanced APPL1-dependent cAMP signaling. To investigate this further, APPL1 was immunoprecipitated from control GLCs, indicating LH-mediated increase in PKA-dependent phosphorylation of APPL1 at serine 410. In summary, we have shown that LHR activity is tightly controlled at a spatial level, and we suggest that alterations in serine/threonine and tyrosine phosphorylation of APPL1 accounts for the aberrant cAMP response to LH in PCOS GLCs.

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P265

Non-invasive assessment of liver abnormalities in turner syndrome: A Follow-up Study

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Background
We have previously reported abnormal liver function tests (LFTs), FIB-4 scores and liver stiffness measurements (LSM, Fibroscan) in patients with Turner syndrome (TS), but longitudinal data defining the impact of TS on liver phenotype are limited.
Methods
We undertook a retrospective longitudinal follow-up audit (OUH; 8348) of 24 women with TS who had abnormal LFTs and underwent at least 2 assessments (median age at baseline 43 years, range 20+/-64). Biochemical measurements (ALT/AST/GGT) and LSM were collected. FIB-4 scores <1.3 were indicative of a low risk of advanced fibrosis; scores >2.67 indicated a high risk of advanced fibrosis. LSM >8kPa indicated significant fibrosis, and >13kPa was suggestive of cirrhosis.
Results
After 4.5+/-1.4 years observation period, in those women with normal AST and ALT at baseline, 53% (8/15) and 50% (5/10) respectively became abnormal, subsequently re-normalising in 3 and 2. In those with baseline abnormal transaminases, 2/7 and 4/12 were normal at follow-up. GGT measurements showed less fluctuation; one patient normalising. Considering FIB-4 scores, 11/20 women remained in the low-risk category, while 3 became indeterminate (comorbidity/drug related), and 3 initially considered indeterminate normalised. Fifteen women had a new Fibroscan after a period of 4.6+/-1.8 years. 13% (2/15) showed LSM suggesting significant fibrosis, including one with LSM >13kPa. Among 14 women who had available LSM measurements at baseline and follow-up, most improved (71%, 10/14): 79% (11) remained below the LSM cut-off of 8kPa, two entered the low-risk and the one with the high LSM measurement improved from 13.9 to 9.4kPa.
Conclusion
Fluctuations in aminotransferases and non-invasive scores (FIB-4) are common in patients with TS. Reassuringly, LSM showed no significant fibrosis in the majority (87%) of patients and no progression to high risk categories. Further longitudinal analysis of liver phenotype in patients with TS in larger cohorts is now warranted.

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P266

The mystery of bulky testes

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A 7 year old boy presented with complaint of scrotal heaviness and swelling more on the right side. He had history of early and disorganised tanner pubertal growth pattern: development of axillary hair > penile enlargement > pubic hair > right testicular enlargement. On examination, he was found to have elevated blood pressure and bilateral testicles were enlarged (right > left) and non-tender. Based on these clinical findings, diagnosis of precocious puberty was suspected. The patient was advised ultrasonography of scrotum and relevant testicular tumour markers like AFP, LDH, hCG levels. USG of scrotum revealed multiple well-defined smooth walled heterogeneously hypo-echoic lesions in bilateral testis, which show internal vascularity on colour doppler. Lesions being bilateral, possibility of systemic cause like infection, secondary due to adrenal gland hormonal secreting neoplasm or central cause like hormone secreting pituitary neoplasm could not be ruled out. To confirm the findings, MRI scrotum with abdominal and pituitary screening was carried out. MRI scrotum showed multiple well-defined conglomerated lesions appearing T1 hyper-intense T2 hypo intense and showing homogenous post-contrast enhancement replacing bilateral testis. MRI abdomen showed bulky bilateral adrenal glands with mildly lobulated margins and heterogenous signal intensity. Laboratory parameters were suggestive of hypokalaemia, hypocortisolism with elevated testosterone and ACTH levels. In this patient with history of precocious puberty with hypertension and hypokalaemia, Diagnosis was made of Congenital Adrenal Hyperplasia(-CAH) with Testicular Adrenal Rest Tumours (TARTs) secondary to 11-beta hydroxylase deficiency. TARTs are an important complication of CAH, which probably develop from ectopic remnants of intra-testicular adrenal tissue stimulated by Adrenocorticotropic hormone (ACTH) hypersecretion. Treatment for TART includes suppressive medical therapy by glucocorticoids which suppresses ACTH. Our patient was started on hydrocortisone tablet and followed up after 6 months. There was reduction in the number and size of lesions in both testis on ultrasound with normalisation of blood pressure

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P267

Kallmann syndrome with unilateral anosmia

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Introduction
Kallmann syndrome (KS) is a rare genetic disorder typically due to defective migration of olfactory-axons and GnRH-neurons. KS results in congenital hypogonadotrophic hypogonadism (CHH) typically associated with absent (anosmia) or reduced (microsmia) sense of smell. Unilateral hypoplastic/absent olfactory bulbs on MRI are reported, although disturbance in smell is usually bilateral. Here, we present an unusual case of KS with unilateral anosmia.
Case Presentation
A woman presented to the endocrine clinic for management of KS aged 18yrs. Her mother and sister were known to have KS (FGFR1-mutation) having presented with

primary amenorrhoea and anosmia. Her mother conceived following ovulation induction. At presentation, she had normal secondary sexual characteristics, and had undergone spontaneous menarche aged 16yrs. Over the preceding two years, she had five menstrual periods followed by secondary amenorrhoea. Unusually, she reported a normal sense of smell via her right nostril, but complete anosmia via the left nostril. MRI-brain revealed unilateral absence of the left olfactory nerve, bulb and sulcus. She had no other medical history, normal BMI (22 kg/m2), didn't report excessive stress or exercise, and took no regular medications. She had an undetectable oestradiol (<100 pmol/l), low LH (0.2 IU/l) and FSH (0.4 IU/l). Pelvic-ultrasound demonstrated a thin endometrium (3mm), consistent with a hypoestrogenic state. After 100mg GnRH-test, she had a normal rise in LH of 24.82 IU/l. After a kisspeptin challenge-test, she had a subnormal early rise in LH of 3.43 IU/l.

Discussion

This lady had spontaneous puberty and menarche indicating some residual GnRH neuronal functionality. Further, she had a small early subnormal gonadotropin response to kisspeptin, rather than the absent response typically observed in complete KS. This, and in keeping with her unilateral anosmia, unilateral olfactory bulb on MRI, suggest that she has an unusual partial/unilateral GnRH-neuronal deficiency.

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P268

Simultaneous adrenal and ovarian vein sampling in the evaluation of androgen excess in women

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Background

Most women with androgen excess have polycystic ovary syndrome (PCOS); however, rarer pathology is considered in a severe phenotype such as ovarian or adrenal androgen-producing tumours. Simultaneous adrenal and ovarian vein sampling is rarely performed to aid the localisation of the androgen excess source. We report four cases that underwent this procedure.

Case descriptions

Case 1: A 27-year-old presented with infertility, long history of menstrual disturbance and hirsutism. Testosterone was 36.5nmol/l without suppression after 96hr dexamethasone or GnRH superagonist. MRI showed left ovarian 2.0cm lesion. Venous sampling showed left ovarian testosterone 710nmol/l. Histology after left oophorectomy confirmed Leydig-cell tumour and testosterone normalised.

Case 2: A 47-year-old presented with 12-months of hirsutism and testosterone 17.4nmol/l without suppression after 96hr of dexamethasone or GnRH super-agonist. Cross-sectional imaging showed no tumours. Venous sampling showed left ovarian testosterone >80nmol/l. Histology after bilateral oophorectomy confirmed Leydig-cell tumour and testosterone normalised.

Case 3: A 64-year-old presented with 15-years of virilisation and testosterone 17.4nmol/l without suppression after 96hr of dexamethasone. Imaging showed bilateral adrenal adenomas (right 2.6cm, left 1.0cm) and normal ovaries. Venous sampling showed right adrenal testosterone 48.9nmol/l. She then developed acute valvular heart failure which precluded surgery.

Case 4: A 24-year-old presented with hirsutism and menstrual disturbance since menarche. High testosterone 4.9nmol/l, DHEAS 15.8 mol/l, and androstenedione 18.8nmol/l triggered adrenal CT which showed 1.0cm right-sided adenoma. Transvaginal ultrasound showed PCO. 96hr dexamethasone suppression test showed no testosterone suppression, DHEAS suppression 11.6μmol/l to 3.2μmol/l, and androstenedione 19.1nmol/l to 13.0nmol/l. Venous sampling showed right and left ovarian testosterone 10.9nmol/l and 14.6nmol/l, respectively. The working diagnosis was PCOS with adrenal hyperandrogenism and incidental adrenal adenoma.

Conclusion

Adrenal and ovarian vein sampling has a role in selected challenging cases of androgen excess in women to localise the source. However, the procedure is non-standardised and requires careful interpretation.

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P269

A case of postpartum hypophysitis initially treated as postpartum thyroiditis

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A 45 yr lady;presented with lethargy and tiredness, amenorrhea with 2 stone weight loss 3 months after delivery of her baby. Her thyroid functions were done showing low free T4 (0.28 mu/l) as well as low TSH (07 pmol/l). (Thought to be cooling off period of post-partum thyroiditis). She was started on Thyroid hormone replacement (levothyroxine 150 mg once a day) Reviewed again after a month in endocrine clinic, she still feeling tired, lethargic and unwell still not having periods. Repeat Thyroid Function Tests showed that she was over replaced, so thyroxine was stopped but on this occasion a full work up was done including complete pituitary profile. She was followed up again with pituitary functions results which showed a low Random Cortisol, followed by that she had a short synacthen test which confirmed adrenal insufficiency [Cortisol at 0 min = 170 ; 30 mins = 248; 60 mins = 267]. FSH 11.6, LH 3.1, estradiol >72. So, she was admitted to the hospital and was diagnosed with Panhypopituitriam and was commenced on Hydrocortisone and levothyroxine at a smaller dose 25 mcg. An MRI pituitary gland was also arranged for her, which showed bulky pituitary gland but no adenoma. She remained on steroid replacement and was subsequently followed up after couple of years, still having symptoms of tiredness, which were attributed to menopause. Her PTH levels were high with slightly low Calcium and normal Vit.D. She was treated as secondary hyperparathyroidismIn with Vit D and calcium replacement. Recently she presented with seizure like episodes and a low random cortisol again, but on this occasion her Short SynacthenTest was normal, so all her steroid therspy was stopped and a repeat MRI pituitary requested.

Conclusion

We should Consider Panhypopituitriam as a differential diagnosis in a patient presenting with postpartum thyroiditis.

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P270

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in pre-eclampsia: A rare case of hyponatraemia in pregnancy

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Hyponatraemia in pregnancy can be precipitated by various factors, including drugs, fluid excess and oxytocin infusion. It is a common complication of pre-eclampsia toxaemia (PET), although concomitant syndrome of inappropriate ADH secretion (SIADH) in this context is rare. We present a case of SIADH leading to hyponatraemia in a PET patient. A 30 year-old primigravid woman with bipolar disorder and hypertension was admitted with pre-eclampsia at gestational week 28. Her medications included nifedipine, labetalol and quetiapine. At week 32, her sodium level dropped to 125 mmol/l. She appeared euvolaemic. Kidney function, glycaemic review and thyroid function were within normal range. She had a serum osmolality of 257 mosmol/kg, urine osmolality of 446 mosmol/kg and urine sodium of 32 mmol/l. The clinical and biochemical features were consistent with a diagnosis of SIADH. Despite fluid restriction, her serum sodium level did not improve. Four days later, an emergency Caesarean section was performed due to signs of foetal distress. Pre-operative serum sodium was 125 mmol/l, but it improved to 133 mmol/l on the first day post-operatively and she was discharged home with a serum sodium of 137 mmol/l. SIADH as a cause of hyponatraemia in PET is rare and only few reported cases are published. The mechanism of SIADH in pre-eclampsia is unclear, but it is thought that the reduced intravascular volume may stimulate excess ADH release. Hyponatraemia carries a prognostic significance and, if untreated, can lead to complications such as seizures in pregnant women and hyponatraemia in neonate. Severe hyponatraemia in this context can be challenging as clinically available drugs to treat hyponatraemia related to SIADH are contraindicated in pregnancy. However, the hyponatraemia usually resolves rapidly following childbirth. This case therefore serves as a reminder of a rare cause of hyponatraemia in PET.

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P271

Are we paying enough attention to detect autoimmune hematological diseases in turner syndrome? Retrospective analysis of a clinic database from a single specialist center

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Introduction
There is limited literature on autoimmune haematological disorders (AIHD) such as autoimmune thrombocytopenia (ITP), autoimmune haemolytic anaemia, and autoimmune neutropenia (AN) in Turner syndrome (TS) although autoimmune disorders are more common in TS.
Methodology
Retrospective analysis of a clinic database, to identify patients with AIHD out of all the patients followed up in a specialised TS clinic. ($n=$ 168) (Audit number–8394)
Results
Three patients were identified out of 168 patients. Karyotypes were 45,X; 45,X/46,X i(Xq); and 45,X/46,XX. Ages at presentation with AIHD were 34 - 38 years. Two patients developed AIHD (one ITP and one AN) during the follow-up for TS. A further patient initially presented with ITP and was diagnosed with TS following a bone marrow biopsy performed for ITP. Presenting symptoms were ecchymosis and gum bleeding (ITP) and recurrent sore throat and sinusitis (AN). Platelet counts were 2 x 10 9/l and 28 x 10 9/l (ITP) and Neutrophil count was 0.1 x 10 9/l (AN). Treatment received were high dose prednisolone ($n=1$) Rituximab ($n=1$) and granulocyte colony-stimulating factor ($n=1$). All three responded and there were no relapses. One had autoimmune hypothyroidism and others had no autoimmune disorders and had negative TPO and TTG antibodies.
Conclusion
Current guidelines do not recommend routine monitoring of full blood count in TS. AIHD are serious conditions and affected 1.67 % of our cohort with TS. AIHD can occur in women with TS, even in the absence of other autoimmune conditions or commonly seen autoantibodies. Our report highlights the importance of maintaining a high level of suspicion of AIHD in TS patients regardless of karyotype to ensure prompt diagnosis and appropriate treatment to prevent potentially life-threatening complications of pancytopenia.

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P272

Spurious elevation of serum alpha-fetoprotein level due to assay interference-challenges in managing discrepant results

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Introduction
Alpha-fetoprotein (AFP), produced by the yolk sac and liver, is the most abundant serum protein in the human foetus. In adults, elevated AFP maybe associated with germ-cell or non-germ cell tumours, gastrointestinal tumours, active liver disease and hepatocellular carcinoma. Our case illustrates diagnostic uncertainties due to persistently elevated AFP values in the absence of any obvious pathology.
Case Presentation
A 22-year-old male was referred for assessment of gynaecomastia. He had no breast discomfort or galactorrhoea. On examination there was bilateral symmetrical gynaecomastia with no palpable breast lumps. Investigations showed normal liver function, gonadotropins, prolactin, testosterone, oestradiol and HCG. AFP was mildly elevated at 8.9 kU/l (normal range 0.1 – 7 kU/l). Ultrasound testes showed a normal solitary left testis with no intra testicular mass. Hepatitis serology and autoimmune screen was normal, but AFP remained elevated at 9.5 kU/l. Whole body cross sectional imaging to look for an occult germ cell tumour showed no significant abnormality within the liver and no pathological retroperitoneal or mesenteric nodes. Assay interference was suspected and paired samples were analysed in different laboratories. AFP analysed using the Siemens assay was elevated at 8.2 kU/l, whereas AFP analysed using the Roche assay in a different laboratory was normal at 4 kU/l (normal range 0 – 6 kU/l), indicating clear biochemical evidence of assay interference with spuriously elevated AFP values in our laboratory.
Conclusion
AFP assays are susceptible to interference by heterophile antibodies which can cause nonspecific false-positive results through usual mechanisms involving the capture and detection antibodies in immunoassays. Assay interference should be considered as a potential cause of persistently raised AFP values if other investigations are normal. This avoids the need for unnecessary surveillance imaging which has both cost and radiation safety implications.

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P273

Severe postmenopausal hirsutism and virilization caused by a virilizing ovarian dermoid cyst

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Introduction
Ovarian dermoid cysts, also known as mature cystic teratomas, are a very rare cause of virilization. Virilization in such cases is usually secondary to Sertoli-Leydig tumours, Leydig cell hyperplasia or Sertoli cell tumour. In some cases, no clear explanation for hyperandrogenism is found. Surgical excision of dermoid cyst results in normalization of androgen levels and resolution of symptoms.
Case Presentation
A 58-year-old female was referred with a short history of new onset hirsutism affecting her face, chest and abdomen, scalp hair thinning, increased muscularity, deepening of voice and reduced breast size. Her symptoms started 12 months previously and were rapidly progressive. Examination showed facial and body hirsutism, increased muscularity, androgenic alopecia, and deep voice. There were no clinical features suggestive of Cushing's syndrome or insulin resistance. Investigations confirmed a markedly elevated testosterone (16.9 nmol/l), FSH and LH in the post-menopausal range and normal androstenedione, DHEAS and 17-OH-Progesterone levels. Overnight dexamethasone suppression test (ODST) was normal. Pelvic ultrasound showed a large complex cyst in the left adnexa suggestive of a dermoid cyst. CT scan of abdomen and pelvis confirmed the presence of a left adnexal lesion suggestive of an ovarian dermoid cyst and a bulky left adrenal gland. An adrenal protocol CT scan showed density and washout characteristics suggestive of an adrenal adenoma. The ovarian cyst was surgically excised, and histopathology confirmed ovarian dermoid cyst with an associated Sertoli cell tumour. Testosterone levels normalized after surgery and the patient reported significant improvement in her symptoms. Whilst it is important to rule out adrenal and ovarian tumours in postmenopausal women presenting with virilization, this case highlights the importance of considering other, less common causes of hyperandrogenism. A high index of suspicion remains the cornerstone of diagnosis.

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P274

Clinical data suggesting variable dynamics between BMI, LH/FSH ratio and FSH alone in a cohort of patients with polycystic ovary syndrome

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Background
Polycystic Ovary Syndrome (PCOS) is characterized as a triad of menstrual irregularities, hyperandrogenism and polycystic ovarian morphology. There is a wide variation in Body Mass Index (BMI) for those fitting PCOS criteria; Identifying differences in relation to Lean BMI patients' endocrine markers such as LH/FSH ratio and other markers could help identify key areas for improved phenotypic classification. We aimed to focus on a sequential cohort of PCOS patients amongst a population of diverse ethnicity.
Method
12 patients who fit the criteria for PCOS seen in the Outpatient Endocrine Clinic at Northwick Park Hospital in London were evaluated and ranked according to BMI, with endocrine data analyzed accordingly. LH and FSH were measured. Given the variation in BMI, the patients were assessed in terms of trends in LH/FSH ratio and LH, FSH alone according to the BMI.
Results
The 12 patients included an extensive range of BMI from 18.7 to 36.2. Within this cohort the 50% of higher BMI had a mean LH/FSH ratio of 2.98 compared to the lower BMI group where it was 2.06 – a 31% difference. However, the 50% of higher BMI had a mean FSH level of 3.68 compared to the lower BMI group where it was 6.28 – a 29% difference in the opposite direction
Discussion
There is large variation in BMI in those with PCOS. Diagnostic error may manifest if classical endocrine features are under-recognised and therefore inappropriate management plans may be enacted. Clarification of variation in hormonal biochemistry between sub-types of PCOS is therefore necessary. We have noted preliminary observational data that LH:FSH ratio may relate to BMI and data in the opposite direction with FSH alone. Further research to classify data based on ethnicity, plus larger cohort studies, will enable improved diagnostic accuracy in such patients.

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P275

Any place for testosterone replacement therapy in functional hypogonadism? A case report

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Introduction
Functional Hypogonadism (FH) is a condition with low circulating serum testosterone and an intact Hypothalmo-pituitary-gonadal axis. The use of testosterone replacement therapy (TRT) use in FH is controversial based on the risk-benefit ratio. This report highlights the benefits of managing FH with TRT.
Case Presentation
47-year-old man presented to the endocrine clinic on account of poor erection, reduction in libido and quick ejaculation of 3 years duration. There was associated infrequent and unsatisfying sexual activities with marital strain. He was diagnosed with diabetes mellitus seven years earlier; glycaemic control has been poor due to non-drug adherence. He takes no steroids or opioids. He has four children in a monogamous family setting, with no other sexual partners. On physical examination, BMI was 30kg/m2. BP-112/78mmhg. Other systemic examinations were unremarkable. He has normal male-pattern hair distribution. Penile length was normal and both testes were descended in the scrotum, with testicular size 20ml bilaterally. He has no gynaecomastia. Investigations revealed elevated FBS(8mmol/l). Fasting Serum Testosterone was low at 2.18ng/ml (2.6-10), SHBG, LH and FSH were normal. Liver and Thyroid function, Prolactin, FLP and PSA were all essentially normal. A diagnosis of Functional Hypogonadism with poor glycaemic control was made and he was commenced on Testosterone gel 50mg daily, anti-diabetic medications, along with lifestyle modifications. Subsequent follow-up visits showed improvement in sexual functions and better glycaemic control with moderate weight loss. After one year of TRT, serum testosterone had normalized: 6.97ng/ml (2.6-10), with restored sexual function, then TRT was discontinued.
Conclusion
This report highlights that TRT is useful in non-reversible FH as it improves sexual functions and cardiometabolic profiles, normalizes testosterone levels with no documented adverse effects. Adequate monitoring of cardiovascular safety and adverse effects is paramount when used in men with FH.

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P375

An unusual case of azoospermia

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Leydig cell tumors are a rare form of hormonally active testicular tumors. They often present as a painless testicular mass. Infertility as the primary presentation is rare in this condition. A 32 year old man, presented with symptoms of infertility and hypogonadism which had occurred over a period of 1 year. He however was found to have a raised testosterone and estradiol levels as well as suppressed gonadotrophin levels. The patient had a historic sperm analysis done 2 years prior which was normal and a second one done 2 months prior to his presentation to us which showed azoospermia. An ultrasound of his testes revealed a 2.9x 1.6cm testicular mass. He underwent a left radical orchidectomy which revealed the mass to be a Leydig Cell tumour. 6 months after his surgery, his testosterone and estradiol levels normalized and a repeat sperm analysis showed a normal sperm count and morphology. We this case we wish to highlight an unusual presentation of Leydig cell tumor in which the primary presenting symptoms was that of infertility with azoospermia and hypogonadal symptoms but with contrasting hyperandrogenism.

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P376

Endocrinological alterations in patients with hiv infection, analysis between variables of a latin american hospital

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Background
Study the frequency of thyroid, adrenal, and gonadal dysfunction in HIV-infected patients and correlate them with CD4 cell count levels. Design: Cross-sectional study of 760 HIV-infected adults. in the period from January 2016 to December 2018.
Methodology
Free T3, free T4, TSH, Cortisol, FSH, LH, testosterone and estradiol were estimated by the radioimmunoassay method. Hormone levels and their correlation with CD4 count were compared. Qualitative variables were evaluated using the Chi-square test or Fisher's exact test, and in the case of numerical or quantitative variables, the Student's T or Mann-Whitney test was used.
Results
Of the total sample, only 43 presented endocrine disorders. The prevalence of gonadal dysfunction (88.3%) was the most frequent endocrine dysfunction, followed by thyroid (60.4%) and adrenal (27.9%) dysfunction. Secondary hypogonadism (68.4%) was more frequent than primary (31.6%). The difference in hormonal dysfunction between genders was not statistically significant ($P > 0.05$). 27.9% of the patients presented multiple alterations. There was negligible or no correlation between CD4 count and serum hormone level.
Conclusion
In our study, endocrine dysfunction was quite common among HIV-infected patients, + there was no correlation between these alterations and CD4 count. Longitudinal studies should be carried out with a larger population to correlate the association of endocrinopathy and HIV as well as its responsible mechanisms and the risks in this population.

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P377

Hypoglycaemia in pregnancy post bariatric surgery: A case series

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Background
Bariatric surgery (BS) is a well-documented treatment targeting weight loss excess. There is little evidence on the impact of BS on antenatal glycaemic control. We present four cases of pregnancy post-BS, reviewed in the joint antenatal clinic, who experienced various degrees of hypoglycaemia during pregnancy.
Case presentations
Four pregnant women (cases A–D, aged 25–36-years-old, 3–8years post-BS) were referred for postprandial hypoglycaemia, presenting with sweating, palpitations, dizziness and loss of consciousness. Oral glucose tolerance tests (OGTT) were performed in cases A,B,C (gestational age 28–30w) at the discretion of the obstetrics team; all three women experienced postprandial hypoglycaemia with the OGTT (blood glucose (BG) at 2hr: 1.8–2.6mmol/l). The women experienced variable degrees of hypoglycaemia during pregnancy, especially pronounced in case A secondary to co-existent hyperemesis gravidarum, and case C due to preconception hypoglycaemia unawareness. Case D fortunately was advised for BG-monitoring only. No delivery was uneventful: case A, induced at 38w, required intravenous glucose-supplementation during delivery; case B underwent emergency caesarean section (CS) at 39w due to failure to progress, under oral glucose-supplementation; case C underwent emergency CS at 38 + 3w, due to reduction in foetal growth velocity (estimated birth weight (BW) 69 → 53 centile) and required intravenous glucose-supplementation throughout admission until postpartum; case D underwent elective CS at 38w, with no glycaemic imbalance during delivery. All newborns were healthy, and babies A,B,D were of low BW (centiles: 15.7, 13.7, 13.7). Post-delivery there has been significant improvement in hypoglycaemic episodes.
Conclusions
Whilst Endocrinologists recommend avoiding OGTTs in women with BS, clear guidelines need to be developed for the multidisciplinary antenatal teams to ensure OGTTs are avoided, as well as guiding management of hypoglycaemia in pregnancy and during delivery. Future studies should investigate the role of BS type and impact on hypoglycaemia in pregnancy.

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P378

Circadian and post-glucose load changes in salivary testosterone concentration

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Background
The diagnosis of male hypogonadism can be difficult. Free testosterone is calculated if total testosterone is close to the lower limit of normal, however, this is inaccurate in conditions that alter sex-hormone-binding globulin. Alternatively, salivary testosterone is thought to reflect free testosterone, but is present at low concentrations, thus requiring sensitive mass spectrometry instrumentation, and there is limited data on the pre-analytical influences, for example circadian rhythm and effect of meal.
Objective
To investigate circadian rhythm and post-glucose load changes in salivary testosterone.
Methods
Saliva samples were collected from 17 male participants at 09:00, 10:00 and 11:00 following an overnight fast and again at 22:00, 23:00 and midnight following a fast from 14:00. Saliva and serum samples were collected before and after a glucose load from 32 male participants undergoing an oral glucose tolerance test (OGTT). Salivary testosterone assay was setup and validated on the Waters Xevo TQ-S micro-LC-MS/MS.
Results
The salivary testosterone concentration decreased by 12.1% (mean ± SD 23.1 ± 20.9 pmol/l, $P=0.0003$) at 11:00 and 37.1% (71.0 ± 62.2 pmol/l, $P=0.0001$) at 22:00 compared to 09:00. There was no significant change between 22:00 and midnight. In the OGTT cohort, the salivary testosterone concentration decreased by 18.1% (32.2 ± 44.6 pmol/l, $P=0.0003$) at 2 h post-glucose load. The decrease in serum total testosterone or calculated free/bioavailable testosterone at 2 h post-glucose load was not significant. Fasting salivary testosterone correlated more strongly with calculated free testosterone ($r=0.755$) and calculated bioavailable testosterone ($r=0.746$) compared to serum total testosterone ($r=0.532$).
Conclusions
A significant diurnal change and decrease in salivary testosterone after an oral glucose load was identified in two different participant cohorts. Further investigations are required to clarify how much of the decrease was due to circadian change or glucose load.

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P379

Protective effects of Betanin against noise and scrotal hyperthermia on testicular toxicity in wistar rats: Role of oxidative stress, apoptosis, and inflammation

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The present study was conducted to investigate the signaling pathway involved in betanin against noise and scrotal hyperthermia and to clarify whether it affects oxidative stress, apoptosis and inflammation in testis of rats. Scrotal hyperthermia was induced by heat exposure of rat testicular for 43ºC for 15 min (3 times per weeks for 14 days). Noise induction was done following exposure of rats with 100 decibel noise level for 14 day and 8 h daily similar to real condition. Betanin at the sub-effective dose of 15 mg/kg/day was administrated by gavage for 4 weeks (5 times in week) to male rats. The animals were sacrificed and testis were dissected and collected in freezer (-80°C). Then, the oxidative stress biomarkers, nitric oxide (NO) level, apoptosis, and inflammatory cytokines levels were studied by the real time polymerase chain reaction (RT-PCR). Our data revealed that noise and scrotal hyperthermia as pollutant caused to testicular toxicity in wistar rats via induction of oxidative damage, apoptosis and inflammatory mediators. In addition, betanin suppressed oxidative stress biomarkers apoptosis induction and caused to significantly decline in TNF-α and IL-6 gene expression level. betanin exhibited protective effects in testis following scrotal hyperthermia and noise induction through multiple pathways. Our results suggest that betanin may attenuate noise and scrotal hyperthermia induced testicular toxicity via inhibition of oxidative stress, apoptosis and inflammatory gene expression level.

Keywords: Noise; Scrotal hyperthermia; Betanin; Oxidative stress; Apoptosis; Inflammation; gene expression

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P380

Development of an LC-MS/MS assay for seven salivary steroids including the 11-oxygenated androgens

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For several years, steroid hormones including testosterone (T), androstenedione (A4) and 17-hydroxyprogesterone (17-OHP) have been utilised in the diagnosis of a range of conditions with clinical features of hyperandrogenaemia including polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia. In recent years a potential role for the 11-oxygenated androgens has emerged in the diagnosis and characterisation of androgenic disorders. Specifically, the 11-oxygenated androgens including 11-ketotestosterone (11-KT), 11-hydroxyandrostenedione (11-OHA4), 11-ketoandrostenedione (11KA4) and 11-hydroxytestosterone (11-OHT), have been shown to be the major circulating androgens in PCOS and the predominant steroids responsible for hyperandrogenaemia in Cushing Syndrome. The use of saliva for diagnostic tests has advantages over blood sampling. Saliva can be collected non-invasively at home without the presence of a healthcare professional and can then be posted to the laboratory, saving the patient a visit to a phlebotomy clinic for venepuncture. We have developed a multiplex LC-MS/MS assay on a Waters TQXS mass spectrometer for salivary T, A4, 17-OHP, 11-KT, 11-OHA4, 11-KA4 and 11-OHT with a run time injection-to-injection of five minutes. Samples were prepared for analysis by supported liquid extraction; we have found optimal sensitivity and negligible matrix effects using a Waters T3 chromatography column, with mobile phases of ammonium fluoride (mobile phase A) and methanol (mobile phase B) giving a two fold greater sensitivity compared to acidic mobile phases. Herein we describe a full bioanalytical validation based on U.S Food and Drug administration standards including studying accuracy, recovery and imprecision. Additionally, we investigate the stability of the seven analytes included in the assay across different conditions including freezer storage, refrigeration, room temperature and 37°C in order to determine the requirements for collecting and sending of samples to the laboratory for analysis. The assay is available for clinical studies as well as routine analysis and we aim to assess intraindividual variability.

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Thyroid

P127

Effects of in utero thyroid hormone exposure on adolescent myelination: Quantitative magnetization transfer imaging in the controlled antenatal thyroid screening study

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Introduction
The Controlled Antenatal Thyroid Screening II (CATS) study, a large randomised trial of thyroxine supplementation for suboptimal gestational thyroid function (SGTF), reported higher attention deficit hyperactivity disorder (ADHD) scores in 9 year-old children exposed to higher thyroid hormone (TH) *in utero*. We investigated if this was accompanied by altered myelination.
Methods
Eighty-five children aged 11-16 years (untreated SGTF ($n=21$), normal GTF ($n=24$), or treated SGTF (optimally treated ($n=21$), over-treated ($n=19$)) recruited from the CATS cohort underwent quantitative characterisation of white matter microstructure and myelination using 3.0T MRI. Myelination was assessed by quantitative magnetization transfer (qMT) and compared to diffusion-weighted MRI (dMRI). qMT parameters included macromolecular proton (bound pool; BPF) fraction. White matter (WM) bundles were reconstructed from dMRI data in tracts known to be affected by TH exposure and/or implicated in ADHD risk (corpus callosum, cingulum bundles, inferior and superior longitudinal fasciculi). The median BPF was calculated for each bundle. Relationships between thyroid hormone, treatment group and BPF for each WM bundle were assessed using linear mixed effects models. Child age, sex and Tanner scores were included as fixed effects.
Results
No associations were found between free T4 or TSH at 12 weeks and median BPF along studied tracts. No effect of treatment group on median BPF was identified, despite significant differences in fractional anisotropy (FA). Linear regression revealed significant effects of treatment on FA in the Corpus Callosum, with posthoc tests revealing greater FA in over-treated compared with the untreated group ($P=0.033$). Correlations between FA and BPF were weak and not statistically significant.
Conclusion
This is the first study to explore the effects of *in utero* TH exposure on myelination in humans. Lack of correlation between FA and BPF suggests that differences in FA observed between over-treated and untreated individuals were not driven by myelin.

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P128

Thyroid hormone profiles on non-standard thyroid hormone replacement

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Context
Approximately 10% of patients on levothyroxine remain symptomatic despite restoration of biochemical euthyroidism. Some therefore utilise alternatives to levothyroxine monotherapy including combination thyroid hormone replacement, T3 monotherapy and desiccated thyroid extract (DTE). We examined thyroid hormone profiles in these patients.
Methods
We examined 49 individuals 14 on combination thyroid hormone replacement,14 on T3 monotherapy and 21 on DTE). Hourly blood tests (TSH, T3 and T4) were undertaken between 8.30am-4.30pm. Area under the curve (AUC) analysis was performed and odds of having a very low TSH (<0.05mU/l) and completely suppressed TSH (<0.02mU/l) at 08:30 were undertaken with adjustment for age.
Results
The highest T3 levels were seen with T3 monotherapy. Combined T3 and T4 dose, T3 dose and T4 dose were not associated with increased odds of a very low or a completely suppressed TSH. T3 monotherapy and DTE had higher AUCT3 levels and lower AUCT4 levels than combination thyroid hormone replacement. AUCT3 was associated with increased odds of very low TSH OR = 2.95 (95%CI 1.45, 6.03) $P = 0.003$ and a completely suppressed TSH OR = 2.21 (95%CI 1.12, 4.38) $P = 0.02$. Maximum T3 was associated with increased odds of very low TSH OR = 2.51 (95%CI 1.24, 5.05) $P = 0.01$ and completely suppressed TSH OR = 2.31 (95%CI 1.13, 4.70) $P = 0.02$. Any T3 level above 7.0 pmol/l was associated with increased odds of a very low TSH OR = 11.7 (95%CI 1.23, 111) $P = 0.03$. No association was seen with AUCT4 or maximum T4 level.
Discussion
T3 levels have a greater negative impact on TSH levels than T4 levels. Notably peak T3 levels have a substantial impact and appear to be more important in influencing TSH levels than total T3 dose. Taken together this suggests that strategies to reduce peak T3, such as slow release T3, should be investigated as a path to enabling moderate T3 doses without substantially suppressing TSH.

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P129

A case for caution: Paediatric reference intervals for thyroid function tests

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Background
Thyroid stimulating hormone (TSH) and free T4 (fT4) were requested on a neonate, on Day 1 after birth. fT4 was flagged as below range, TSH was insufficient for analysis. Day 5-8 newborn bloodspot screening flagged a high TSH, hypothyroidism was confirmed, and thyroxine treatment commenced. Internal investigation into the incident, and the potential impact on the baby of delayed onset of treatment, raised the question of the relevance of our reference intervals (RI) in neonates. Agreed action was to implement evidence-based paediatric RI for TSH, fT4 and free T3 (fT3). Following implementation of **Ca**nadian **L**aboratory **I**nitiative on **Pa**ediatric **R**eference Intervals (CALIPER) RI's, referrals to paediatric endocrinology services from primary care for investigation of hypothyroidism, on the basis of a low fT4, soared. Hence, we sought to establish our own lower limit of normal (LLN) for our RI for fT4.
Methods
Paediatric primary care TSH and fT4 results, between ages 1-18yr (368), were assessed between Jan-2020 and May-2022. Only fT4 results with TSH within the RI were included (201). Kolmogorov-Smirnov test showed non-normal fT4 distribution (skewness 0.8; kurtosis 1.09). LLN was calculated using bootstrapped $(N+1)p$ quantiles.
Results
Introduction of the CALIPER fT4 range for our method and instrument (11.4 – 17.6 pmol/l) involved a dramatic shift in LLN from our adult range (9.0 – 19.1 pmol/l). In a population of Norfolk children, the calculated LLN was substantially lower, providing the range 9.3 – 17.6 pmol/l. Implementation of this new LLN for fT4 resulted in a dramatic reduction of inappropriate referrals for hypothyroidism from primary care from healthy children.
Conclusions
CALIPER RI are an invaluable resource for laboratory medicine, but care must be taken in implementing these without due consideration of the applicability to your local population, and the potential impact on secondary care services.

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P130

Radioactive iodine treatment outcomes at imperial college healthcare NHS Trust

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Background
Before radioiodine (RAI) therapy patients undergo a technetium 99m thyroid uptake scan and anti-thyroid medication is stopped prior to treatment following clinical review with the nuclear medicine team. Once treated, patients are followed up in the post-radioiodine telephone clinic. Thyroid function is checked at 3, 6, 9 and 12 weeks. Levothyroxine is started once the fT4 is <14 pmol/l.
Purpose
To assess success rates 1 year post RAI treatment, between January 2015 and January 2021.
Methods
Electronic patient records were reviewed, information included demographics, diagnosis, percentage of uptake on pre-treatment scan, dose of RAI, blood results and time to 'cure'.
Results
257 patient records were reviewed, two were excluded due to loss of follow-up and six were excluded as a second RAI had been given during the analysis period Of these patients, 30% were euthyroid or hypothyroid at 3 weeks, this proportion rose to 75% at 9 weeks and 96.4% at 1 year and 3.6% remained hyperthyroid. The failure rate for Grave's disease was 3% and response time was similar for males and females. 7.4% of Toxic Multinodular Goitre and 3% of autonomous nodule treatments failed but responders did so at 7-9 weeks

	Female	Male
Grave's disease	136	53
Toxic nodule	23	10
Toxic multinodular goitre	22	5

Conclusions
The RAI service at Imperial College Healthcare demonstrates better than average cure rates at one year than is reported in the literature, 96.4% vs 85-94%. Rapid results were demonstrated, with 75% of patients becoming hypothyroid or euthyroid within 9 weeks but RAI had higher failure rates in those with TMNG and females with Grave's. The findings should encourage clinicians to recommend RAI as a first line treatment for thyrotoxicosis, as suggested by NICE guidelines.

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P131

Can aetiology of hypothyroidism and prenatal dose help to predict need for dose increment of levothyroxine during pregnancy – Insights from a clinical audit

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Introduction
The newly proposed RCOG guidelines suggests dose increment of thyroxine based on prenatal thyroxine doses. The aim of our retrospective audit was to assess if the aetiology of hypothyroidism (and dose of thyroxine) prenatally could help predict the need for dose increment during pregnancy.
Methods
$n = 100$. Local guidelines advised maintaining TSH <2.5 throughout pregnancy. Outcomes of thyroxine adjustment at the first and last visit (in third trimester)

reviewed. Data was analysed based on

- aetiology of hypothyroidism: primary (including hemithyroidectomy) vs iatrogenic (radioactive iodine or post total thyroidectomy).
- prenatal dose of thyroxine $\leq$ 100mg vs $>$100mg

Results

Among the iatrogenic group, all 4 patients who did not require a dose change had total thyroidectomy for thyroid cancer and were on supraphysiological replacement of thyroxine. Among patients on $>$100mcg, 11 of the 12 iatrogenic patients required dose increment, which is significantly higher than the primary group.

	Dose increase	No Change	Dose decrease
Aetiology of hypothyroidism			
Primary hypothyroidism $n=87$			
First antenatal visit	58 ($\leq$ 25mg increment: 52, 50mg increment:6)	27	2
Final antenatal review	61	23	3
Iatrogenic hypothyroidism $n=13$			
First antenatal visit	9 ($\leq$ 25mg increment: 4, 50mg increment: 5)	4	0
Final antenatal review	10	3	0
Prenatal thyroxine dose			
Thyroxine $\leq$ 100mcg/d, $n=74$ (primary 73; iatrogenic 1)			
First antenatal visit	53 $\leq$ 25mg increment: 47, $>$25mg increment in 6	21	0
Final antenatal review	54	20	0
Thyroxine $>$100mcg/d, $n=26$, (primary 14; 12 iatrogenic)			
First antenatal visit	14 $\leq$ 25mg increment:10, $>$25mg increment: 4	10	2
Final antenatal review	17	6	3

Conclusion

Dose increment needed during first trimester can be quite variable. Patients with post radioactive iodine or total thyroidectomy induced hypothyroidism represent a significant sub-cohort where dose increment is invariably required, with their higher prenatal dose being a marker of lack of endogenous thyroid activity.

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P132

Hypothyroidism in elderly residents of karu village, abuja in North Central Nigeria

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Objective

To determine the prevalence of hypothyroidism among elderly subjects living in Karu village in the Federal Capital Territory.

Methods

A community-based cross-sectional study involving 308 elderly subjects. A structured interview administered questionnaire was used for relevant data collection including biodata, clinical signs, and symptoms of hypothyroidism. Weight, height, waist circumference, presence and estimated size of goiter, and blood pressure were measured. The sample population had their thyroid function accessed, along with their serum electrolytes, fasting lipid profile, and complete blood count.

Results

308 elderly subjects were recruited, 154 males and 154 females. The mean age of the subjects was 70$\pm$8.7. The prevalence of overt hypothyroidism was 9.1% while that of subclinical hypothyroidism was 15.6%. Overt hypothyroidism was present in 3.2% of the subjects while 7.8% had subclinical hyperthyroidism. 64.3% were euthyroid. There was a female preponderance among subjects with overt hypothyroidism M: F 1:3.7. There was a female preponderance among subjects with subclinical hypothyroidism with M: F, 1:2. Hypothyroid subjects had a statistically significantly higher number of subjects with constipation, cold intolerance, and fatigue than euthyroid subjects {42(55.3), 26(34.2), 30(39.5)} vs. {14(7.1), 24(12.1), 28(14.1)} respectively $P<0.05$. The Mean TSH values were statistically significantly higher in the hypothyroid subjects than the euthyroid subjects, 8.6$\pm$2.2 vs. 2.5$\pm$1.5, $P<0.05$. FT4 and FT3 values were statistically significantly lower in the hypothyroid subjects compared to euthyroid subjects, 8.93.1 vs. 11.1$\pm$2.2 and 4.0$\pm$ 1.7 vs. 4.6$\pm$ 0.7 respectively, $P<0.05$.

Conclusion

The prevalence of overt hypothyroidism in the study was 9.1% and that of subclinical hypothyroidism was 15.6%, this prevalence is similar to that seen in other studies in developing countries.

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P133

Radioactive iodine (I-131) in hyperthyroidism: Does weight gain remain a risk?

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Background

Radioactive iodine (RAI) is a safe and effective treatment for management of hyperthyroidism caused by Graves' disease and multinodular goitres. However, patient engagement with this therapy is limited by concerns regarding significant weight gain following treatment. We therefore aimed to audit weight changes in individuals receiving RAI within our service and identify factors that may influence this outcome.

Methods

We audited all patients who underwent RAI therapy at Forth Valley Royal Hospital between January and November 2021. Weights were obtained at the time of administering RAI, and follow up weights were either self reported or obtained via electronic records. Biochemistry at presentation, antithyroid drug regimen, and post-treatment thyroid stimulating hormone and levothyroxine usage was also obtained.

Results

Twenty-seven individuals (59.3% female) received RAI during the audit period with a median follow up of 13 months. No significant difference in participants weight before and after the use of RAI (median weight change: 0.5 kg; 95% CI -10, 19) was observed. There was no difference between individuals who received carbimazole dose titration (44%; -0.5 Kg; 95% CI -10, 11.3) verses a block and replace regimen (56%; 0.5 Kg; 95% CI -1.6, 19) prior to RAI. A trend was observed in males experiencing higher weight gain than females (median increase 10kg; $P=0.051$) following RAI.

Conclusion

This audit identified no significant change in the weight of individuals that received RAI treatment. Our results indicated that males may be at higher risk of weight gain. Research relating to weight gain in RAI suggests the risk is high. However, these studies are largely retrospective, uncontrolled pre-post analyses with limited sample size. Prospective analyses comparing RAI to long-term antithyroid drug usage are required to compare this risk and inform the potential advantages and disadvantages of RAI in this patient group

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P134

Identifying risk factors that predict medical treatment failure in Graves' disease: a 4-year follow-up study in a single centre

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Background

Graves' disease (GD) is the commonest cause of primary hyperthyroidism. First-line treatment involves 12-18 months of anti-thyroid drugs (ATD). Subsequently, around 50% of patients will relapse, requiring definitive treatment. Identifying risk factors that predict relapse or treatment failure can guide management. We aimed to explore risk factors that identify patients at high risk of relapse or medical treatment failure, to allow prioritisation for definitive treatment.

Methods

We retrospectively evaluated data on consecutive patients with first presentation of GD who had positive TSH receptor antibodies (TRAbs $>$0.4 IU/l) at diagnosis at Royal Berkshire Hospital and required ATD, between February 2017-December 2018. Baseline demographics, TRAbs, thyroid function tests (TFTs) levels, and thyroid eye disease (TED) at diagnosis were recorded. RSR Elisa TRAb 2nd generation assay and Roche Cobas Elecsys Gen II assay were used to measure TRAB and FT4, respectively.

Results

We included 154 individuals: mean age 51.6 years, 71.4% female, 15% TED at diagnosis. The median (IQR) TRAb level was 2.7 (1.7, 5.7)IU/l, and median (IQR) FT4 level was 52.6 (30.3, 81.4) pmol/l. The median follow-up of TFTs was 48 months. Median duration of ATD was 18 months. 102 (66.2%) participants relapsed or had treatment failure (ATD duration $>$ 24 months). Gender and median TRAb values were similar in both groups. Subsequently, patients were divided into 3 sub-groups according to TRAb values (1st tertile: 0.5-1.9 IU/l, 2nd: 2.0-4.3 IU/l, 3rd: 4.4-31.0 IU/l) . Individuals in the 3rd tertile vs. the 1st, had more often TED (30.4% vs. 11.1%, OR 3.5; $P=0.05$), higher FT4 levels (72.4 pmol/l vs. 31.6 pmol/l; $P=0.0001$), and significant risk of treatment failure (77.4% vs 54.2%, OR 2.9; $P=0.02$).

Conclusions

We showed that medical treatment failure or relapse is commoner in patients with TED, higher TRAb and FT4 levels, prompting early referral for definitive treatment.

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P135

Using nurse led clinics (including telephone and virtual reviews) in NHS Grampian to improve patient satisfaction following a diagnosis of hyperthyroidism

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Using nurse led clinics (including telephone and virtual reviews) in NHS Grampian to improve patient satisfaction following a diagnosis of hyperthyroidism.

Aims

To reduce waiting times for patients with hyperthyroidism, nurse led clinics were introduced. Telephone and virtual follow up reviews are offered after commencement of thyroid treatment (e.g. anti-thyroid medication or radioactive iodine (RAI)). Nurse-led thyroid clinics aim to improve the overall support the patient receives, complimenting rather than replacing existing medical thyroid clinics (which lack capacity).

What we have done

Nurse-led virtual clinics were initially established to facilitate follow up of post radioiodine patients. The virtual clinic then evolved to allow more patients to contact us and receive advice on their thyroid biochemistry in between clinic appointments. The virtual thyroid clinic allows remote review of thyroid biochemistry results and advises patients of any changes to their medication. Overall review and support are provided via e-mail and/or telephone. Nurse-led telephone clinics allowed review of thyroid biochemistry results and give guidance regarding their anti-thyroid medication. In addition, their overall health status would be reviewed including potential thyrotoxic symptoms. Follow up appointment and further thyroid blood testing would also be arranged. A structured formal clinic letter is sent to both the GP and patient.

Progress to this point

Thyroid Nurse led clinics have helped to reduce waiting review times for patients. Nurse thyroid appointments increased from 101 (Apr 2018 to March 2019) to 798 (April 2022 to March 2023). Medical thyroid return appointments dropped from 865 to 666 in the same time period. Patients appreciate the prompt service and primary care feels reassured that effective and timely thyroid clinic follow up is undertaken.

Discussion

We are pleased to share our experience of our very useable frameworks for both nurse telephone and nurse virtual thyroid clinic follow ups.

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P136

Thyroid hormone resistance: Diagnostic challenges and management

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Introduction

Resistance to thyroid hormone (RTH) is an autosomal dominant condition with mutation of thyroid hormone receptor beta (THR-β) gene. We present 2 cases with unusual thyroid picture posing challenge to diagnosis.

Case 1

31-year-old lady presented with 6-month history of anxiety, tremors, insomnia and headache. She suffered from asthma and had a family history of hyperthyroidism. On examination, she was overweight (BMI 28kg/m2), tachycardic, tremulous. Cardiovascular examination was normal, smooth palpable goitre, no eye signs. Biochemistry revealed high fT4 57.4 pmol/l (RR 11-23), fT3 17.6 pmol/l (3.5-6.5), TSH 9.75mU/l (0.35-5.5); positive TPO antibodies, absent heterophile antibodies, unremarkable MRI pituitary. Genetic analysis confirmed RTH. 9years later, she was commenced on TRIAC (triiodothyroacetic acid) with symptomatic improvement at 24weeks but had weight gain. 5years later, she developed diabetic ketoacidosis and discontinued TRIAC.

Case 2

26-year-old lady presented with one-year history of tiredness, fatigue, palpitations and hypersomnia. She suffered from depression and had a family history of hyperthyroidism. On assessment, she was overweight (BMI 19.4 kg/m2), normal cardiovascular examination, no palpable goitre, or ophthalmic signs. Biochemistry revealed high fT4 29.8 pmol/l, fT3 9 pmol/l, non-supressed TSH 2.76mU/l, normal pituitary profile and alpha subunit. Familial dysalbuminaemic hyperthyroxinaemia screen and heterophile antibodies negative. MRI head was normal. Genetic testing was heterozygous for THR-β gene mutation, confirming RTH-beta. Trial of beta blockers was unsuccessful. TFT's were monitored with no intervention. Next step is to screen first-degree relatives with similar TFT's.

Discussion

RTH should be suspected with elevated fT4 and fT3 with normal/high TSH and minimal symptoms of thyroid dysfunction. Differentials include TSH-secreting pituitary adenoma, RTH and heterophile antibodies. Treatment depends on predominant symptoms with thyroid hormone replacement, beta-blockers, TRIAC or a combination.

Conclusion

Our two cases showcase the challenges with diagnosis and management. Prompt diagnosis is dependent on clinical suspicion and systematic clinical and biochemical evaluation.

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P137

Combination Levothyroxine and Liothyronine therapy: Evaluation of a new local management pathway

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Background

Combination treatment with Levothyroxine (LT4) and Liothyronine (LT3) in primary hypothyroidism has been debated recently due to restrictions placed by local health boards. National guidance suggests that a short-term trial of combination LT4/LT3 treatment may be considered for individuals who report persistent symptoms despite adequate LT4 replacement.

Method

We created a prescribing protocol for combined LT4/LT3 in clinic using a structured, non-blinded approach, based on national guidance. Prescribing was evaluated in 11 female patients (median age 55y (IQR 48-62); SIMD 4/5 ($n=8$)) switched from LT4 to combination treatment over a six-months trial. Doses of LT4 and LT3 were adjusted during the treatment period according to TFT, patient-reported symptoms and ThyPro-39 questionnaire.

Results

At baseline median serum TSH was 0.11 (0.04-0.88) mU/l decreasing to 0.06 (0.02-0.49) after 6 months. Proportions of patients with a TSH <0.01mU/l increased from 36.4% to 81.8%, with LT4 doses declining by a mean of 52.3 micrograms, and mean LT3 doses being 16.1 micrograms. At baseline, 54.5% of reported adverse overall quality of life (QOL) declined to 9% of patients after 6 months. Median (IQR) hypothyroid symptoms score at baseline and 6 months were 62.5 (43.8-81.3) and 18.8 (12.5-43.8) respectively. The composite scores which reflected the psychological and social aspect of QOL also improved from a median of 54.5 (IQR 44.3-77.3) to 22.7 (IQR 13.6-40.9).

Conclusion

The local management pathway facilitated combination LT4/LT3 prescription in a systematic manner and improved patient reported outcomes in most patients, but only at doses that put them at risk of potential harm. Achieving a safe level of LT3 replacement was challenging without suppression of TSH below 0.1 mU/l. The local protocol should be supplemented with advice on cardiac and bone health monitoring for patients with persistently low TSH levels (target ideally 0.3-2 mU/l).

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P138

An unusual presentation of Grave's disease with severe osteoporosis and pathological femoral fracture

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Grave's disease is an autoimmune condition commonly presenting with symptoms of hyperthyroidism including weight loss, palpations and tremor; rarely, it presents more atypically.A 35-year-old male (non-smoker, no significant history) presented with an atraumatic femur fracture. He was incidentally noted to have a large goitre, tachycardia and mild proptosis but no symptoms of hyperthyroidism. Further bloodwork revealed iron deficiency, unremarkable tumour markers including LDH, PSA, AFP, CEA and CA19.9, and a negative myeloma screen. Computed tomography (CT) imaging confirmed a goitre and a distal femur fracture. Multiple small soft tissue densities were noted throughout the length of the femur reported as consistent with benign red marrow rests with no evidence of malignancy. Subsequent imaging included a DEXA revealing severe osteoporosis at the hip and spine (T score femur -2.9, spine -4.5) and chronic grade 1 vertebral insufficiency

fractures; an unremarkable CT thorax, abdomen and pelvis and an isotope bone scan demonstrating no evidence of metastasis or other pathology. The fracture underwent surgical fixation. Hyperthyroidism is being treated with carbimazole and beta-blockers. Severe osteoporosis is being managed in the context of longstanding unrecognised hyperthyroidism. This is rarely reported in the literature, usually in the paediatric population; a pathological fracture is even rarer. Prolonged untreated hyperthyroidism can lead to severe osteoporosis and increased fracture risk in otherwise healthy adults. Grave's disease should be considered in the differential in such scenarios.

Table 1 Presents relevant biochemistry

	Result (reference)		Result (reference)
Thyroid Stimulating Hormone (TSH)	<0.01 mU/l (0.35-5.00)	Adjusted calcium	2.38 mmol/l (2.20-2.60)
Free T4	46.6 pmol/l (9.0-21.0)	Phosphate	1.21 mmol/l (0.8-1.5)
T3	5.7 nmol/l (0.9-2.5)	Alkaline phosphatase	158 U/l (30-130)
TSH receptor antibodies	11 U/l	Vitamin D	18 nmol/l (>50)
Thyroid peroxidase antibodies	>1000 U/mL (<6.0)	Testosterone (am)	18 nmol/l (10.0-36.0)

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P139

Iodine concentration and palatability of milk from cows fed the common red seaweed species Himanthalia elongata

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Cow's milk remains a key source of iodine in the UK. However, there are concerns around the environmental impact of methane emissions from dairy cattle. Initial work suggests that adding certain seaweed species to the diet of cows can reduce enteric methane emissions and may increase the content of certain minerals such as iodine in milk. Little is known about the simultaneous effect of this feeding practice on milk organoleptic characteristics. This study investigates the impact of seaweed inclusion in cows' diets on milk iodine content and acceptability and palatability. Fifteen lactating Holstein dairy cows were offered one of three diets: each contained (on a dry matter basis) 40% concentrates and (i) 60% grass silage (CON), (ii) 56% grass silage, 4% *Hilmanthalia elongata* extract (CSE) and (iii) 56% grass silage and 4% *Hilmanthalia elongata* (CSW). Approximately 60 litres of milk were collected, on day 14, after the commencement of the experiment, homogenised and then refrigerated prior to pasteurisation (63°C for 30 minutes). A sample from each group was taken to be analysed for iodine while the remaining milk was frozen at -20°C in 500 ml food-grade sealed bottles. The iodine concentration of milk recovered from cows fed CON, CSE and CSW was 411.8, 669.6, 666.4 µg/kg respectively. In a consumer test panel, 25 adults were provided with samples of each milk. There were no significant differences ($P \geq 0.05$) noted between CON, CSE and CSW milk samples when scored for appearance, aroma, taste, aftertaste, mouth feel, and overall acceptability using a 9-point hedonic scale. Including Hilmanthalia elongata seaweed in dairy cows' diet increases milk iodine concentrations without affecting organoleptic characteristics and can be used to improve milk iodine concentration when this may be low (e.g., during the cows' grazing season or when cows are fed glucosinolate-containing feeds).

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P140

Levothyroxine allergy subsequently managed with desensitization – a highly challenging but definitely not sinister case

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Levothyroxine, the standard therapy for hypothyroidism, is usually well tolerated and very few cases of true allergy to levothyroxine have been reported to date. In these cases mechanisms have not been conclusively identified but have been hypothesized to be allergies to excipients. Here we report a rare occurrence of levothyroxine allergy and the effectiveness of desensitization. A 56-year-old lady with no previous history of allergies required a total thyroidectomy for Graves' Disease. Post-operative recovery was initially unremarkable, however on the second day post-operation she developed facial flushing, urticaria and a rash on her chest and abdomen within 15 minutes of receiving a 125 micrograms dose of levothyroxine composed of 2 different brands. She remained hemodynamically stable with no airway compromise and was treated with antihistamine and steroid. The following day, she was re-administered levothyroxine and developed similar but more pronounced and rapid symptoms. Tryptase levels confirmed true allergy. It was felt that excipients in levothyroxine were the most likely cause. She was therefore tried on levothyroxine elixir (containing no shared excipients with the previous two formulations), but again developed urticaria and a rash, albeit more modest, despite being treated concurrently with antihistamine and steroid. However, she tolerated liothyronine well, with no allergic symptoms. We then undertook desensitization to levothyroxine with incremental doses every 30 minutes starting from 0.05microgram levothyroxine built up to 75 micrograms levothyroxine over the course of a day. A rash appeared at higher doses but treatment was continued and the rash settled within 24 h. She is currently tolerating 100 micrograms a day of levothyroxine with no adverse effects. Given her lack of other allergies and as the levothyroxine excipients are common in other drugs and food stuffs, we are currently investigating an allergy to dextrothyroxine (an enantiomer of levothyroxine, present in small amounts in levothyroxine formulations).

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P141

A rare but important side effect of anti-thyroid medication: Propylthiouracil-induced vasculitis

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Background
We present a 47-year-old female, who is known to have recurrent Graves' disease, developed vasculitic skin lesions upon treatment with propylthiouracil (PTU).
Case details
She was diagnosed with Graves' disease in 2020 and was started on propylthiouracil as she could not tolerate carbimazole. Propylthiouracil was stopped after 18 months. Her thyrotoxicosis recurred after 6 months. Two months after propylthiouracil was restarted, she developed a new onset rash on her face followed by necrotic skin lesions on the back of her legs and her back. The rash was not worsened with sun light exposure. She did not recall any intercurrent illness or use of any other new medication. The clinical examination was unremarkable apart from fever and the skin lesions. There was no evidence of mucosal involvement. Her blood tests revealed positive anti-neutrophil cytoplasm (ANCA) antibodies: ANCA Myeloperoxidase (MPO) Antibodies * 3.8 kU/l (0 - 3.4), ANCA Serine Proteinase 3 (PR3) Antibodies *21.0 kU/l (0 - 1.9) while ANA and ENA antibodies were negative. Her computed tomography (CT) of chest, abdomen and pelvis was unremarkable apart from axillary lymph adenopathy. Her blood cultures showed no growth. A diagnosis of propylthiouracil-induced vasculitis was made by dermatologists. Propylthiouracil was discontinued and she was offered definitive treatment with either radioiodine or surgery. She was systemically well and her skin lesions showed signs of healing after drug withdrawal.
Conclusion
This case highlighted a rare though serious adverse effect of commonly prescribed antithyroid medications. Although one should exclude idiopathic vasculitis and vasculitis mimics in the first instance, propylthiouracil-induced vasculitis remains a possibility. Most patients respond to drug withdrawal or sometimes to immunosuppressants. Several studies reported the prevalence of PTU- induced vasculitis from 20% to 64%. Most patients have raised MPO-ANCA level while a small number have PR3-ANCA.

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P142

'Not just another Hashimoto's!'

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Hashimoto's thyroiditis is the most common cause of hypothyroidism in iodine-sufficient areas of the world, cause is thought to be a combination of genetic susceptibility and environmental factors. The pathology of the disease involves the formation of antithyroid antibodies that attack the thyroid tissue, causing progressive fibrosis. We present the case of a 38 year old male with history of hypertension, type 2 Diabetes and pre-existing hypothyroidism who presented with 2 weeks history of painful neck swelling, odynophagia, cough and fatigue. On examination, he had a 3 cm firm and tender swelling in right lobe of thyroid. Blood tests showed FT4 17.8, TSH 7.86, WBC 11.9, CRP 133.3 and TPO > 600. Ultrasound neck showed features of thyroiditis and marked right cervical lymphadenitis. He was treated with IV antibiotics and oral steroids. Repeat US scans showed a persistent subcentimetre abnormal level 6 lymph node. Thyroid biopsy was advised. FNAC was attempted but unsuccessful as the nodule was found to be extremely firm in consistency. A core biopsy was then arranged. It showed damage to the thyroid follicles with replacement of normal architecture by diffuse fibrosis. Immunohistochemistry showed an extensive lymphocytic infiltrate with germinal centre formation and features in keeping with Hashimoto thyroiditis. The patient had to be continued on steroids for 7 months as attempts at stopping steroids resulted in recurrence of painful thyroiditis. Six months after stopping steroids, he presented again with symptoms of neck pain but milder rise in CRP. Steroids were restarted at a dose of 20 mg with plans to wean down gradually. US scan was unchanged, but less vascularity was noted. Hashimoto's thyroiditis usually presents as painless, diffuse enlargement of the thyroid. In our case, symptoms of painful thyroiditis are persistent 15 months after initial presentation. Discussion in MDT +/- surgical option may need to be explored.

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P143

A patient presenting with Carbimazole induced haemolytic anaemia- A case report

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Background
Haematological side effects of Carbimazole including aplastic anaemia, thrombocytopenia and agranulocytosis are widely reported, but haemolytic anaemia is a rare occurrence. In such situations, the management options available for treating overactive thyroid disease will be limited, especially in frail elderly individuals. We report a case of Carbimazole induced haemolytic anaemia successfully treated with steroids and omitting the medication.
Case presentation
An 83 year old female presented with tiredness, low mood, indigestion, palpitations and anxiety. She was mildy thyrotoxic with no clinically evident goitre. Her TSH was suppressed at < 0.02mU/l with high fT4 (32.9 pmol/l). The thyroid receptor antibody (TRAb) was negative and Thyroid uptake scan revealed a total thyroid uptake of 0.7% (normal 0.3-3%). Both lobes of the thyroid appeared relatively large and had heterogeneous uptake without a discrete avid nodule. The diagnosis of hyperthyroidism was made and she was started on carbimazole 10 mg once daily. Three weeks later on therapy, she presented with yellowish discoloration of her body and worsening tiredness. She was found to be anaemic with haemogloblin of 63g/l, high retic count of 412 x 109/l, polychromasia and spherocytes confirming haemolytic anaemia. She had positive auto anti-e, pan reactive indirect antiglobulin test (IAT) and the diagnosis of Carbimazole induced haemolytic anaemia was made. She was transfused with 3 units of packed red cells. Carbimazole was discontinued and she was started on high dose steroids with gradual tapering for which she responded well. She remained euthyroid and no further anti-thyroid medications were required.
Conclusions
Carbimazole induced haemolytica anemia is an extremely rare adverse effect of the medication. The awareness and timely management can prevent the patients from having disastrous complications and outcomes.

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P144

Syndrome of inappropriate secretion of TSH, it's complicated

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Introduction
Deranged thyroid function tests are frequently referred to the endocrine team and are generally secondary to the assay interference.
Case Report
We Report a case of 33 years old lady referred with symptoms of dizziness, palpitations, cold intolerance and poor sleep with no associated tremors or weight changes. No goiter was observed on clinical examination. Thyroid function test showed abnormal hormone levels of T4 (32 pmol/l) and TSH (3.11mu/l) with negative TPO (12.2 IU/ml) and thyroid stimulating antibodies (0.13 IU/l). Thyroid function test was then rechecked to assess for methodological interface and results were consistent with raised TSH (23.50 mul/l) with raised free T4 (20.8 pmol/l) and T3 (5.7 pmol/l). Further history suggested patient's development was delayed during early years with no suggestion of thyroid disorders in family. MRI pituitary was normal with no evidence of pituitary adenoma. In view of symptoms she was initiated on carbimazole 10mg once daily with slight improvement. Genetic testing for familial dysalbuminaemic hyperthyroxinameia was also negative. Weaning off of carbimazole resulted in worsening patient's symptoms. 2013 European thyroid association guidelines for Thyrotropin secreting pituitary tumors were reviewed in Endocrine MDT and in view of patient being symptomatic it was deemed reasonable to proceed with TRB gene testing than dynamic testing with TRH or T3 suppression test. Genetic testing for TRB gene are waited.
Conclusion
Deranged thyroid function test can present as a conundrum in clinical practice. Thyroid Hormone resistance is a rare autosomal dominant genetic syndrome with TRB gene mutation in 80-85% patients. Pituitary thyroid hormone resistance is typically associated with goitre and symptoms related to thyrotoxicosis. Family history remains crucial in guiding the diagnosis. TSHoma remains the main differential with evidence of pituitary adenoma in 30% of patient.

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P145

Severe and protracted Type 2 Amiodarone Induced Thyrotoxicosis (AIT) presenting 6 months following discontinuation of Amiodarone

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Background
Amiodarone induced thyroid dysfunction can be either thyrotoxicosis (AIT) or hypothyroidism (AIH). AIT is classified as Type 1 and Type 2. Type 1 occurs in patients with underlying thyroid pathology and Type 2 AIT is a destructive thyroiditis. We describe a patient with severe Type 2 AIT with a protracted course.
Case History
A 40 year old male with Atrial Fibrillation, Obesity and Obstructive Sleep Apnoea had been on Amiodarone from October 2020 till July 2022. His TSH in March 2022 was normal. In December 2022, he saw the GP for abdominal pain. The investigations showed supressed TSH with FT4 > 100 pmol/l and FT3 21 pmol/l. Carbimazole was started in the primary care. Three weeks later, patient was admitted with abdominal pain and vomiting. His FT3 > 50 pmol/l, FT4 > 100 pmol/l, ALT 218IU/l and calcium 2.99mmol/l. He was treated with IV fluids and antiemetics. Once vomiting settled and calcium normalised, he was discharged. A week later he was readmitted and referred to Endocrinology as persistently high TFT despite high dose Carbimazole. The US and Technetium uptake scans were compatible with thyroiditis. TRAb was negative. The diagnosis of AIT Type 2 was made. Prednisolone 40 mg was started and Carbimazole discontinued. Thyroid function improved gradually and returned to normal after 4 months. Attempts to reduce steroids caused a relapse hence protracted course.
Discussion
Amiodarone induced thyrotoxicosis can occur months after discontinuing Amiodarone due to its long half-life but usually occurs whilst on Amiodarone. Our patient had severe thyrotoxicosis due to Type 2 AIT leading to deranged liver functions and hypercalcaemia. He had a protracted recovery leading to increased cardiovascular risk. He is on high dose corticosteroids with risk of weight gain, diabetes and osteoporosis. This presentation highlights the importance of regular monitoring of thyroid function on Amiodarone, accurate diagnosis and urgency of referral in severe thyrotoxicosis.

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P146

Unmasking the hidden link: Primary hypothyroidism unleashing severe pericardial effusion

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Introduction
Primary Hypothyroidism is a commonly encountered endocrine disorder and can be associated with pericardial effusion and cardiac tamponade in severe cases. Early detection of Hypothyroidism is key since it is a potentially treatable and reversible cause of pericardial effusions.
Case Presentation
A 53-year-old female was admitted following a fall. Clinical history was remarkable with symptoms of persistent tiredness and fatigue for six months. She had no known medical conditions and was not taking any regular medications. Vital signs were stable. Physical examination revealed bilateral pitting pedal oedema and a tense abdomen with shifting dullness. The cardiovascular and respiratory examinations were normal. Notably, the patient exhibited delayed relaxation of deep-tendon reflexes bilaterally at the patellar and ankle sites.
Investigations
Pertinent laboratory findings showed an elevated thyroid-stimulating hormone (TSH) level of 151.69 milliunits/l, a low free thyroxine (fT4) level of <5.4 pmol/l, a haemoglobin level of 85 g/l, and a markedly high anti-thyroid peroxidase antibody level of 957.35 IU/mL. An electrocardiogram revealed a normal sinus rhythm with a low-voltage QRS complex. Chest X-ray findings indicated cardiomegaly suggestive of left heart failure. An emergent trans-thoracic echocardiography (TTE) demonstrated a large pericardial effusion measuring 5.4 cm posterior to the left ventricle.
Treatment
The most likely aetiology in this case was severe primary hypothyroidism. She initially received intravenous liothyronine 10 micrograms every 4 h, followed by oral liothyronine 5 micrograms twice a day in conjunction with levothyroxine 100 micrograms once a day. Adrenal reserve assessment was satisfactory. An urgent pericardiocentesis was performed, draining a total of 900 mL of serosanguinous fluid. Serial echocardiograms demonstrated the absence of residual effusion.
Conclusion
Hypothyroidism is a relatively uncommon cause of pericardial effusion. By ensuring early detection and appropriate treatment, we can optimise patient outcomes and prevent potential complications associated with untreated hypothyroidism.

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P147

A Challenge to treat Grave's Disease

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Although NICE guidelines recommend that radioiodine is the first-line treatment for Graves disease, carbimazole is often used initially to get control of the hyperthyroidism. This patient was exquisitely sensitive to carbimazole initially, and despite initial recurrence, he cannot be treated with radioiodine as he now has intermittent hypothyroidism.
Case
A 42-year-old male was diagnosed with Grave's disease and initially treated for twelve months with low-dose carbimazole. One year later, he relapsed with biochemical evidence of hyperthyroidism (TSH: <0.01 milliunit/l, Free T4 = 32 pmol/l, Free T3 = 14.2 pmol/l) and an elevated TSH antibody level of $>$ 30 unit/l, necessitating the initiation of therapy. Three months into treatment, he developed hypothyroidism, requiring the withdrawal of carbimazole due to a rise in thyroid-stimulating hormone (TSH) to 65 mu/l and a drop in Free T4 to 5.4 pmol/l. The table demonstrates the exquisite sensitivity the patient had to carbimazole despite his high antibody titre throughout the follow-up period. At present, he continues to exhibit biochemical signs of hypothyroidism (TSH: 47.9 milliunit/l, free T4: 8.6 pmol/l, and free T3: 2.9 pmol/l), despite being on no treatment for five months Despite the significant level of TSH receptor antibodies, the development of hypothyroidism is suggestive of the existence of inhibiting antibodies. He remains at risk of subsequent recurrence, and we are now ready to offer definitive treatment as soon as he has a recurrence.

TSH (mu/l)	Free T4 (pmol/l)	TSH antibody (unit/l)	Carbimazole dose (mg, daily)
<0.01	32	>30	30
65	<5.4		Discontinued
<0.01	18	>30	5
65	7.5		Discontinued
<0.01	22.9	>30	5

Conclusion
This case would emphasize the need for an individualized treatment approach, close monitoring of thyroid function, and long-term follow-up.

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P148

Abstract withdrawn

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P149

Thyroid storm from Graves with AF, CHF, PE, proximal myopathy, lymphadenopathy, raised CA-125

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Introduction
Thyroid storm presents as multiorgan dysfunction. Diagnosis is purely clinical, and early diagnosis improves the outcomes.
Case presentation
45-year-old lady without significant illness presented with breathlessness, productive cough, anxiety, and weight loss. Chest x-ray showed right pleural effusion and left consolidation. She was in fast AF with NT-proBNP >27000. initially treated as chest sepsis with CHF. Echo showed mild LVSD. TFT: TSH $<$ 0.01mu/l, FT4 44.4 pmol/l, FT3 23.5 pmol/l and TRAb 34.1 U/l. Graves' ophthalmopathy present. BWPS 65 - thyroid storm. Admitted in ITU - carbimazole, beta-blocker, steroids, and inotropic support. US thyroid - diffuse enlargement with hypervascularity. CT-PA and CT abdomen-pelvis - acute PE, bilateral pleural effusion, gross ascites, generalised lymphadenopathy, and a pelvic mass. Search for intrabdominal malignancy - peritoneal cytology was negative for malignancy. CA-125 was raised (1861 Ku/l) - normalised later. MRI pelvis - large degenerated subserous fibroid with no ovarian mass (not struma ovarii). After ITU step down, she remained bed bound for many weeks due to proximal muscle weakness secondary to thyrotoxic proximal myopathy. She developed hypercalcemia (highest Calcium 3.04 and PTH 0.3) secondary to immobility +/- thyrotoxicosis. She developed necrotic lesions affecting her abdominal wall and lower limbs which was later found to be apixaban related leukocytoclastic vasculitis. These improved after apixaban being switched to rivaroxaban. Biopsy of the enlarged axillary lymph node was planned. However, they were found resolved at the planned biopsy date.
Discussion
AF and arterial/venous thrombosis are common. Other features include cardiomyopathy, cardiac/respiratory/renal failure, rhabdomyolysis, hepatic/haematologic/neurologic manifestations. Hypercalcaemia Generalised lymphadenopathy are reported in severe untreated Graves'. CA-125, a well-established marker of ovarian cancer, is an indicator of CHF, and a guide to decongestion therapy. Apixaban is a rare cause of leukocytoclastic vasculitis mandates switch to different agent, and immunosuppression(if skin necrosis).

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P278

Effect of smoking status on TSH Receptor Antibody (TRAb) levels following treatment for Graves' disease

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Background
Graves' disease is an autoimmune condition leading to hyperthyroidism and characteristically elevated TSH receptor antibody (TRAb). TRAb levels typically

fall post-treatment with anti-thyroid drugs (ATDs) and are used in identifying risk of relapse. Tobacco smoking is a risk factor for reduced treatment efficacy of ATDs. We intended to evaluate the effect of smoking on changes in TRAb levels in patients treated for Graves' disease.
Methods
We analysed a database that prospectively collected information regarding patients treated for Graves' disease at Queen Elizabeth Hospital, Gateshead. Inclusion criteria was any patients treated for 9 months or longer with ATD. TRAb level data was taken at treatment initiation and 12 months (+/- 3 months). Patients without data at these two time-points were excluded ($n=60$). Smoking status was recorded as current smoker (CS), ex-smoker (XS), or life-long non-smoker (NS). TRAb reduction from baseline was measured as a percentage change for each group, using multivariable linear regression analyses. Other independent variables included were age, sex, race and duration of treatment with ATDs.
Results
In 374 patients, mean baseline TRAb levels for the NS, XS and CS groups were 8.9, 8.0 and 9.5 U/l, respectively. Smoking status was an independent predictor of the percentage drop in TRAb levels at 12 months ($P=0.03$). Current smokers had higher 12-month TRAb levels with lesser relative reduction. The number of cigarettes smoked daily demonstrated negative independent correlation with change in 12-month TRAb ($P=0.03$).
Conclusions
There is a significant correlation between smoking status and TRAb at 12-months, both as a relative and absolute value, which probably explains the higher relapse risk seen in CS. The extent of tobacco consumption also appears relevant, highlighting that reducing the number of cigarettes smoked may be beneficial in lowering TRAb levels and potentially the risk of relapse after ATD cessation.

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P279

Concurrent Myasthenia gravis (MG) and Graves' ophthalmopathy (GO)

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Myasthenia gravis (MG) and Graves' ophthalmopathy (GO) share many clinical characteristics but may also co-exist. Both are autoimmune disorders mediated by organ specific pathogenic autoantibodies to membrane surface receptors. Differential diagnosis and/or co-existence provides a potential management challenge, and there is a paucity of demographic information regarding precise prevalence rates and concurrence of disease.
Method
Retrospective chart review from a single institution registered as a Quality Improvement project. Demographic data were cross-referenced from the comprehensive Myasthenia Gravis database and Graves' Ophthalmopathy databases to identify dual diagnoses.
Results
858 patients were identified with MG and 270 patients GO. Five patients had both MG and GO. Thus, in MG, prevalence of GO was 0.58% and prevalence of MG in GO patients was 1.9%. The predominant diagnosis was MG in all 5 patients. Four of the five patients initially presented with ocular myasthenia (80%). One patient, initially diagnosed with generalised MG, subsequently developed ocular symptoms. Acetylcholine receptor antibodies were positive in all patients, with a mean level of 156 (range 6-514). Mean age of primary diagnosis of MG was 49 years (range 30-76 years). There was a slight female predilection (40% male, 60% female). Concurrent thyroid dysfunction was diagnosed incidentally, on biochemical screening, in all patients. TSH receptor antibodies were elevated in 4 patients where available (mean 1.68 (range 0.5-3.2). All patients were treated initially with pyridostigmine. One patient required rituximab/methyprednisolone combination treatment for active thyroid eye disease with extra ocular muscle enlargement on MRI imaging.
Conclusion
Coexisting pathology is not uncommon, and important to consider when managing patients where presentation is perhaps less typical with either condition. Imaging is helpful as appearances of GO are distinctive. TFT and possibly TRAb should be considered in all patients with ocular MG. The potential for steroid sparing co-management with Rituximab needs further research.

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P280

Molecular genetic testing in advanced thyroid cancer patients for the purposes of targeted systemic therapy

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Introduction
With the advent of specific gene targeted therapies for advanced thyroid cancers it has become important that molecular genetic testing is requested to identify patients suitable for these treatments, for example with BRAF, RET or NTRK inhibitors. We investigated the proportion of patients with advanced thyroid cancer in a specialist thyroid cancer clinic who had undergone appropriate testing.
Participants and Methods
56 patients with advanced thyroid cancer were identified from clinic records. Patients were divided by histological subtype, with 36 differentiated (DTCs), 16 medullary (MTCs), and 3 anaplastic (ATCs) cancers, as well as one NUT carcinoma initially thought to be DTC. Patients were excluded if they had extensive comorbidities (1) or were responding to conventional treatments (12). For the remaining 43 patients (24 DTCs, 15 MTCs, 3 ATCs, and 1 NUT carcinoma), records were checked for molecular testing.
Results and discussion
The majority (86.0%) of patients had undergone genetic testing. This included the NUT carcinoma and all ATC patients, compared to 20 (83.3%) of DTC and 13 (86.7%) of MTC patients. Of those eligible and tested, 20.0% of DTC patients had a genetic mutation identified, compared to 84.6% of MTC patients. Whilst this difference is not unexpected, a particularly high rate of MTC patients with RET mutations is explained by the clinic being a referral centre for a clinical trial of a RET specific therapy. Whilst most patients had had the appropriate testing, a small number were identified who needed this to be requested, to allow identification of treatment options.
Conclusion
Genetic testing is essential to identify patients suitable for targeted systemic therapies. These treatments can transform the patient's quality of life and prolong their survival. Additionally, this project has shown genetic testing helps identify rarer subtypes, such as NUT carcinoma.

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P281

A digital dashboard to manage graves' disease

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Introduction
Graves' disease (GD) is the most common cause of thyrotoxicosis with antithyroid drugs (ATD) being first-line management. Consultations and monitoring required for ATD therapy are resource intensive. We evaluated the potential for a digital thyrotoxicosis monitoring pathway (DTP) on GD treatment outcomes and efficiency of care.
Methods
We constructed a dashboard using Palantir Foundry to identify patients with a coded diagnosis of thyrotoxicosis, excluding nodular disease. A historical control cohort was identified using the same diagnostic codes to identify those treated pre-dashboard. A pharmacist-led protocol to identify those requiring dose adjustments from the dashboard was developed. Clinic appointments continued as standard care during this initial evaluation. Demographic data, free thyroxine (fT4) results, and appointment details were collected from electronic health records and compared between patients who were being currently managed with and before the DTP.
Results
280 patients were included in this study, with 134 in the dashboard cohort and 146 receiving prior standard care. The mean age of participants was 46.8 ± 14.7 years and 83.9% were female. No statistically significant difference was noted between the cohort's time to fT4 <23.0 pmol/l or <14.4 pmol/l ($P=0.8656$). The dashboard cohort had a significantly greater risk of hypothyroidism ($P=<0.0001$). As the dashboard was used in parallel with standard care in this initial study, patients in the dashboard cohort received a significantly higher mean number of total appointments (5.9 vs. 2.5, $P=<0.001$), but with a significant difference in the number of face-to-face, telephone and virtual review consultations ($P=<0.0001$).
Conclusion
The DTP facilitated more remote modes of monitoring, such as note reviews, while providing as effective clinical outcomes as standard care. A full evaluation will now proceed to determine if the dashboard can fully replace clinic attendances.

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P282

Thyroid eye disease in pregnant women with Graves disease: Experience from a specialized thyroid eye clinic

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Background
Thyroid eye disease (TED) affects 25% of patients with Graves' disease (GD). GD affects nearly 1% of pregnancies. However, data on TED incidence, course, management and outcome in pregnancy are limited.
Aims
To describe the prevalence, course and outcomes of TED in pregnant females.
Methods
A retrospective analysis of electronic health records was conducted in a specialized Joint Thyroid Eye Clinic in Oxford. Individual health records of females in the reproductive age group (18 to 50 years) were screened to identify disease activity and severity of TED during pregnancy and post-partum.
Results
Among 256 patients reviewed in this clinic between 2017 and 2023, 199 were females and 69 were in the reproductive age at the time of first visit. Three patients had TED during pregnancy. All were on pharmacological treatment for thyrotoxicosis throughout pregnancy. TED onset was before pregnancy in all. Two of them remained mild-to-moderate in severity and inactive throughout the pregnancy and puerperium period. One patient required blepharotomy (eyelid lowering) post-partum. One patient developed severely active TED six months post-partum and was successfully managed with rituximab.
Conclusions
The prevalence of TED in pregnancy is rare. In our experience two of three patients remained inactive and mild-to-moderate in severity without the need for specific treatment. It is unclear whether this is due to avoidance of pregnancy with hyperthyroidism/TED or amelioration of autoimmune disease during pregnancy.

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P283

Addressing unresolved controversies in thyroid hormone replacement for hypothyroidism: A systematic review

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Objective
Levothyroxine (LT4) is the gold standard of care for primary hypothyroidism. For most patients, it fully resolves the symptoms of hypothyroidism. However, a small proportion of treated individuals continue to experience symptoms even when euthyroid. The management of such patients has generated significant controversy and public attention throughout the years. This systematic review aims to analyse and evaluate the existing evidence for the benefits of alternative thyroid hormone replacements compared to the standard LT4 monotherapy. This includes combination therapies in the form of LT4/LT3 or Desiccated Thyroid Extracts (DTE) and LT3 monotherapy.
Method
A systematic search of the online literature was conducted on PubMed, EMBASE, Cochrane Library and Web of Science in November 2022. Out of 6,176 studies, thirteen were included and were assessed for our primary and secondary outcomes. Primary outcomes included quality-of-life scores and thyroid function tests while secondary outcomes assessed hypothyroid-related symptoms (cognitive function, cardiovascular health, body profile, psychological health) and patient preferences.
Conclusion
We observed no overall difference in clinical outcomes between combination therapies (LT4/LT3 or DTE) and LT4 monotherapy for the treatment of primary hypothyroidism in adults. Yet, consistent with previous clinical trials and meta-analyses, we observed that a higher proportion of patients preferred combination therapy over LT4 alone. Moreover, we noticed a tendency favouring combination therapies when either higher doses of LT3 or DTE were used. Our most important observation was that a significant improvement in quality of life was evident only when combination therapy was used for patients with residual symptoms or an autoimmune related pathogenesis of hypothyroidism. Regarding treatment with LT3 alone, the evidence was insufficient and definite conclusion could not be made. To resolve this controversy and validate the observations seen above future homogenous trials should be developed to address the limitations of current study designs.

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P284

Systematic review and meta-analysis (SRMA) of RAI monotherapy vs combination therapy for toxic nodular goiter (TMNG)

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Background
Treatment options for patients with toxic multinodular goitre (TMNG) include antithyroid medications, thyroidectomy, and radioactive iodine (RAI) therapy. Our aim was to investigate the efficacy of RAI alone compared to combination therapy that includes RAI with medical therapy.
Methods
Search was performed using MEDLINE, MEDLINE In-Process (PubMed platform), Embase (Elsevier platform), BIOSIS and Cochrane was performed. Randomized controlled trails (RCTs) and prospective cohort studies were included that explored efficacy of radioiodine treatment for TMNG in adults aged over 18. Random effect meta-analysis was performed to estimate the efficacy of radioiodine therapy either as monotherapy or as combination therapy in achieving cure.
Results
6 RCTs (364 participants) and 14 cohort studies (2117 participants) were eligible for final analysis. On comparing monotherapy to combination therapy of radioiodine in TMNG, pooled results from the RCT's showed that monotherapy was found to have higher cure rates at 1 year (83.3% vs 67.5%; RR 1.14; 95% CI 0.93 to 1.40, I2 = 70%, pheterogeneity < 0•006), though not statistically significant ($P = 0.20$). In the pooled results of 4 cohort studies where follow up was available for 1 year there was no difference in outcomes of cure rates between monotherapy or combination therapy (RR 1.11; 95% CI 0.93 to 1.33, I2 = 81%, pheterogeneity < 0•00001). In terms of recurrence at 1 year in RCT's, monotherapy was associated with lower rates of recurrence (19.8% vs 27.6%; RR 0.58; 95% CI 0.32 – 1.04), $P = 0.07$. The rate of recurrence from the pooled cohort studies undergoing monotherapy was 12%. Only 1 study reported on recurrence rates from combination therapy. In terms of side effects only 2 RCT's reported a 10% nausea rate following RAI.
Conclusions
RAI monotherapy in comparison to combination therapy has better cure and lower recurrence rate in the treatment of toxic multinodular goitre.

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P285

Dietary and supplemental iodine intake in a cohort of pregnant women in Northern Ireland

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Since the 1990's, eight survey studies have demonstrated iodine deficiency during pregnancy across the UK and Ireland. Both countries lack an iodine fortification programme, unlike many European countries. Therefore, women must rely on dietary adjustments and supplementation to achieve the iodine intake required in pregnancy. The World Health Organisation (WHO) recommends an increase from 150 to 250 μg/day during pregnancy. Pregnant women in Belfast were recruited to, and provided written consent to participate in, a cows' milk intervention study, and were asked to complete a four-day food diary following their booking clinic appointment, at around 12 weeks gestation. Of the total cohort of 119, 65 women submitted a food diary(54.6%). The online dietary analysis software Nutritics® was used. Forty-two women (64.6%) reported taking an iodine-containing multivitamin. The most popular iodine-containing supplement taken during pregnancy in this group contains a total daily dose of 140 μg of iodine in the form of potassium iodide. The range of iodine content of the supplements reported was 0 – 150 μg, with one participant taking a preparation containing no iodine and one containing 75 μg. The median daily iodine intake was 261 μg/day (IQR 121 – 289 μg/day), which is below the WHO recommended intake during pregnancy. Those taking an iodine-containing supplement had a significantly higher iodine intake compared to those not taking one (265 vs. 127

μg/day) ($P<0.001$) and met the recommended intake. In the absence of a fortification programme, pregnant women may benefit from improved education and information to increase their dietary intake of iodine and to consider an iodine-containing supplement. The Pregnancy Book, provided to all pregnant women in Northern Ireland at their booking appointment, has recently been updated to include a brief section on dietary sources of iodine, which is a small but important step forward.

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P286

Parameters impacting excessive weight gain in patients treated for hyperthyroidism

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Background
Overshoot of weight regain following the treatment of hyperthyroidism is well described. Notwithstanding, there is a large interindividual variability in the observed weight changes. This study aims to identify parameters predicting excessive weight gain in hyperthyroidism patients.
Methods
In a retrospective study of a prospectively completed database, we recruited consecutive patients with overt hyperthyroidism and compared those with excessive weight gain ($\geq$10%, Group A) to those with less gain ($<$10%, Group B) based on initial anthropometrics, demographics, and disease-related characteristics, using appropriate statistical tests.
Results
We recruited 91 patients (70.3% females, median age 50 years) treated for hyperthyroidism with a median follow-up of 2 years. Excessive weight gain (GpA) was observed in 50% of patients. GpA had significantly higher ft4 levels and disease-related weight loss at presentation.

Parameters	Group A: ≥10% weight gain n (%) or median	Group B: <10% weight gain n (%) or median	*P*-value
All	45 (49.5%)	46 (50.5%)	
Sex			0.104
Male	19 (61.29%)	12 (38.71%)	
Female	26 (43.44%)	34 (56.67%)	
Ethnicity			0.449
Cypriots	38 (51.35%)	36 (48.65%)	
Non-Cypriots	7 (41.18%)	10 (58.82%)	
Smoking status			0.105
Smokers	17 (56.67%)	13(43.33%)	
Ex-smokers	1 (14.29%)	6 (85.71%)	
Never smokers	22 (46.81%)	25 (53.19%)	
BMI-0 (kg/m2)	24.31	25.16	0.592
TSH-0 (mIU/l)	.010	0.14	0.156
ft4 (t=0) (ng/dL)	52.94	36.92	<0.001
Disease-related weight loss (t=0) (kg)	8.17	2.68	<0.001
TRAb levels (t=0) (IU/l)	10.04	10.54	0.390
Peak TSH levels (mIU/l)	6.137	5.39	0.475
Treatment			0.535
ATDs	40 (51.28%)	38 (48.72%)	
ATDs & surgery	5 (45.45%)	6.1 (54.55%)	
Diagnosis			0.311
Graves' disease	41 (52.56%)	37 (47.44%)	
Toxic Nodular Goiter	3 (30%)	7 (70%)	

Conclusion
The severity of thyrotoxicosis and the disease-related weight loss were predictive of excessive weight gain post-treatment. This information alongside the presentation BMI may allow risk stratification for excessive weight gain, hereby permitting early intervention strategies.

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P287

Using TRAb as a predictor of relapse in Graves' disease

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Background
Thyroid stimulating receptor hormone receptor antibodies (TRAb) markers are useful in confirming diagnosis of Graves' disease, but also recognised as a predictor of relapse. Good practice dictates that a TRAb is measured at the commencement of treatment, to confirm a diagnosis of graves' disease. Repeating the TRAb before discontinuation of treatment can assist in guiding treatment. If TRAb remains elevated, the chances of relapse are increased. A persistently elevated TRAb is one of the predictors of relapse.
Method
100 patients with confirmed Graves' disease, having completed 18 months treatment on anti-thyroid medication, were selected at random using hospital data systems. Using a quantitative methodology approach, data was collated relating to TRAb at diagnosis and at the end of 18 months treatment for those receiving Anti Thyroid Drugs (ATDs).
Results
Of the 100 patients, 27= male, 73 = female. 98 patients had a TRAb checked at diagnosis. Following treatment, 61 patients had a confirmed relapse of Graves' disease within 12 months. Of these, 22 patients had their TRAb repeated at the end of 18 months treatment. 4 of these patients returned an elevated TRAb and relapsed within 7 months. The remaining 18 patients had a normal TRAb, with 6 relapsing in the following 12 months. 78 patients had discontinuation of treatment with no TRAb repeated, 50 of which relapsed within 12 months.
Conclusion
All patients with an elevated TRAb at the end of 18 months treatment proceeded to relapse within 12 months. 50 patients also relapsed but without a repeat TRAb. We could assume that if the TRAb had been repeated in those 50 patients, found to be elevated and the 18 month treatment regimen extended, definitive treatment options could have been broached much sooner.

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P288

Dual presentation of struma ovarii and autoimmune thyroiditis unmasked by salpingo-oophorectomy

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Introduction
Struma ovarii is often initially diagnosed as a suspected ovarian malignancy due to atypical characteristics on the imaging and hyperthyroidism is only seen in about 8% of presentation making thyroid function test (TFT) an unreliable test to suspect it pre-operatively. There are few case reports on its varied structural and functional characteristics in the literature. However, there are no reports of the influence of an intrinsic thyroid disease on its functional characteristics.
Case report
A 40-year-old lady with dual presentation of struma ovarii and autoimmune thyroiditis with presentation of overt hypothyroidism after salpingo-oophorectomy for a suspected ovarian malignancy. She initially presented to Gynaecologist with intermittent post-coital right sided sharp abdominal pain, bloating and no weight changes. The point of care pelvic ultrasound confirmed an enlarged irregular highly vascularised multilocular solid-cystic lesion in right ovary suspicious of a malignancy. The initial blood tests include tumour makers CA125 39 kIU/l (0-35), CEA 1.1 (0-3.4) mg/l, CA19 2 kIU/l (0-27), AFP 2.2 kIU/l (0-6) and TSH of 3.79. Other routine biochemistry within normal limits. She underwent salpingo-oophrectomy and the histology confirmed struma ovarii with atypia. No pathogenic mutations were identified and RNA based NGS testing showed no NTRK fusions. Following the result of histology, patient was referred to Endocrinology clinic with unintentional weight gain of 4 kg within two months and repeat TFT showed TSH of $>$100 and FT4 2.2. Further investigations include TPO of 1300 IU/ml (0-60) and thyroid USS suggestive of autoimmune thyroiditis (Hashimoto's). She was commenced on Levothyroxine which improved her symptoms.
Conclusion
This case illustrates the uncertainty in TFT pictures that could be associated with struma ovarii in the presence of intrinsic thyroid disease and this could further complicate the ongoing constraints of pre-operative suspicion of struma ovarii before histology diagnosis. To our knowledge, this is the first report of such association.

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P289

Cure rates after a single dose of radioactive iodine to treat hyperthyroidism

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Introduction
Radioactive iodine (RAI) has been used to treat hyperthyroidism for over 70 years. Some centres use a fixed dose regimen while others use a calculated dose regimen. Cure rates range between 80% and 100%, with some patients requiring two or more doses. We use the fixed-dose regimen at our centre. We therefore evaluated our cure rates after a single dose of RAI to treat hyperthyroidism.
Methods
We reviewed the medical records of patients who received their first dose of RAI between 2016 and 2021. Patients had telephone follow-up and biochemical assessment every six weeks until six months post-RAI therapy, then every three months thereafter until cured. Patients were deemed cured when they developed persistent hypothyroidism or euthyroidism after a single dose of RAI.
Results
One hundred and thirty-eight patients received their first dose of RAI during the study period. The group had a mean $\pm$ standard deviation age of 56.9 $\pm$ 15.3 years and included 101 women and 37 men. The median duration of hyperthyroidism was 34 months, and 62% of patients had Graves' disease. A majority (90%) were on an antithyroid drug prior to RAI therapy. The median (interquartile range) dose of RAI received was 559 (546-577) megabecquerels. Four patients (2.9%) reported adverse events after receiving RAI. Our overall cure rate was 87.7% after a single dose of RAI therapy [96 patients (69.6%) developed hypothyroidism and 25 patients (18.1%) remained euthyroid]. Our one-year cure rate was 84.1%. Furthermore, women had a greater cure rate when compared to men (92% vs 75.7%, $P = 0.017$).
Conclusions
Our centre had an overall cure rate of 87.7% after a single dose of RAI therapy given to treat hyperthyroidism, and a one-year cure rate of 84.1%. Our results are comparable to that reported at other centres using a similar dosing regimen.

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P290

Secondary hypothyroidism? a challenging diagnosis

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Introduction
Secondary hypothyroidism can be a difficult diagnosis to make in patients presenting with fatigue. About 30% of females can develop hypopituitarism post-partum and report symptoms after losing any of the anterior pituitary hormone axis. Central hypopituitarism can occur secondary to various structural and vascular abnormalities but can present with pure hormonal abnormalities.
Case
We present a case of a woman in her late thirties, who presented to the Endocrinology clinic with worsening fatigue, hair loss, weight gain, floaters and dry eyes for 4 years. She felt that her symptoms started post-partum and originally diagnosed with post-partum thyroiditis treated with oral Levothyroxine 125 mg which did not alleviate her symptoms. She denied any thyroid related illness.
Investigations
Her serial TSH were consistently low with normal Free T4 (negative TSH receptor antibodies). Further anterior pituitary screen showed a deficiency of TSH, LH and FSH which raised a strong suspicion of possible central hypopituitarism. This patient's thyroid ultrasound excluded thyroiditis but her Pituitary MRI scan showed a 2mm cystic micro-adenoma or Rathke's cyst confirming her diagnosis.
Management and Discussion
Our case highlights the challenge of differentiating between primary and secondary hypothyroidism. In above patients case her serum TSH was used to titrate her oral Levothyroxine which aggravated her symptoms. This patient showed an improvement in her symptoms after diagnosis was revised to secondary hypothyroidism which was treated with much higher dosage of oral Levothyroxine. This dosage titration is based on her clinical symptoms instead of using her body weight as a reference for estimating her daily requirements. All these decisions around complex decision making have to be undertaken in an MDT setting for this group of patients.

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P291

Pembrolizumab Induced Hypothyroidism in a Patient with Pre-existing Thyrotoxicosis due To Grave's Disease

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Thyroid dysfunction by Immune Checkpoint Inhibitors (ICPI) is a common Immune-Related Adverse Event (IRAE). Thyroid dysfunction is prevalent in cancer patients receiving pembrolizumab treatment (ICPI). Most prevalent clinical manifestations are reversible destructive thyroiditis and overt hypothyroidism. Pembrolizumab-induced thyroid IRAE's have been reported to range from 3.2% to 10.1%.
Case Report
This case reports a 64-year-old lady who treated for relapse of Grave's thyrotoxicosis and developed overt hypothyroidism after commencing therapy with Pembrolizumab, for squamous cell carcinoma of the left lung. Initially thyrotoxicosis treated with carbimazole and Levothyroxine for 18 months, discontinued treatment in February 2020. She had relapse of Grave's thyrotoxicosis in July 2020 and commenced carbimazole 20 mg twice daily. Routine TFT's 6 weeks later showed TSH 1.6mU/l, Free T4 10.4 pmol/l. She remained biochemically euthyroid on carbimazole 15mg per day. She was diagnosed with squamous cell carcinoma of left lung in June 2022 and commenced on combination ICPI therapy in July 2022. 5 weeks post ICPI treatment: TSH 35mU/l, Free T4 4.3 pmol/l, TPO $>$600kIU/l, consistent with immune therapy induced thyroiditis. Carbimazole dose reduced to 5mg per day. Subsequent routine TFT with oncology team, carbimazole discontinued and commenced levothyroxine 50mg per day in view of being symptomatic of hypothyroidism. She remained biochemically euthyroid and Levothyroxine discontinued in January 2023. Her TFT in February 2023 showed TSH 53mU/l, Free T4 2.3 pmol/l. Levothyroxine recommenced 75mg per day, TSH showing downward trend; 6.5mU/l, Free T4 15.7 pmol/l. Combination ICPI therapy continues, alongside levothyroxine.
Conclusion
ICPI can convert pre-existing Graves' disease to autoimmune hypothyroidism. When employing ICPI in patients with pre-existing autoimmune thyrotoxicosis, a multidisciplinary team approach is essential. Close biochemical monitoring and awareness of the risk of evolution toward hypothyroidism should be considered with ICPI treatments.

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P292

Carbimazole patient information leaflet improves rate of educating patients on agranulocytosis

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Background
Carbimazole is a commonly used and effective treatment for hyperthyroidism. Although on the World Health Organisation's list of essential medicines, it comes with the potentially significant side effect of agranulocytosis. We set out a Quality Improvement Project to improve communication with patients to ensure their understanding through creating a patient information leaflet.
Methods
30 patients receiving Carbimazole treatment between July and December 2021 were identified in a district general hospital, 15 from each consultant in the department. Clinic letters and replies to GP referrals were analysed to determine if side effects of carbimazole were counselled. We produced a Carbimazole patient information leaflet explaining the drug's purpose, side effects and symptoms to be aware of. We educated clinical team members that the leaflet was to be distributed to patients taking Carbimazole. 29 patients from February to June 2023 were studied post-intervention to compare if the number of patients educated had increased. We also spoke to 10 randomly chosen patients to see if they found the leaflet useful.
Results
Prior to the leaflet being produced, 16 of 30 (53.3%) patients had documented evidence of discussion about side effects of Carbimazole. After the team became familiar with the leaflet, 22 of 29 patients (75.9%) had documented evidence of discussion of side effects. In one patient Carbimazole was appropriately stopped. 7 of 9 (77.8%) patients felt the leaflet was beneficial with two preferring verbal communication. One was unable to be contacted.

Conclusions
This study was performed during a period where novel communication methods were used during the COVID-19 pandemic. Virtual and telephone clinics brought new challenges to starting patients on medications. There was a numerical increase in documented discussions held following intervention. This project ensures patients have a copy of important information about their healthcare at a time of strained resources.

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P293

Rebound worsening of amiodarone-induced thyrotoxicosis after discontinuation of pulse methylprednisolone despite treatment with oral steroids and thiamazole

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Background
Amiodarone-induced thyrotoxicosis (AIT) is sometimes very difficult to treat. Pulse methylprednisolone in addition to oral steroids appears effective in treatment of AIT, but effects of such treatment may be transient.
Presentation of The Case
A 65 year old man was admitted our Department because of drug-resistant AIT. He had a history of atrial fibrillation, treated with amiodarone since 2019, and NSTEMI myocardial infarction (2020). In 2022 he had suffered another NSTEMI and was found to be thyrotoxic (TSH $<$0.005 uIU/ml, free T3 (fT3) 22.43 pmol/l (3.1-6.8), free T4 (fT4) $>$100 pmol/l (12-22)). Amiodarone was stopped, but he failed to respond to thiamazole (20 mg tds). On admission he had episodes of confusion and hypotension (about 80/60 mmHg) associated with rhythms above 130/minute. He was markedly thyrotoxic: fT4 $>$7.77 ng/dl (0.93-1.7), fT3 14.95 pg/ml (2-4.4). Thyroid ultrasound was unremarkable, while titres of all anti-thyroid antibodies were normal. He was treated with thiamazole 20 mg tds, prednisolone 40 mg od and pulse methylprednisolone 500 iv and then 250 mg iv once a week. After six doses his fT3 decreased to 2.05 pg/ml and fT4 to 2.41 ng/dl. Methylprednisolone was stopped. After about three weeks (despite continuation of thiamazole and prednisolone) he presented with rebound thyrotoxicosis: fT4 $>$7.77 ng/dl, fT3 5.46 pg/ml. Methylprednisolone was restated (500 mg and then five doses of 250 mg) that was followed by a decline in fT4 to 2.51 ng/dl and fT3 to 1.92 pg/ml. He subsequently underwent successful thyroidectomy - one week post thyroidectomy fT4 0.92 ng/dl, fT3 1.3 pg/ml, TSH 0.06 uIU/ml.
Conclusions
Pulse intravenous methylprednisolone may be a useful adjunct therapy in cases of refractory amiodarone-induced thyrotoxicosis, but there is a danger of a rebound worsening of thyrotoxicosis after discontinuation of this therapy.

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P294

Development of a thyroid patient database in conjunction with the IT system development team at a DGH

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In September 2021 the pathology department announced it would be going paperless, a change that resulted in endocrine monitoring being added to the trust risk register. To manage this risk several options were considered including the DAWN system used by rheumatology and systems used by other local hospitals. Unfortunately, none of these were viable options. Discussions were started with the IT systems development team about building a database for management of thyroid patients. As a large patient cohort reliant on regular blood testing there were already concerns about ensuring timely reviews of blood test results; the move to paperless prompted the need for a robust system change. Following several meetings with the IT development team the first version of the database was trialled in June 2022 with the system going live in August 2022. Thyroid patient details were uploaded by the system development team into the thyroid database prior to its launch.
The database alerts the user to recent blood test results (based on TSH) but also records:

- Diagnosis
- Start of treatment
- Long term treatment plans
- Referral for definitive treatment dates
- Dose of carbimazole/propylthiouracil/levothyroxine

To date, 540 patients have been entered into the database, of which 220 have been discharged. All thyroid blood test results are actioned within a week and treatment dosing is tracked alongside blood test results. The thyroid service can be audited in multiple ways although this is still under development. This has led to a qualitative improvement in patient care. Going forward, additional arms will be added to the database for other endocrine conditions, such as hyperparathyroidism. The system developer that has worked with the endocrine team deserves huge credit for this database; he has responded to all requests and gone above and beyond with this project.

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P295

Recurrent postpartum thyroiditis with negative test for anti-thyroid peroxidase antibodies

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Introduction
Postpartum thyroiditis (PPT) occurs during the first postpartum year with a prevalence between 1.1% and 16.7%. It presents either as transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by transient hypothyroidism. Anti-thyroid peroxidase antibodies (TPOAb) levels are high in 60-85% of cases, while the less measured anti-thyroglobulin antibodies (TgAb) can also be high. Risk factors for PPT include presence of thyroid antibodies prior to pregnancy and a history of previous PPT. We present a woman who had PPT affecting three consecutive pregnancies.
Case presentation
A 33-year-old woman presented with heat intolerance, palpitations, and breathlessness three months after delivery. She had a history of PPT occurring after two previous pregnancies. The first episode occurred three months postpartum. She subsequently developed transient hypothyroidism requiring levothyroxine replacement for three months. The second episode also occurred three months postpartum and was followed by transient hypothyroidism three months later. She had no other medical history, not on regular medication and was a non-smoker.
Investigations and management
Initial results revealed mild thyrotoxicosis with exacerbation a month later, while on beta-blocker therapy (Table). Ultrasound scan demonstrated increased vascularity consistent with thyroiditis. TPOAb and thyroid receptor antibodies (TRAb) were negative, but TgAb were positive. She developed worsening hypothyroidism over the second and third month, followed by spontaneous recovery over the fourth and fifth month.
Conclusion
This woman had the classic triphasic pattern during all three episodes of postpartum PPT, with negative test for TPOAb but positive test for TgAb. This case serves as a reminder to check TgAb in patients with TPOAb-negative PPT.

Test	Initial result	Month 1	Month 2	Month 3	Month 4	Month 5
Thyroid stimulating hormone (0.3-4.2 mU/l)	0.26	0.01	1.60	20.3	5.46	3.14
Free thyroxine (12.0-22.0 pmol/l)	21.4	23.9	10.8	8.9	9.8	11.4
Free triiodothyronine (3.1-6.8 pmol/l)	6.2	7.4	3.2	3.6	3.9	4.3

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P296

A case of intravenous immunoglobulin induced thyroiditis in pregnancy

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Intravenous Immunoglobin (IVIG) therapy is used in recurrent miscarriage, despite its efficacy being limited to specific sub-groups such as those with underlying immune conditions. The indications, efficacy and side effect profile of IVIG when used in pregnant women are not established. We present the case of a 41-year-old

pregnant woman with one previous miscarriage, who had received IVIG as part of her fertility treatment and subsequently developed profound symptoms and biochemical evidence of thyroiditis at twelve weeks' gestation. Prior to the IVIG therapy, she was euthyroid with no family history of thyroid disorders. Her fertility team additionally prescribed prednisolone, aspirin and folic acid. Two weeks after receiving IVIG, a viable intrauterine pregnancy of six weeks gestation was confirmed. In the following weeks, she experienced tachycardia, weight loss, heat intolerance, and tremor in the absence of Graves' defining features. Her thyroid function tests demonstrated the following: TSH <0.01mU/l, Free T3 (FT3) 11.3 pmol/l and Free T4 (FT4) 45 pmol/l. The degree of thyrotoxicosis and ratio of thyroid hormones rendered gestational thyrotoxicosis less likely. She was therefore commenced on Propylthiouracil (PTU) 100mg daily pending TSH receptor antibody (TSHrAB) results. Two weeks later, following normalisation of her FT4 values, and negative TSHrAB confirmation, PTU was discontinued. Within four weeks, she developed a low FT4 (FT4 8.4 pmol/l, TSH <0.01mU/l) and low dose levothyroxine was commenced (50mg daily). The negative TSHRAb together with the later hypothyroid phase suggested a thyroiditis, which was thought to be precipitated by the IVIG. The definitive method of confirming this: a technetium uptake scan, is contraindicated in pregnancy. The indications, efficacy and side effect profile of IVIG in pregnancy are not fully established. This case would suggest that the safety profile requires further consideration. We believe this case demonstrates the first recorded instance of IVIG-induced thyroiditis in pregnancy.

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P297

Thioamide-resistant Graves' Disease: Successful total thyroidectomy

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Background
Thioamide-resistant severe Graves' thyrotoxicosis (SGT) is rare and often poor patient adherence to therapy is suspected. Management is truly challenging.
Case Report
36-year-old female with SGT was referred for further management. The diagnosis was made 5 years ago following delivery of her first son. During her second pregnancy 2 years ago, she required emergency caesarean with the indication of foetal tachycardia. She received high dose of carbimazole and/or propylthiouracil. Previous attempts of surgery failed. She did not achieve euthyroid with lugol iodine. She attended A&E 10 times in 12 months with SGT. Clinically, she had signs of SGT, large goitre, thyroid bruit and significant thyroid eye signs.
Investigation
Her Free T3 was always above the assay measurable upper limit. Thyroid stimulating antibody (TSI) was marginally raised. MRI obit confirmed changes with chronic thyroid eye disease.
Management
Carbimazole 20mg TDS and propranolol 80mg TDS were started. Weekly follow up was arranged. Patient accidentally continued to take PTU 100mg BD for 2 weeks. Adherence to therapy was evidenced by empty blister packs and side effects with generalised urticaria. TFT did not change. 3 weeks later, Lithium 250mg TDS was started. Urgent hospital admission was arranged to control SGT and planned semi-emergency thyroidectomy. Colestyramine 3g TDS, prednisolone 30mg OD were prescribed. Lugols solution was given 10 days prior to surgery (during the junior doctors strikes). Her TFT stabilised and she had successful thyroidectomy on day 14.
Discussion
We presented truly thioamide-resistance case that needs significant co-ordinating effort of prescribing, monitoring, admitting to hospital and MDT approach against an NHS front door pressure. The case also highlights the lack of correlation between TSI and severity of Graves

TSH	<0.01 ml/l	0.35 – 4.94
Free T4	43.6 pmol/l	9.0 -19.1
Free T3	>30.7 pmol/l	2.4-6.0
(TSI)	6.18i u/l	<0.56

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P298

A case report of Lithium induced autoimmune thyroiditis in a previously hypothyroid patient

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Background
There is a well-documented relationship between lithium exposure and thyroid dysfunction via multiple mechanisms. Lithium is commonly associated with goitre, hypothyroidism, and subclinical hypothyroidism. Lithium-induced autoimmune hyperthyroidism is rare and poorly understood. We report a case of autoimmune thyroiditis, Graves' disease (GD), in a patient with longstanding primary hypothyroidism believed to be induced by Lithium.
Case report
A 77-year-old lady presented to her GP with a 5-month history of thyrotoxic symptoms, including weight loss and palpitations. Medical history included a 20 year history of hypothyroidism, treated with Levothyroxine, type 2 diabetes, chronic kidney disease, and longstanding depressive psychosis, controlled with lithium. Levothyroxine was stopped; despite this thyroid function (TFT) remained abnormal (serum-free T3 16.4 pmol/l; serum-free T4 37.3 pmol/l; and serum TSH $<$ 0.05 mIU/l. She was referred to Endocrine outpatient clinic and started on Carbimazole 20mg once-daily pending her appointment. She had high Thyroid-specific Antibodies, with TSH receptor antibodies at 18.10 IU/l(Range) and Thyroid peroxidase antibodies at 544 IU/mL(Range). Thyroid Technetium scanning confirmed increased uptake and diffuse toxic goitre, features suggestive of GD. She continued titrated dose Carbimazole guided by regular TFT and clinical thyroid status. Due to concerns about declining renal function, lithium was withheld by the psychiatric team. The plan is to treat definitively once her thyroid status stabilises with Antithyroid medication.
Discussion
This case is noteworthy, given the rare association between lithium exposure and autoimmune hyperthyroidism. The presentation of GD was also unusual as our patient had previously been managed for primary hypothyroidism for several years, which raises discussion points on lithium affecting circulating thyroid autoantibodies and potentially converting existing autoantibodies from a suppressing to an activating form.

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P299

Amiodarone induced thyrotoxicosis type 1 (AIT1) without Graves' disease or toxic nodular goitre

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Introduction
AIT1 usually occur on a background of Graves' disease or toxic nodule goitre. The disease usually requires higher doses of carbimazole than Graves', might need rescue thyroidectomy, and can be treated with radioiodine with higher than standard radioiodine doses after iodine contamination has come down.
Case presentation
57-year-old gentleman with history of HTN, T2DM, dyslipidemia, aortic stenosis, recurrent paroxysmal atrial flutter, previous multiple DC cardioversions and multiple amiodarone loading. He had an ablation procedure on March 2021, was symptom-free for nearly one year. Got readmitted with a new AF and was treated with intravenous amiodarone followed by cardioversion. He was referred to endocrine for new onset hyperthyroidism: TSH 0.04, FT4 34.6, noted within few days of receiving amiodarone. TFT's prior to this were normal. No evidence of thyroiditis, goitre, or thyroid eye disease. TRAb: negative. US thyroid: no nodules, normal vascularity. Pertechnetate scan: normal uptake. Commenced on carbimazole with diagnosis of AIT1 on normal thyroid, requiring 40-60mg up to week-20. Patient didn't receive steroids. FT4 levels were 50.6 (week-6), 50.8 (week-10), 38.2 (week-16), and 21.9 (week-20). Carbimazole reduced from this time. Received 602 MBq radioiodine in Jan 2023 (11-months post-diagnosis). From June 2023 developed overt hypothyroidism and is on levothyroxine.
Discussion
Points supporting AIT1: rapid onset thyrotoxicosis after amiodarone, progressive increase in FT4 despite higher carbimazole doses. AIT1 should receive carbimazole until euthyroidism, and thereafter definitive therapy with RAI or thyroidectomy. Time elapsed from initiation of amiodarone and occurrence of thyrotoxicosis is much shorter in AIT1 than AIT2. As iodine-replete thyroid of AIT is less responsive to thionamides, very high carbimazole doses for longer periods are needed before restoring euthyroidism. In iodine-replete patients on amiodarone, absent RAIU is invariably found in all. Standard US has low diagnostic value in AIT. CFDS provides a non-invasive assessment of vascularity.

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P300

Elevated thyroid stimulating hormone (TSH) and Free T4 (FT4) – what could it be?

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Mrs X (aged 79) had a history of longstanding hypothyroidism (levothyroxine 100 micrograms daily). Her Free T4 (FT4) had been slightly raised with normal TSH until in Dec 2019, where both became elevated (TSH 5.4 mU/l and FT4 29.4 pmol/l). Repeat TFT in January 2020 also showed the same. Mrs X felt well on Levothyroxine, with no thyrotoxic features. Endocrine clinic investigations (October 2020) showed no evidence of assay interference. Alternative diagnoses such as thyrotropinoma (TSHoma) or thyroid hormone resistance were considered. Mrs X was advised to stop levothyroxine in September 2021. Anterior pituitary hormones measured seven weeks later were unremarkable (FSH 69.6 IU/l, LH 33 IU/l, prolactin 498 mIU/l, negative macroprolactin, IGF 17.2 nmol/l and cortisol 672 nmol/l). Alpha subunit was raised at 19.85 IU/l. Contrast Pituitary MRI was unremarkable. Thyrotropin-releasing hormone (TRH) stimulation test showed a brisk TSH response to TRH stimulation (baseline TSH 15.8 mU/l, 30 minutes 44.9 mU/l, 60 minutes 39.4 mU/l), suggesting either hypothyroidism or thyroid hormone resistance. Mrs X felt tired and struggled to function off levothyroxine. Her TSH was 16.9 mU/l and FT4 was 34 pmol/l whilst off levothyroxine. She was restarted on levothyroxine 50 micrograms daily in December 2021. Repeat TFT 1 month later showed TSH of 4.3 mU/l, and FT4 of 57.4 mU/l. She remained clinically well with no thyrotoxic features. Nevertheless, a repeat alpha-subunit in January 2022 was 23.30 IU/l. Due to progressive weight loss, CT chest-abdomen-pelvis performed showed metastatic pancreatic cancer. She is currently receiving palliative chemotherapy from the oncology team. Whether this is coincidental to her abnormal TFTs is speculative. However, this case highlights the need to consider occult malignancy where no clear reason for new thyroid hormone resistance can be found.

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P301

Thyroid eye disease manifestation following radioactive iodine treatment in patients with Graves' disease

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Background
Thyroid eye disease (TED) is common among patients with Graves' disease (GD), with an estimated prevalence of 25-58%. While radioactive iodine (RAI) therapy is effective in managing GD, there are concerns regarding the risk of TED after RAI. Therefore, studying the effects of RAI on TED is essential for improving clinical decision-making.
Aim
To determine the incidence of the development or exacerbation of TED in patients undergoing RAI for GD in our service and to identify the risk factors that are associated with this outcome.
Method
Data from 204 GD patients treated with RAI in 2022 at the Christie were collected from the Electronic Patient Record. The follow-up period was 6-16 months. Baseline and post-RAI thyroid function, smoking status, and patients' medical background were recorded. Fisher's exact test and Student's t-test were used.
Result
Follow-up data were available for 143 patients (70.1%). Among them, 4 individuals (2.8%) developed or experienced worsening TED after RAI, with 3 having pre-existing TED. Two of these patients required immunomodulatory treatment for TED. Uncontrolled thyrotoxicosis before RAI (OR 8.3, $P=0.045$) and early fluctuations in thyroxine levels (hypothyroidism within 4-8 weeks post-RAI [OR 11.29, $P=0.012$]), were significant risk factors for TED development. Active smoking status (OR 1.87, $P=0.593$) and known TED (OR 3.23, $P=0.299$) did not demonstrate statistical significance. However, 94.1% of patients (16/17) with pre-existing TED and 67.9% (19/28) of active cigarette smokers received prophylactic steroids. Female gender, co-existing autoimmune disorders, and type 2 diabetes were not associated with an elevated risk.
Conclusion
Well-controlled thyrotoxicosis before RAI and prophylactic steroids in high-risk patients may reduce the risk of TED development post-RAI. An emphasis on regular and early (<6 weeks) clinical and biochemical follow-up after RAI may reduce this risk. Larger studies and meta-analyses are needed to further elucidate the relationship between RAI and TED.

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P382

Inevitable succession: Give them one endocrinopathy and they'll take three

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We present the case of a 58-year-old Caucasian woman with a medical history of Hashimoto's hypothyroidism who presented with several months of orthostasis, unintentional weight loss, nausea, and vomiting. Initial laboratory investigations revealed severe hyponatremia to 106 mmol/l, which prompted admission to the intensive care unit. TSH and free T4 were normal. She had orthostatic hypotension. Her outpatient medications were levothyroxine 50 mg daily and as-needed ondansetron which her integrative wellness doctor recently prescribed for nausea and vomiting. On examination, she was noted to be underweight with generalized skin hyperpigmentation, including over non-sun-exposed areas of the body such as the back, buttocks, and palmar creases. Investigations revealed autoimmune primary adrenal insufficiency as the cause of her symptoms. She was initiated on treatment with glucocorticoid and mineralocorticoid replacement therapy, with normalization of her sodium levels. Latent autoimmune diabetes mellitus was also uncovered due to significant hyperglycemia while she was receiving stress dose steroids. Assays were markedly positive for 21-hydroxylase, thyroid peroxidase, and glutamic acid decarboxylase antibodies. Due to the combination of autoimmune primary adrenal insufficiency, Hashimoto's hypothyroidism, and latent autoimmune diabetes mellitus, she was given a diagnosis of autoimmune polyglandular syndrome type 2 (APS 2). APS 2 is a rare autoimmune-mediated disease that affects a cluster of different endocrine glands. It is typically characterized by the primary presence of primary adrenocortical insufficiency associated with autoimmune thyroid disease and/or autoimmune type 1 diabetes mellitus (T1DM). Other autoimmune conditions may also be involved. It is a rare disease that may occur at any age but most commonly between 30-40 years, and women tend to be more affected than men. In about half the cases, adrenocortical insufficiency is the initial endocrine abnormality. Our patient was counseled extensively on this diagnosis and was discharged home with instructions for outpatient endocrinology follow-up.

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P383

A case of thyroid hormone resistance with hyperthyroidism

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A 33-year-old woman was seen in the Endocrinology Clinic in May 2023 due to abnormal thyroid function tests with normal TSH and persistently elevated free T4 and free T3. She had been under investigation for tiredness, palpitations, and weight gain. The differential diagnosis was TSH-secreting tumour or thyroid hormone resistance. Her bloods were sent to Basingstoke Hospital and assay interference by heterophilic antibodies was excluded. She underwent a thyroid ultrasound which revealed a mildly enlarged gland, with normal reflectivity and slightly coarse echotexture. Between her appointments, she suffered from palpitations, dizziness, and collapses. The Cardiology team organised a 24-h Ambulatory ECG monitoring which showed 42 episodes of sinus tachycardia and a transthoracic echocardiogram which was unremarkable. To manage her symptoms, propranolol 160mg MR OD was commenced.
Her thyroid functions tests were as below:

	10/01/2023	09/05/2022	06/12/2021
TSH (0.34-5.6)	1.79	1.86	1.33
FT4 (7.7-15.1)	28.5	26.6	26.6
FT3 (4.3-6.8)	9.1	8.6	8.3

She had an MRI of her pituitary with gadolinium in June 2023, revealing no pituitary lesion. She then underwent a TRH stimulation test in August 2023. Her TSH went up from 2.24 at 0 minutes to 20.59mu/l at 20 minutes post TRH stimulation. It then dropped to 11.39 mu/l 60 minutes following the TRH administration, a response

consistent with thyroid hormone resistance. In contrast, the pituitary response is blunted in the case of a TSH-oma. Genetic testing followed which revealed a causal mutation (Ala279Val) in the Thyroid Receptor Beta gene. This leads to insufficient negative feedback on the pituitary but a normal response to thyroid hormones by peripheral tissues. The patient is heterozygous and inheritance is autosomal dominant. Treatment with triiodothyroacetic acid was proposed to suppress TSH as it does not act on peripheral tissues and cannot have thyrotoxic effects. In addition, the patient will receive cardioselective Beta-blockers.

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P384

Thyroid peroxidase Antibodies (TPO), Does it change your management plan?

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This audit investigated the utilization of thyroid peroxidase antibodies testing in our trust. TPOAb, which emerges as a response to thyroid injury, is found in up to 27% of the population and is associated with autoimmune thyroid disorders. However, it is not considered a disease-causing factor or transmitted from mother to fetus. TPOAb is commonly requested in the community. The retrospective audit reviewed 282 requests from the adult service to the laboratory. After excluding 18 requests, 264 samples underwent analysis. The laboratory rejected 69 samples due to unclear indications, including 15 with known hypothyroidism on Levothyroxine, 29 with normal thyroid function test results, and 25 with Graves' disease. Among the processed 230 samples, 83 tested positive and 130 tested negative for TPOAb. Four positive results were from cardiology patients undergoing screening for Amiodarone treatment. All patients with a TSH level below 10 had negative results, and their treatment was unaffected by TPOAb. In the emergency department, eight patients were tested for thyrotoxicosis, relying on thyroid receptor antibody and uptake scan results for management. In the outpatient department, TPOAb testing was performed on thirteen patients as part of their annual screening for T1DM. From the antenatal fourteen samples were sent for patients aged 21-35. Among them, four tested positive for TPOAb, all of whom were already on Levothyroxine. Ten samples had negative results, resulting in no change in management. Out of the 213 samples from general practice, 94 showed positive thyroid receptor antibody results for subclinical hypothyroidism. Only two of these patients received Levothyroxine, with a mean TSH level of 7.5. Forty samples were from patients already on Levothyroxine treatment, and all had negative results, with a mean TSH level of 8. Overall, the audit did not find any change in patient management based on TPOAb results. Most patients are treated independently regardless of TPOAb

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P385

Link between thyroidectomy and the development of osteoporosis in a south american population

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Introduction
Patients undergoing thyroidectomy could be subject to osteoporosis, therefore, we evaluated the potential for fractures among 123 men and 134 controls from a South American hospital between 1999-2018.
Materials and methods
The influence of thyroidectomy on the incidence of fractures was evaluated using basic methods of analysis. In the primary analysis, the frequency of fractures in the operated cases was directly compared with that of the controls. The proportion of cases and controls with fractures prior to the index date was compared using the McNemar test.
Results
With 2,204 person-years of follow-up in each group, survival free of any fracture of the vertebra, proximal humerus, distal forearm, pelvis, or proximal femur was similar in the two groups ($P=0.31$), and the relative risk of any of these fractures for thyroidectomized patients vs their controls increased by 1.8-fold (95% CI, 0.5–2.9).
Conclusion
The difference is fully explained by a statistically significant excess of proximal femoral fractures in men with thyroidectomy. Risk factors included older age at surgery and greater extent of surgery. It is pertinent to carry out this type of study in Latin American populations given the scarcity of literature in this regard.
DECS/MESH: Surgery, thyroid, osteoporosis.

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P386

Hypothyroidism and transient adrenal insufficiency after nivolumab treatment in a renal cell carcinoma woman

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Introduction
Immune checkpoint inhibitors (ICIs) have gained popularity as a standard cancer treatment in recent years. IrAEs, or immune-related adverse events, are specific immunological side effects that are linked to ICIs. Thyroid dysfunction is a prevalent irAE, but the cause, severity, and clinical appearance might vary. The most frequent thyroid irAEs brought on by ICIs are destructive thyroiditis and hypothyroidism, whereas immune-related adrenal insufficiency is uncommon. We describe a case of hypothyroidism and transient adrenal insufficiency after nivolumab treatment in a renal cell carcinoma woman.
Case Presentation
A 54-year-old woman developed overt autoimmune hypothyroidism 5 months after she had started nivolumab (anti-PD-1) therapy for a metastatic renal cell carcinoma. The only complaint she had was extreme fatigue. Her TPO and Tg autoantibodies were positive, TSH and ACTH were high, and Ft4 and cortisol levels were low. For the evaluation of other pituitary hormones were assessed: FSH, LH, and prolactin. The patient was given hydrocortisone right away, followed by L-thyroxine and selenium a week later.
Conclusions
Autoimmune hypothyroidism and adrenal insufficiency can be induced by anti-PD-1 treatment. An elevated level of clinical suspicion is required for the diagnosis of endocrinopathies due to an upward trend in endocrine disorders among cancer patients receiving immunotherapy. Early management of ICIs-induced endocrinopathies improves the quality of cancer care.

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P387

Rapid levothyroxine absorption test to diagnose ft4 pseudomalabsorption

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Young man with high BMI and known iatrogenic hypothyroidism, post radioactive iodine (RAI) treatment (2015) for Graves' thyrotoxicosis (2011) was referred to endocrinology due to significantly raised TSH (at 50 mu/l) and low FT4 (5.0 pmol/l). He was actually admitted with progressive nausea, vomiting over last three weeks. He also complained of abnormal stool consistency (like semi-solid) intermittently. His past medical history also includes gastric bypass with gastro-jejunal anastomosis in 2015, depression and OSA. He mentioned that, since he had surgery he normally has vomit, at-least one episode every month. He was taking tab levothyroxine 200 mg daily on empty stomach and honestly mentioned he could miss the tab levothyroxine at-least twice a month. Before surgery his TSH was stable and within range but post-surgery it was fluctuating. He complained of feeling more tired and lethargic for more than 6 months. He did not have goitre and pulse rate was normal. We did a modified rapid levothyroxine absorption test while he was inpatient by giving stat dose of 1000 mg oral levothyroxine and the result (mentioned below) suggested that he was absorbing the medication well (rise in FT4 almost four times from baseline). I discussed the option of weekly and daily regimen for levothyroxine and patient opted for weekly once tab 1000 mcg.

	Baseline	1 h	2 h	4 h	8 h
TSH mU/l	50.1	48	46.8	44.5	43.6
FT4 pmol/l	5.0	12	18	18	15
FT3 pmol/l		2.7	3.0	3.0	3.0

Conclusion
A supervised rapid levothyroxine absorption test can assist in diagnosis of pseudo-malabsorption and safe time and resources. A rise in FT4 of 2.5 times or more can convincingly rule out any malabsorption disorders.

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P388

Cost effectiveness of Inpatient thyroid function test- a snap shot from Great Western Hospital, SwindonTarek Abdellatif, Auditi Naziat

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Background
In our Hospital, we have noticed a large number of thyroid profile are being requested without any clinical suspicion, which has led to difficulty in interpretation of the results, dilemmas in subsequent management and an increment of inpatient Endocrine referrals.
Objective and Aim
To evaluate our local practice in ordering thyroid function tests and to identify strategies to reduce unnecessary testing and inappropriate referral to endocrine department.
Methods
retrospective analysis; sample identified from inpatient endocrine referral list; 1st November 2020 - January 2021.
Summary
A total of 32 thyroid related inpatient referrals were received during this period. 19.35% known hypothyroid, 6.45% overt hyperthyroidism, 22.5% subclinical hyperthyroidism, 13% amiodarone induced thyroid dysfunction; 3.22% pregnancy related thyroid illness; and 25.8% had TFTs done during acute illness. Following Endocrine review 79% did not need any intervention. We have proposed a variety of interventions - removing the TFT request from routine blood test bundle; populating guidelines during doctors' induction; e-learning decision aids for TFT request. We aim to repeat the study in 6 months to assess the improvement in our service.
Conclusion
In our lab the monthly expenditure for TFT is £ 8875. The low detection rate of new thyroid disease suggests that unselective screening of all admissions is not justified. However, the morbidity of untreated thyroid disease suggests that biochemical screening of TFTs in a selective group of medical inpatients patients may be justified. TFTs should be offered to only targeted group of patients with clinical symptoms or risk factors.
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P389

Thyroid associated ophthalmopathy due to radioactive iodine therapy in patient with right thyroid toxic adenoma

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Thyroid-associated ophthalmopathy (TAO) is an inflammation of the extraocular muscles and periorbital connective tissue caused by autoantibodies against common antigens to both the thyroid and orbit. The release of antigens and induction of hypothyroidism caused by radioactive iodine (RAI) therapy may cause or exacerbate TAO. Radioactive iodine therapy has been associated with worsening TAO, particularly in smokers. A 57 years old female treated with radioactive iodine therapy (RIA) for right toxic thyroid adenoma who presented with symptoms of puffiness around the eyes, protrusion of both eyes, conjunctival oedema, ophthalmoplegia, double visions, and pain in the both eyes 12 months after RAI. Clinical assessment did confirm a feature of TAO, and clinical activity score was 5 out of 7. MRI Scan of the orbit shown a feature of TAO in both eyes. TSH is 0.3 miu/l, FT4 20 pmol/l, Thyroid stimulating antibodies were high at 64.7 (NR 1-1.8 U/l) and before RAI it was negative. She has no symptoms or clinically features of TAO before went for RAI therapy. She develops hypothyroidism 4 months following radioactive iodine therapy, and thyroid function test is stable in levothyroxine treatment for the last a few months with TSH 0.4 before she develops symptoms of TAO. No other risk health issues and she is non-smoker. She had treatment with intravenous methyl prednisolone infusion to control her symptoms and she had a response to the steroid therapy and she is a under regular review in our endocrine clinic.
Conclusion
Our case report highlights the importance of thinking out of the possible developing TAO in non-autoimmune hyperthyroidism and to our knowledge this is unusual association of TAO in patient with nodular thyroid disease treated with RAI.

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P390

Radioiodine and Graves Orbitopathy (GO): lessons learned from an internal audit of 101 patients

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Graves' orbitopathy (GO) development or reactivation is a well-recognised complication of radioactive iodine (RAI), with possible lower incidence in a recent series. We performed a retrospective audit of Graves' disease patients treated with RAI at our centre over a 5-year period. We recorded the GO incidence after RAI treatment, risk factors present, and steroid prophylaxis use. Data collected: smoking status, thyroid-stimulating hormone receptor antibody (TRAb), GO history, Graves' disease duration, eye features pre- and post-treatment, prophylactic corticosteroids, RAI dose given, post-RAI thyroid status, duration until hypothyroid. 101 patients were included, with median Graves' disease duration 36 months. 34/101 (33.7%) were active/ex-smokers, 86/101 (85.1%) were documented TRAb-positive, 11/101 (10.9%) had a GO history; 32 (31.7%) had eye features present. Median RAI dose given was 596MBq. 8/101 (7.9%) patients received prophylactic corticosteroid. 89/101 (88.1%) achieved hypothyroid state in the year after RAI. GO developed in 5/101 (5.0%), of which 4/5 (80%) were de novo in high-risk individuals who did not receive steroids. One was a GO reactivation despite steroids. Two required intravenous steroids with/without orbital radiotherapy, one completed oral steroid taper, the remainder were treated conservatively. Our cohort had a lower GO incidence than historically reported in the literature, but a higher proportion arising de novo. Risk factors identified for de novo thyroid eye disease were very high TRAb levels and short duration from diagnosis to RAI. Changes implemented as a result of this audit include establishment of a Joint Thyroid-Eye clinic to facilitate collaboration between clinicians and appropriate patient selection for RAI referral, ensuring baseline eye assessments are carried out with specialist Ophthalmology input, risk factors are documented/modified where possible, and a holistic approach is taken towards the decision for steroid prophylaxis. Our consent form and patient leaflets have been updated to ensure future patients are well-informed.

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P391

Alemtuzumab-induced Graves' disease management in pregnancy

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Alemtuzumab is a monoclonal antibody used in the treatment of relapsing-remitting multiple sclerosis (RRMS). Thyroid dysfunction is a common side effect. Alemtuzumab induced Graves' disease (AIGD) is notable for its fluctuating and unpredictable course. We present the case of two women with RRMS who required total thyroidectomy to manage AIGD and were followed up in our antenatal endocrine clinic during their pregnancy. The first patient is a 31-year-old lady who developed AIGD one year after initiation of alemtuzumab. Her thyrotoxicosis remained difficult to control on high dose carbimazole and she underwent total thyroidectomy 18 months after the initial diagnosis. She presented to our antenatal endocrine clinic 3 years later. Her thyroid function tests (TFTs), as well as her thyroid stimulating hormone receptor antibodies

(TRABs), were monitored throughout her pregnancy. The latter remained positive 4 years after her initial diagnosis and 5 years after her last alemtuzumab course, therefore, an ultrasound to look for foetal goitre was arranged in her 3rd trimester and the baby was monitored for signs of thyrotoxicosis post-delivery. Our second patient is a 40-year-old lady who developed AIGD three years after initiation of alemtuzumab. She had a history of several miscarriages and was actively seeking conception. In view of her age, total thyroidectomy was recommended in preparation for pregnancy. She was treated with a block and replace regimen whilst surgery was awaited. She underwent total thyroidectomy 3 months after her initial presentation and is now in her 2nd trimester of pregnancy, with TFTs being monitored every trimester. Total thyroidectomy should be considered in women of reproductive age with AIGD, especially if their hyperthyroidism is difficult to control or there are immediate plans for conception. TRABs should be monitored during pregnancy in these patients, as they can remain positive several years after alemtuzumab is stopped.

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P392

A rare but important side effect of anti-thyroid medication: propylthiouracil-induced vasculitis

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Background
We present a 47-year-old female, who is known to have recurrent Graves' disease, developed vasculitic skin lesions upon treatment with propylthiouracil (PTU).
Case details
She was diagnosed with Graves' disease in 2020 and was started on propylthiouracil as she could not tolerate carbimazole. Propylthiouracil was stopped after 18 months. Her thyrotoxicosis recurred after 6 months. Two months after propylthiouracil was restarted, she developed a new onset rash on her face followed by necrotic skin lesions on the back of her legs and her back. The rash was not worsened with sun light exposure. She did not recall any intercurrent illness or use of any other new medication. The clinical examination was unremarkable apart from fever and the skin lesions. There was no evidence of mucosal involvement. Her blood tests revealed positive anti-neutrophil cytoplasm (ANCA) antibodies: ANCA Myeloperoxidase (MPO) Antibodies * 3.8 kU/l (0 - 3.4), ANCA Serine Proteinase 3 (PR3) Antibodies *21.0 kU/l (0 - 1.9) while ANA and ENA antibodies were negative. Her computed tomography (CT) of chest, abdomen and pelvis was unremarkable apart from axillary lymph adenopathy. Her blood cultures showed no growth. A diagnosis of propylthiouracil-induced vasculitis was made by dermatologists. Propylthiouracil was discontinued and she was offered definitive treatment with either radioiodine or surgery. She was systemically well and her skin lesions showed signs of healing after drug withdrawal.
Conclusion
This case highlighted a rare though serious adverse effect of commonly prescribed antithyroid medications. Although one should exclude idiopathic vasculitis and vasculitis mimics in the first instance, propylthiouracil-induced vasculitis remains a possibility. Most patients respond to drug withdrawal or sometimes to immunosuppressants. Several studies reported the prevalence of PTU- induced vasculitis from 20% to 64%. Most patients have raised MPO-ANCA level while a small number have PR3-ANCA.

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P393

Challenging graves disease (GD) case

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GD is a common thyroid disorder which in majority of cases respond to medical treatment with thionamides.A proportion of these patients will need definitive treatment with either radioiodine ablation or total thyroidectomy. We present a case of a 21 yr old woman with a year history of overt thyrotoxic symptoms. She lost 2 stones of weight, had palpitations, heat intolerance and noticed shaky hands. On examination:She had large symmetrical goitre with bruit, tachycardic and sweaty. There were no features of thyroid eye disease. Lab investigations:TSH: > 0.01, fT4: > 100, TRabs:550(reference range < 0.9) The patient was started on Carbimazole and propranolol with up titration of the dose, but she failed to improve both clinically and biochemically. Medication script frequency & reported concordance with treatment were assessed at this & each subsequent step. High dose corticosteroids were added to the regime. Despite that, there was no improvement. Cholestyramine was started in addition. A decision was made that the patient should go for total thyroidectomy as very resistant to medical therapy. The high positive titre of antibodies pointed to difficult and relapsing pattern of disease. The problem was the severe thyrotoxic state she was in which made it very difficult for anaesthetics and surgeons. In fact, she had surgery cancelled twice because of concern about precipitating thyrotoxic storm. The patient was started on Lithium in addition to the other medications. With close monitoring and achievement of therapeutic levels we managed to control her T4 and T3 levels to prepare for surgery. She had total thyroidectomy complicated with hypocalcaemia (hypoparathyoiroidism)which is under control now. Learning points: -Very high positive antibodies titre can predict the difficulty in controlling GD -While non-concordance with treatment is a common issue very resistant disease is also an explanation for poor clinical responses. -Using multiple concurrent agents, as described, including Lithium is uncommon in practice but may be required in resistant cases. -Early consideration of definitive treatment should be considered.

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P394

Use of TRAB values to predict the need for second dose of Radio-iodine therapy (RAIT)

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Background and Aim
RAIT is successful in achieving cure of thyrotoxicosis. However, 10-15% patients require further doses, usually administered at 4-6 months after the initial dose. We assessed the role of TRAB values in predicting the need for redosing, which could have useful implications.
Patients and Methods
We measured TRAB at diagnosis and at the time of 550MBq RAIT in 54 patients with Graves' disease. We recorded demographic data and thyroid status at 6, 12, 24 weeks post-RAI, during which antithyroid agents were started as required. Thyroid status at 6 months was correlated to FT3, FT4 and TRAB values.
Results
71% women, mean age 48 years. 9 (16%) patients were not cured by 6 months. Median (IQR) TRAB at diagnosis and at the time of RAIT were lower in patients cured by RAI compared to patients not cured [3.4 (1.4–9.0) IU/l vs 19.0 (10.6-40.0) IU/l, $P=0.001$ and 3.3 (1.4–7.5) IU/l vs 7.8 (3.5–29.5) IU/l, $P=0.032$ respectively]. Similarly, T4 and T3 at the time of diagnosis were lower in patients cured by RAI compared to patients not cured [21.7 (17.0–32.2) vs 40.5 (25.1–50.9) pmol/l, $P=0.016$ and 9.1 (6.0 – 16.6) vs 37.1 (19.7–46.1) pmol/l, $P=0.003$, respectively]. Median TRAB, T4 and T3 at diagnosis and pre-RAI TRAb were 5.6, 2.4, 1.9 and 4.1-fold higher, respectively, in patients not cured by RAI compared to patients cured by RAI. TRAB at diagnosis had the maximum area under the ROC curve to identify patients not cured post-RAI.
Conclusions
Initial TRAB measurement at diagnosis of Graves' thyrotoxicosis and prior to 550MBq RAIT dose can help to identify patients likely to require further RAI doses. Addition of these predictors to the currently established ones can have useful clinical implications.

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P395

Assessing outcomes in graves' thyrotoxicosis and predictors of relapse ten years after thionamide withdrawal

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Purpose
To establish the risk and time course of recurrent thyrotoxicosis following withdrawal of anti-thyroid drugs (ATD) and risk factors for recurrence.
Methods
An observational study in people with a first episode of Graves' thyrotoxicosis who completed a course of ATD ($n=290$). Recurrence of thyrotoxicosis was

assessed over a ten-year period and factors associated with recurrence were identified.
Results
Recurrent thyrotoxicosis occurred in 54% of individuals over a ten-year period, with 73% of recurrence occurring within 2 years. Younger age at diagnosis (41 years [33 – 51] vs. 47 [39 – 56], $P=$ 0.011), higher TSH receptor antibody (TRAb) at diagnosis {8.8 IU/l [4.9 – 17.2] vs. 6.0 [4.1 – 9.9], $P=$ 0.002), higher TRAb at cessation of ATD (1.3 [$<$0.9 – 2.3] vs. 1.0 [$<$0.9 – 1.3], $P<$ 0.001), longer time to normalisation of TSH (6 months [3 – 9] vs. 4 [2 – 7], P 0.013) and longer time to normalisation of fT4 (2 months [1 – 3] vs. 1 [1 – 2], $P=$ 0.001) were all associated with relapse within 10 years. Recurrence within 10 years occurred in 74% of individuals with TRAb $>$12 IU/l at diagnosis but only 44% of those with TRAb $<$5 IU/l at diagnosis ($P=$ 0.001). TRAb (at diagnosis and cessation) and age were independently associated with relapse in multivariate analysis.
Conclusions
Most recurrent thyrotoxicosis occurs within the first few years after ATD withdrawal. TRAb concentration, both at diagnosis and cessation of ATD, is a clinically useful predictor of recurrence risk and can be used to inform decisions on the optimal approach to primary therapy.

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P396

Rhabdomyolysis associated with severe hypothyroidism

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Patients with clinical hypothyroidism often complain of muscular symptoms i.e., cramps, weakness and fatigue. However, rhabdomyolysis triggered by severe hypothyroidism is rarely reported. In most cases, external triggers (use of statins or excessive exercise) can be easily identified and modified. In absence of beforementioned triggers, it is prudent to look for other causes of rhabdomyolysis. On the forefront, it would be crucial to exclude myocardial ischaemia, followed by inflammatory myopathies, use of illicit drugs, electrolyte abnormalities, seizure, trauma, and finally hypothyroidism. We report a case of 40-year man, an avid gym enthusiast, who presented to GP Assessment Unit at the Leicester Royal Infirmary with tiredness and myalgia. His blood work showed acute kidney injury stage 2 with creatinine kinase readings of 14599 IU/l. It was assumed rhabdomyolysis was related to strenuous exercise as patient was known to exercise daily. He was commenced on intravenous fluids and admitted onto an acute medical unit. His ECG showed normal sinus rhythm with no evidence of ischaemia. Upon further questioning, it became apparent that patient has stopped going to the gym 6 weeks prior due excessive tiredness and proximal muscle weakness. Further labs were ordered which revealed TSH $>$150 mIU/l, with free thyroxine (T4) of 2.6 mIU/l, and thyroid peroxidase antibody of 455 mIU/l. Subsequently, patient was commenced on 75 mg of levothyroxine along with intravenous fluids for the duration of 48 h. On 3 monthly follow up, labs showed TSH of 0.24 mIU/l, free thyroxine (T4) of 25.4mIU/l and creatinine kinase of 230IU/l. In addition, patient reported near complete resolution of myalgia and proximal weakness. This case illustrates the importance of screening for hypothyroidism in patients with rhabdomyolysis and no other plausible etiologies.

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P397

Is it euthyroid sick syndrome or central hypothyroidism?

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73-year-old gentleman presented to AEC with 3-week history of shortness of breath, cough with sputum production, generalised weakness and loss of appetite. He was found to have iron deficiency anaemia and hyponatraemia (120mmol/l). He had history of type2 diabetes, and hypertension. On workup for hyponatremia, both free T3 and free T4 are reduced with suppressed TSH 0.01 uIU/ml. TSH receptor antibody was negative. He was started on levothyroxine 50mg on suspicion of secondary hypothyroidism. On further workup, CT imagings and biopsy confirmed Diffuse Large B Cell Lymphoma (non-germinal centre type). MRI(pituitary) demonstrated normal pituitary gland with no evidence of altered enhancement confirming no lymphoma infiltration. Pituitary biochemical profile showed normal ACTH, IGF and prolactin levels with low free testosterone and high LH and FSH, suggesting primary hypogonadism, likely age-related. Given the above pituitary profile and MRI(pituitary) findings, he was clinically diagnosed as severe euthyroid sick syndrome. There are many proposed mechanisms regarding the pathogenesis of euthyroid sick syndrome. One cause suggested is that presence of thyroid-binding hormone inhibitors in the serum and different body tissues inhibits the binding of the thyroid hormone to the thyroid-binding protein. The euthyroid sick syndrome is also caused by cytokines such as interleukin 1, interleukin 6, tumour necrosis factor-alpha, and interferon-beta affecting the hypothalamus and pituitary glands, thus inhibiting TSH, thyroid-releasing hormone (TRH), thyroglobulin (TG), T3, and the thyroid-binding globulins (TBG) production. Cytokines were also thought to reduce the activity of type 1 deiodinase and decrease the binding capacity of the T3 nuclear receptors. Another mechanism suggested that expression of thyroid hormone receptors(THRs) and their coactivators are diminished in acute illness.
Conclusion
Biochemical pictures of severe sick euthyroid syndrome can resemble secondary hypothyroidism. Differentiating features would be associated severe non-thyroidal illness and raised cortisol.

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P398

Unexpected testosterone results in a man complaining of low libido

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A 50-year-old half Jamaican gentleman was referred urgently to the endocrinology clinic with thyrotoxicosis. He had lost 2 stone in weight over a 2 month period and was complaining of lethargy, low libido and loose stools. His bloods showed a fT4 $>$100 pmol/l, fT3 32.7 pmol/l, and TSH $<$0.02mU/l. Subsequently his TSH-R Ab returned elevated at 5.5IU/l ($<$2.9IU/l), confirming a diagnosis of Graves' disease. His GP also checked his testosterone level on the initial bloods due to low libido. He was found to have an elevated total testosterone level of $>$50nmol/l (NR 8.6-29nmol/l) and an SHBG of $>$200nmol/l (NR 20-75nmol/l). He responded rapidly to carbimazole treatment and was treated using a dose-titration regime. Repeat testing of his testosterone level, once he was euthyroid, showed complete normalisation of his SHBG (58nmol/l) and consequently his total testosterone level (9.7nmol/l). This case highlights the link between hyperthyroidism and testosterone levels. Hyperthyroidism is thought to lead to an elevation in total testosterone in males due to an increase in hepatic synthesis of SHBG. SHBG also decreases the metabolic clearance rate of testosterone which contributes to the increase in serum total testosterone levels observed in hyperthyroid men. In most cases, normalisation of the sex hormones occurs once euthyroidism is achieved. This case serves as a reminder to always check thyroid function if faced with unusual sex hormone results in men.

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Author Index

Abali, Zehra Yavas P16
Abbara, Ali OC4.3, OC4.4, P116, P267
Abbas, Afroze P186, P6, P9
Abdalaziz, Mohamed P77
Abdalraheem, Ali **P270**
Abdalrazag, Osman P226
Abdel-Aziz, Tarek OC5.3, P125, P188, P276
Abdel-Wahab, Yasser HA P354
Abdelgadir Musa, Abdelmajid **P106**
Abdelgawwad, Amira OC6.1
Abdella, Osama **CC9**
ABDELLATIF, TAREK **P314**
Abdellatif, Tarek **P388**
Abdelrahman, Hiba **P311**
Abdi, Lida OC4.1, OC5.1
Abdi-Aziz, Nabila OC3.6
Abdulkareem, Mustafa **P136**
Abdullah, Mohamed P15
Abdulrahim, Emad P330
Abedo, Itopa P373
Abha, Abha **OP2.3**, P212
Abouglila, Kamal P115, P20, P269, P387, **P389**
Abraham, Anu **P215**
Abraham, Dr Prakas P135
Abraham, Elizabeth P113
Abraham, Prakash OC3.2, P153, P163
Abrahamsen, Bo EC1.3
Acuñþa Hernandez, Marylin **P359**
Adaikalakoteswari, Antonysunil OP2.3, P212
Adam, Safwaan CC5, P171, P199, P301, **P302**, P93
Adams, Holly R. P66
Adapa, Shashank **P60**
Adcock, Holly V. P66
Adetunji, Tajudin P124
Adewale, Folaranmi P69
Adeyemi, Taiwo P124
Adiat, Mojeed P348
Adolf, Christian OC5.1
Aftab, Faseeha P209, P216, P71
Agan, Shalom **P235**
Agbana, Stephanie **OC2.5**, S3.2
Aggrawal, Naveen P384
Agha, Amar P369
Agha-Jaffar, Rochan OC7.5, P296
Agravatt, Ashishkumar P324
Agwuegbo, Uche OC4.6
Ahamed Sadiq, Dr Shafana **P325**
Ahluwalia, Rupa OC3.2, P118, P27, P45, P94
Ahmed, Aftab P140
Ahmed, Ammar OP4.4
Ahmed, Hashim OC2.4
Ahmed, Khaled **P10**
Ahmed, Mohammed P369
Ahmed, Nabeel P215, P244, **P40**
Ahmed, S Faisal P261, **ENS1.3**, OP3.1
Ahmed, Shadman P162, P7
Ahmed, Sufia **P198**
Ahmed, Syed Faisal P12, P16, P161
Ahsan, Masato OC3.2, **P102**, **P23**, **P263**, **P374**
Ahuja, Chirag K OC3.1, P82
Aithal, Guruprasad P53
Akalestou, Elina **OC6.1**, **P207**, P344
Akbar, Shahzad OC3.5, OP1.3, P233, P253, **P303**, P348
Akhtar, Hassan **OC1.6**
Akker, Scott P175, P46
Al Busaidi, Ayisha P366
Al Disi, Sara **OC5.6**
Al Jumaah, Ali **OC7.6**, **P120**, **P173**
Al Wattar, Bassel H P117
Al-Aghbari, Maram NM P295
Al-Hayali, Mohammed CC5
Al-Mrabeh, Ahmad **P352**
Al-Qaysi, Amina **P197**
Al-Salihi, Ahmed **OP5.3**
Al-Salihi, Omar P366
Al-Sarraj, Safa P366
Al-Sayed, Yasmin **P358**
Al-Sharefi, Ahmed P107
Alam, Ali P227
Alansari, Mustafa P245
Alawami, Fatimah **P258**
Alazawi, William P53
Albanese, Assunte P125
ALEEM, ALLI P341
Alexander, Emma OC4.4
Alexander, Louise OP4.4
Alexandrescu, Daniela P87
Alexiadou, Kleopatra P243
Alfiky, Mohamed P297
Ali, Anyat P226, P74
Ali, Asif P203, P44
Ali, Hisham P248
Ali, Hisham Elhag P39
Ali, Mudassir **P361**, **P387**
Ali, Sadaf **P54**
Ali, Salma R P16, P161
Ali, Sarah N P377
Ali, Syed **P298**
AlKhyeli, Fatima P101
Allcock, Rebecca CC5
Allessi, Dario OC2.5
Alli, Aleem P347
Allsopp, Rebecca OC7.6
Almarzouqi, Abdulla P101
Alshamsi, Shamma **P105**, **P75**
Alsters, Suzanne P201
Altayeb, Abdalaziz P115
Altieri, Barbara OC2.3
Alvergne, Alexandra OP3.2
Alvi, Syed Faraz Danish **P272**, **P273**
Amar, Laurence OC5.1
Amin, Anjali P105
Amin, Nadia P16
Amiyangoda, C G K OP3.1, **P271**
Amjad, Wajiha P118, **P122**, **P307**
Amodu, Bosede **P124**, P69
Amr, Nermine H P16
Anand, Viswesh **P250**
Anandappa, Samanth P338
Anandhakrishnan, Ananthi **P227**
Anderson, Cameron OC5.3
Anderson, Jennifer P364
Andreou, Persefoni P214
Andrew, Ruth OC5.6, P316, P360
Anjum, Suzana **P46**
Ansari, Prawej **P354**
Anthony, Amarah V. OC4.1
Antonescu, Costin RET2.1
Anujan, Priyanka **P264**
Anumah, Felicia P132
Appenzeller, Silke CC1
Arabi, Noon **P334**
Arampatzi, Panagiota OC2.3
Areloegbe, Stephanie **P109**, **P220**, P235
Areloegbe, Stephanie E. P217, P260
Arlt, Wiebke CC1, OC4.1, OC5.1, P1, P162, P7
Armaforte, Emanuele P139
Armeni, Eleni OC2.2, P121, P165, P189, P308, P377, P43
Armonis, Panagiotis P312
Armstrong, Nicola **NS2.1**
Arooj, Aneela P128
Arshad, Amynta **P268**
Arshad, Muhammad Fahad **P160**, P177, **P89**
Arstad, Erik **OC5.3**
Artham, Dr Satish CC3
Ascione, Raimondo OC5.6
Asha, Hesarghatta P166
Asha, Hesarghatta Shyamasunder **P237**

Asia, Miriam P155, P162, P268, P7
Aslam, Aisha **P36**
Aspray, Terence OP6.1
Atapattu, Navoda P16, P161
Athar, Syed P101
Atherton, Dr Philip CC3
Aung, Ei Thuzar **P14**
Aung, Nwe **CC2**
Austin, Argentieri OP3.2
Avari, Parizad P243
Avery, Amanda P67
Awadelkareem, Abuzar OP6.4, P335
Awais, Ramla OC5.3
Aye, Mo P185, P303
Aylwin, Simon P366
Ayuk, John OC3.2
Azeez, Taoreed P124
Azharuddin, Mohammed P311
Aziz, Tarek Abdel P126

Baachaa, Zuro P42
Bachega, Tania P16, P161
Baciu, Ionela P84
Baculescu, Nicoleta P84
Bagamasbad, Pia P202
Bahl, Suhani **P336**, **P362**
Bahowairath, Fatima **P147**, **P30**
Baig, Fraz Ahmed **P39**
Bailey, Maira **P64**
Bain, Joshua **P5**
Bakke Hansen, Benjamin **EC1.3**
Balafshan, Tala P14
Baldeweg, Stephanie P188, P288
Baldeweg, Stephanie E. OC3.2
Ball, Mia **P168**
Ballav, Chitrabhanu CC2
Ballout, Safia OP1.2
Balmuri, Laxmi ManoharRao P36
Banerjee, Ritwik P182, P270
Banga, Davina OC2.6
Banka, Siddharth OP5.3
Bano, Gul **P201**
Bantounou, Maria Anna P90
Barazi, Sinan P366
Barbu, Carmen Gabriela P86
Barker, Guy P219
Barnes, Kayley P139
Baroncini, Marc P371
Baronio, Federico P16, P161
Barrowcliffe, Mary P120, P172, P173
Barry, Sayka **P80**, OC3.1
Bartelt, Alexander **S2.1**
Barwell, Julian P120
Basavaraju, Navya P136
Bashir, Al-Amin P235
Bassett, John P78
Bassett, Paul OC4.3
Basu, Ambar P144
Batavanis, Michael **P225**
Bates, Suzanne P8
Batten, Lucy **P185**
Bawden, David **P10**
Baynes, Kevin P343
Beale, Tim P125
Beall, Craig P59
Beards, Sue CC5
Bech, Paul OC4.4
Beck, Katharina J OP3.1
Beck, Katharina J Beck P110
Beckett, Samuel P251
Begalli, Federica OC3.1, P363
Behan, Lucy Ann P258, P351
Behary, Preeshila CC4, P322
Behjati, Sam EC1.4
Bellingham, Michelle OP3.4
Belston, Lleyton P230
Benny, Archana **P77**
Berg, Jonathan P198
Berkeley, Rhiannon P104, P13
Berry, Simon **OP5.1**, **P8**
Bertherat, Jerome OC5.1
Bertsch, Thomas P111
Beuschlein, Felix OC5.1
Bevan, Charlotte OC2.4, P319
Bezbradica Mirkovic, Jelena P221
Bezuidenhout, Louise P316
Bhagi, Ridhi P99
Bhagi, Ridhi P292
Bhardwaj, Neil P173
Bhargava, Raghav P127
Bhasin, Shalender OC4.3
Bhatia, Kunwar OC7.5
Bhattach, Supriyo P65
Bhattacharya, Beas P238, P313
Bhattacharyya, Shiuli **P117**
Bhatti, Sumbal OC3.2
Bianco, Antonio **PL1.1**
Biehl, Michael OC4.1, OC5.1
Bijani, soroush **P379**
Birch, Lara **OC5.5**
Birchenough, Amy P215
Birkebaek, Niels H P16, P161
Birney, Susie P70
Bishop, David P21
Bishop, Dr David CC3
Blanco, Edgar P323, **P342**, P376, P385
Bleach, Rachel OC2.5, S3.2
Bloomfield, Laura P127
Blower, Philip OC2.1, OC7.1
Boam, Alicia P99
Boardman, Felicity P208
Bodi, Istvan P366
Boelaert, Kristien OC2.1, **S5.3**
Boharoon, Hessa **P101**
Bonanos, Efstathios OC3.2
Bonewald, Lynda **S1.1**
Bonfig, Walter P16, P161
Boot, Dr Chris P234
Bouloux, Pierre P189
Bousfield, George OC4.6, OP3.3
Bouvier-Ellis, Catherine P49
Boyer, Pierre Nicolas OC1.5
Bozkurt, Emir S3.2
Bradley, Karin OC3.2
Bradley, Mark **ENS5.3**, **NS3.2**
Brady, Angela OP4.1
Brain, Caroline OP7.1, P125, P126, P276
Breen, Louise OP7.2, **P154**, P155, **P4**
Bremner, Emma P102, P120, P172, P173
Brempou, Dimitria OP1.1
Brennan, Caroline H. OC3.6
Brett, Ryan P214, **P59**
Brindle, Rachel P41
Brisnovali, Niki OC6.1
Brooke, Antonia **ESD1.1**, OC3.2
Brookes, Katie OC2.1, OC2.6, **OC7.1**
Brotherton, Sophie P244, P40
Broughton Venner, Jacob P213, **P52**
Brown, Alastair P62
Brown, Alastair JH P213
Brown, Janet **S3.1**
Brown, Morris OC5.3
Brucker, Cosima P111
Bruno, Vito Domenico OC5.6
Bryce, Jillian OP3.1, P16, P161, P261
Buch, Harit N P394
Buhidma, Yazead OC5.3
Bujanova, Jana P367
Bujawansa, Sumudu P14
Burcea, Iulia P84
Burke, Kevin P369
Burn, Florence **P297**
Burns, Angela D. OC4.3
Busch, Sophia **P32**
Butler, Colin P125, P126, P276
Butler, Eve **P281**
Butt, Saad **P226**, **P74**
Butterly, Elaine W **P138**
Byrne, Bernadette OC3.3

C. Shekar, Nitin **OP6.4**, **P335**
Calanchini, Matilde P110, **P265**
Calebiro, Davide P157
Calvo Latorre, Julia **P391**
Campbell, John OC4.3

Campbell, Michael **P296**
Capatina, Cristina P84, **P87**
Caplin, Martyn OC2.2
Carey, Dr Peter CC3
Caro Uribe, Patricia P359
Carroll, Paul OP7.2, P312, P337
Carroll, Paul V OP7.1
Carroll-Moriarty, Leigh P238
Carswell, Alexander **OC1.1**
Casanova Libreros, Rosangela P359
Casey, Ruth P51
Cassidy, Ben OC1.3, **P210**
Cassidy, Samantha P3
Catteau-Jonard, Sophie P371
Cattini, Peter A. **P218**
Caughlin, Cori OP8.3
Cavalcante-Silva, Jacqueline JA2
Ceccato, Filippo OC5.1
Chabrier, Gwladys OP2.1
Chachlaki, Konstantina OC4.4, P371
Chacko, Ari P237
Chan, Carmen **P71**
Chan, Denise P309
Chan, Li CC1, OC5.2, OP5.2, OP5.3, P15
Chan, Sigmund **P229**
Chandramohan, Anuradha P166
Chang, Ruby OC7.3
Chang, Wehan P204
Chaudhury, Nadia **OP8.2**
Chauhan, Rajveer P330
Chauhan, Rakhee OP7.1
Chen, Keran P65
Chen, Lilian CC5
Chen, Lillian Ruiheng **P199**
Chen, Xianjiang P139
Cheng, Leslie **P381**
Cheow, Heok P85
Cheow, Heok K OP8.1
Cherian, Anish P166
Cherian, Kripa P166
Cherian, Kripa Elizabeth P237
Cheung, Jason P215
Chhabra, Rajesh OC3.1, P82
Chikthimmah, Vineeth P194
Child, Louisa **P240**
Chinnappa, Shanmugakumar P226
Chipchase, Allison OP6.2, P118, **P129**, P27, P45
Chirila-Berbentea, Veronica **P238**, **P313**
Chizooma, Eugine P197
Chohan, Dr Muhammad Tahir **CC3**, **P234**
Chohan, Muhammad P123
Choo, Alwyn Yung Zhuang **P45**
Choudhury, Muhammad OC4.4
Choudhury, Sirazum CC4, P169, P17, P184, P26
Christian, Mark OP2.3, P211, P212
Christodoulou, Dimitra OP7.2, P312
Christodoulou, Marilena OP6.1
Christudoss, Pamela P237
Chu, Guistina OP6.4
Chua, Aldons P155
Chuah, Ling Ling P366
Chung, Pei-En **P204**, P68
Chung, Teng-Teng OC5.3, P178, P188, P19
Cielo, MD, Frances Melissa **OP4.2**
Ciliberti, Maria **P323**, P342, **P376**, **P385**
Cima, Luminita OP3.1
Claahsen-Van der Grinten L., Hedi P161
Clapp, Carmen P111
Clarke, Noel CC5
Clarke, Sophie P117, **P371**
Clarke, Sophie. A OC4.4
Clarke-Burns, Rosanna P244
Clarke-Burns, Rossana P40
Cleland, James P390
Cobbold, Jeremy P265, P53
Coco, Mohamed **P333**
Cohen, Eliel P339
Cole, Timothy **OC5.4**
Colosimo, Santo **P53**
Comninos, Alexander CC4, **TAA1.1**
Comninos, Alexander N P116, P267, P322, OC4.4
Connelly, Paul P133
Cooke, Heather P6
Cools, Martine P161
Cordero-Monroy, Luis P218
Corley, Elizabeth A **P125**
Costache Outas, Mariana **P103**
Cotellessa, Ludovica P371
Couvelard, Anne JA4
Cowell, Adrian OP8.4
Cox, Jeremy CC4, OC7.5, P322
Cozma, Lawrence P292, P99
Cozma, Silviu Lawrence P167
Coêlho, Caio Fernando Ferreira P371
Crane, James OP7.4, P366
Crastin, Ana OC1.3, P210, P346, **P66**
Crasto, Winston OP8.2
Crawford, Rosy OP1.2
Cresswell, Emily **P221**
Criseno, Sherwin **P151**, P246, **P364**, P37
Critchley, Hilary OP3.2
Crockett, Elin **P167**
Crossland, Helen P186
Crossley, Victoria OC7.3
Crotty, Michael P70
Cui, Wenhao P231
Cullen, Fenn OP5.2
Culley, Fiona P340
Cunningham, Margaret P206
Curtis, Anna **P344**
Cussen, Leanne OC4.1, **P369**
Cutillas, Pedro P80
Cvascuic, Titus OP4.4

da Silva Xavier, Gabriela P54
Dales, Jolyon P179
Dancyger-Stevens, Luka P89
Daniels Gatward, Lydia BSW1.3, **OC6.3**
Daniels, Lorna **ECS1.1**, P57
Darby, Denise OP5.3
David, Joel P279
Davies, Eleanor OC5.1, OC5.5
Davies, Jessica P17
Davies, Justin H P16, P261
Davies, Kate **P155**
Davies, Nils P111
Davies, Rhianna P259
Davies, Sara-Louise **P11**
Davis, Penn OP8.4
Davitadze, Meri P209, P216, P71
Dayan, Colin OC7.2, P128
De Groote, Katya OP3.1
de Jong, Mechteld P200
De Jong, Mechteld Christine P284
De Luca, Carmela P65
de Sanctis, Luisa P161
de Vries, Liat P16, P161, P261
De, Parijat P215
Dean, Andrew P96
Dearden, Laura OC6.5
Dearlove, David OP2.2
Debono, Miguel OP5.1, P160, P177, P8
Decoster, Laurine OC4.4
Deiktakis, Eleftherios E JA3
Deinum, Jaap OC5.1
Delbene, Leanne P304
Delli, Virginia OC4.4
Demel, Isabel P312
Demir, Korcan P261
Dennedy, Conall OC5.1
Deplanque, Dominique P371
Desai, Nirali **P312**
Deshmukh, Harshal **P108**, P253, P303
DeSilva, Akila P300
Desouza, Bianca P243

Detlefsen, Sönke JA4
Dewdney, Charlotte P317
Dewisme, Julie **P371**
Deyanova, Yana OP3.1
Dhage, Shaishav P301
Dhandapani, S S OC3.1
Dhar, Mili **OP7.4**
Dhatariya, Ketan P94
Dhawan, Sangeeta P65
Dhillo, Waljit S P116, P259, P267, P344, P371
Dhillo, Waljit S. OC4.3, OC4.4
Di Marco, Aimee OC7.5
Dias, Renuka P58
Diaz-Cano, Salvador CC1
Dickson, John OC5.3
Diddhenipothage, Shani A D Mathara P271
Dimarco, Aimee OP4.1
Dimitriadis, Georgios P366
Dimitriadis, Georgios K P239, P92, OC4.1
Dinesh, Athul P308
Dinouri, Rania P346
Dissanayake, Harsha **P282**
Dobre, Ramona P84
Docherty, Kevin **LOE1.3**
Dodiya, Manoj **P394**
Dogar, Azeem P42
Doherty, Lucy OC6.3
Doig, Craig OC6.2, P156
Dolmans, Marie Madeleine S4.2
Donelly, Neil P96
Donn, Rachelle P345
Dooht, Sarine OP4.4
Dorita, Alina Ioana P86
Dorward, Neil OC3.1, P94
Dočkal, Tereza OC4.2
Drake, William P320
Drake, William M OC3.5, OP1.3, P233, OC3.2
Drakou, Eftychia E P239, P92
Druce, Maralyn P232, P283
Duffy, Joanne P324
Dugal, Neal P18
Duggan, Sinead P351
Dulcey, Luis P323, P342, P376, P385
Dumitrascu, Anda P87
Duncan, Emma **OC1.5**
Dunn, Rachel P31
Dunstan, Rosalyn P35
Dunsterville, Cecilia P204, **P213**, P61
Dusceac, Roxana P84
Dussmann, Heiko S3.2
Dutta, Pinaki OC3.1, P82
Dyson, Pam OC6.6

Eastell, Richard P33
Ebnet, Johannes P111
Economides, Panayiotis P286
Edaan, Esra OC5.3
Ede, Obiamaka **P275**, **P76**
Eftychiou, Nicolas OP7.2
Eisenhofer, Graeme OC5.1
Elajnaf, Taha OC3.4
Elamin, Aisha P298, **P83**, **P95**
Elder, Charlotte P160
Elena-Singh, Andrada P330
Elford, Sue P12
Elhariry, Maiar **P222**
Elhassan, Yasir **CC1**, P12, P162, P268, P7
Elhassan, Yasir S P17
Eligar, Vinay P128
Elkhenini, Hanaa P334
Elliott, Jonathan OC7.3
Ellis, Peter OP4.4
Ellis, Peter K P91
Ellis, Tracey P334
Elsayed, Solaf OP5.3
Elsedfy, Heba P16, P161, P261
Eltayeb, Randa P43
Eng, Pei Chia P267
Enikuomehin, Adenike P223
Ereño-Orbea, June P371
Espinosa-Flores, Aranza Jhosadara OC3.6
Evans, David OC1.2
Evans, Marc P195
Evans, Roisin P17
Evans, Rosemary **P180**
Ezenwa, Chima P391

Fahad, Khalid **P141**, **P392**
Falconer, Emily **P152**
Falowo, Durodoluwa P215
Fandrich, Robert P218
Fanelli, Francesca OC3.3
Farah, George P332
Farooq, Qaisar **P355**
Farooq, Zara OC4.5
Farrell, Terence P369
Fasanmade, Olufemi P275, P76
Fassnacht, Martin CC1, OC2.3
Faulds, Karen P206
Fauzi, Luqman P15
Fazil, Mohamed P209, P216, P71
Fearon, Patricia OP4.4
Fedorenko, Olena P262
Fenn, Jonathan **P378**
Fernandes, Alysid P197
Fernandez James, Cornelius P149, P181, P25, P28, P299
Fernandois, Daniela P371
Ferrar, Melloney P177
Fica, Simona OP3.1, P100, P29, P86
Filer, Andrew P66
Finucane, Francis P70
Firkins, Louise P210
Firth, George OC2.1
Fisher, Stephen P310
Fitchat, Tracey P175
Flannagan, Daniel P159
Flatt, Peter R. P354
Fleming, Suzannah **P236**
Fletcher, Claire **OC2.4**, P48
Florent, Vincent P371
Floyd, Ruairí **P114**, **P351**
Flueck, Christa E P16, P161
Foka, Anna P134, P332
Forbes, Ben OC4.4
Ford, Clare P324, P378
Ford, Rebecca P67
Forlano, Roberta P53
Fountas, Athanasios **OC3.2**
Fowkes, Robert **OC7.3**
Fowler, Paul **BSW1.1**
Fowler, Paul A. OP3.4
Franco, Izzy OC6.1
Frank, Amy **P2**
Franks, Stephen P264, **PL4.1**
Fraser, William OC1.1, P31
Fraser, William D OP6.2
Frasser, William OP6.1
Freel, E. Marie OC3.2
Freeman, Adrian OC5.6
Frizelle, Isolda **OP7.2**
Frost Munk Nielsen, Morten EC1.3
Frost, Gary P62
Fryer, Caroline **NS1.3**
Fu, Antony P161
Fuller, Peter OC5.4
Fullerton, Josie OC5.5
Funge, Gregory P363
Furigo, Isadora **OC6.5**
Furniss, Dominic

Gadelha, Monica R. OC1.4
P399
Gage, Matthew **OP2.1**
Gajda, Maciej Jan **P280**
Gallagher, Alison P209, P216, P71
Gallagher, Meurig P180
Galliford, Thomas P391
Galoiu, Simona P84
Gama, Rousseau P324, P378
Gan, Dr Earn H CC3
Ganea, Catalina OP8.4
Gangitano, Elena P63
Garcez, kate P93

Garcia, Cristina Iglesias P371
Garcia, Virginia Rozalen P276
Garcia-Haro, Luisa P339
Garstang, Joanna P58
Gaston-Massuet, Carles P363
Gathercole, Laura P63, P64
Gattazzo, Nives **P350**
Gazarkova, Tatana **P158**
Gazet, Marianne P46
Gazárková, Tat'ána P316
Geberhiwot, Tarekegn P324
George, Lindsay P195
Georgiadou, Eleni P65
Gevers, Evelien P125
Ghaffari, Parisa P345
Ghenoiu, Sandra P87
Giacobini, Paolo OC4.4, P371
Gibb, Fraser P317, **P395**
Gibney, James P258, P351
Gibson, Martin P230
Gifford, Rob OP5.4
Gilbert, Jackie P366
Gill, Henry P378
Gillett, Caroline D. T. OC4.1
Gillett, Dan P85
Gillett, Daniel OP1.2, OP8.1
Gilligan, Lorna CC1, P1, P5
Gilligan, Lorna C. OC4.1
Gimenez-Roqueplo, Anne-Paule OC5.1
Gireesh, Rayasandra P42
Gittoes, Neil P151, P324, P37
Giwercman, Aleksander JA3
Giwercman, Yvonne Lundberg JA3
Glaser, Matthias OC5.3
Glatzel, Hannah P112
Gleeson, Helena OC4.1, P151, P268
Globa, Evgenia OP3.1, P16, P261
Glover, Amy P144
Gluchowska, Monika P254
Glyn, Tessa **P398**
Glynn, Nigel P232
Gnanananthan, Pairavi P130
Gnanasegaran, Gopinath OC2.2
Go, Cara P259
Goh, Edwina CC1
Gohil, Shailesh OC7.6, P120, P172, P173, **P263**, P396, **P51**
Goldney, Jonathan P236
Gomes, Larissa G. OC4.1
Gomez, Jaime P323, P342, P376, P385
Gondane-Sweetman, Purnima P334
Gonsahn-Bollie, Sylvia P222
Gonzales, Christine **P239**, P92
Gonzalez Dominguez, Carolina OC6.3
Goodchild, Emily P175
Gordeladze, Marine P386
Gordon, Nadia P366
Gordon, Patricia OP4.4
Gorrigan, Rebecca CC8
Gorvin, Caroline P157
Goss, Charlotte P340
Goudie, David P198
Gould, Gwyn P206
Goux, Aurelie P67
Gouya, Laurent OP5.3
Gowri, Mahasampath P166
Gowrishankar, Shravan P312
Graham, Duncan P206
Gramlich, Susanne CC1
Grant, Bonnie **OC4.3**
Graveling, Alex P163, P327
Graveling, Dr Alex P135
Gray, Calum OC6.4
Gray, Gillian OC5.6
Gray, Laurence P140
Green, Deirdre P369
Green, Kathryn **P133**
Greenfield, Sheila M P208
Greenfield, Sheila Margaret P58
Greeves, Julie OC1.1
Greig, Justin **P206**
Greiner, Philipp OC4.2
Grey, Joanna **RET1.4**
Grey, William OP7.1
Gribble, Fiona P204
Grieve, Joan OC3.1
Griffin, Emma P369
Griffin, Liezel OP5.3
Grinspon, Romina P261
Grixti, Lydia OC3.2
Grossman, Ashley P189, P43
Grounds, Kerrie P287, **P291**
Grover, Liam M. P66
Grunberg, Nil OC2.4
Grundy, Megan **OP8.3**, **P309**
Guaragna-Filho, Guilherme P161
Guarnier, Giulia P371
Guerra-Junior, Gil P261
Gulamhusein, Aziz CC5, P171
Guma, Muna **P384**
Gupta, Amrit **P72**
Gupta, Vishal **P349**
Guran, Tulay P16, P161
Gurnaani, Jenil P82
Gurnell, Mark CC7, OC3.2, OP1.2, OP8.1, P318, P85, P96
Guven, Ayla P16, P161

H Ahmed, Mohamed P197
Haberbosch, Linus OP1.2, **OP8.1**, **P85**
Hackett, Rhiannon P247
Hadoke, Patrick P316
Hag, Sara P147, P30
Hagsund, Agnes JA3
Hall, Charlotte P15
Hall, Charlotte L **OP1.1**
Hamblin, Ross OC3.2
Hamdan, Khaliq P251
Hamdan, Mohd Khaliq P336
Hameed, Saira P60
Hameeduddin, Ayshea P46
Hamilton, Amanda **P242**, P287
Hamilton, Graham OP3.4
Hampson, Stephanie OC5.1
Hanna, Stephanie P128, P140
Hannan, Fadil **OC1.2**, OC1.4, PL10.1
Hannan, Fadil M OC3.4
Hannan, JMA P354
Hannema, Sabine E P16, P161
Hanyaloglu, Aylin OC4.5, P264, P62
Hanyalolgu, Aylin OC3.3
Hardowar, Lydia OC6.2, **P55**
Hardy, Kate P264
Hardy, Rowan OC1.3, P346
Hardy, Rowan S. P210, P66
Harfield, Alyson OP4.4
Harid, Anes **P159**
Harman, David P53
Harper, Lorraine OC1.3, P210
Harris, David P111
Harris, Laura P244, P40
Harris, Steve P324
Harrish, Garresori JA4
Harrold, Christopher P330
Harvey, Adrian OP8.3
Harvey, Aeysha **P367**
Hasan, Faisal P398
Hashim, Ibrahim **P113**
Hassan, Fahim-UI P337, OP7.2
Hassan, Samar P15
Hassan, Sharjeel **P382**
Hassan-Smith, Zaki P37
Hatton, Rebecca P40
Hawley, James P380, P5
Hawley, James M. OC4.1
Haworth, Oliver OC3.6, P80
Hayashi, Natsuho P231
Hayes, Aimee OC2.2
Hayes, Maria P139
Hazlehurst, Johnathan P38
Hazlehurst, Jonathan P183, P190, P193
Head, Simeon P13
Heague, Megan **OC3.5**, OP1.3, P233
Heald, Adrian **OC7.2**, P128, **P230**, P345, **P78**, P88
Heaselgrave, Samuel **P156**
Heazell, Alexander E.P. OP2.3, P212

Hebbar, Meghna P215
Hebblethwaite, Neil P273
Hebden, Sophie OC3.5, **OP1.3**, P233
Hege, Elvebakken JA4
Heidari, Zeynab OP3.4
Hepzhibah, Julie P166
Heraghty, Neil OP7.4
Herbison, Allan **MTE7.1**
Hermann, Pernille EC1.3
Hernandez, Gillian P137
Herrmann, Gloria OP3.1
Hevey, David P114
Higgins, Kath P209, P216, P71
Higham, Claire OC3.2, P32
Higham, Claire E OC3.5, OP1.3, P233
Higham, Claire Emily P199
Hill, Arnold P18
Hinds, Catherine P114
Hiwot, Tarekegn P54
Hjortland, Geir Olav JA4
Ho, Cindy W L OC7.4
Ho, Jan P171
Ho, Jan Hoong CC5, P302
Hobson, Sam OP2.1
Hodson, Alexander P312
Hodson, Leanne OP2.2, P205, P214, P59
Hoffmann, Eva S4.3
Hofsli, Eva JA4
Holliday, Rachel **P21**
Holmes, Michael OC1.4
Homer, Natalie **OP5.4**
Honzlová, Petra OC4.2
Hoong Ho, Jan P93
Hopkins, Thomas OC4.5, OC4.6, **OP3.3**
Horne, LInda P230
Hosseini, Mir-Jamal **P379**
Houdek, Pavel OC4.2
Howard, Sasha R OP1.1, P267
Howe, David P330
Howell, Lesley OC4.5
Howell, Simon CC5, P35
Howles, Sarah OC1.4
Hoy, Sonja P381
Hrabovszky, Erik P371
Htet, Swe P228
Htoon, Kyaw Naing **P241**
Htun, Kyaw Z P73
HTUT, ZIN **P343**
Htut, Zin **P146**, **P81**
Htwe, Nyi P25
Huang, Biao P259
Huang, Qin Qin S4.3
Hubbard, Jonathan P338
Hughes, Nessa P114
Huhtaniemi, Ilpo T JA3
Hui, Elaine P243
Hulse, Richard OC6.2, P55
Hunter, Ann Louise **BSW1.2**
Hunter, Steven J. OC3.2
Hurles, Matthew S4.3
Hussain, Alisha **P346**
Hussein, Ziad CC9, OC3.2, P83
Huws, Sharon P139
Huynh, Kevin A OP8.1
Hyer, Dr Steve P325
Hyer, Stephen P381
Hyndman, Brandy RET2.1
Hyrcza, Martin OP8.3

Iacuaniello, Davide **P365**
Icoresi-Mazzeo, Cecilia EC1.4
Idampitiya, Chandima P143, P145, P252
Ieronymaki, Eleftheria JA3
Ifarajimi, Raphael P341, P347
Iftikhar, Zara P107
Iftimie, Madalina P50
Ikem, Rosemary P124
Ingraham, Holly **PL6.1**
Investigators, ZiPP P31
Iotova, Violeta P16, P161
Iqbal, Ahmed CC9, OP5.1
Iqbal, Zohaib **P171**, P93
Isand, Kristina OC3.2
Islam, Quazi P189, **P43**
Izard, Rachel OC1.1
IZATT, Louise **RET1.2**
Izatt, Louise **OP7.1**, OP7.2, P126, P337
Izzi-Engbeaya, Chioma P60

J Griffiths, William P360
Jackson, Adam OP5.3
Jackson, Portia P10
Jackson, Sarah OC1.1
Jacob, Anu **P320**
Jadwiga, Furmaniak JA5
Jafar-Mohammadi, Bahram P321
Jajah, Bilal P335
Jamaluddin, Aqfan **P157**
James, Carol-Ann OC5.6
James, Charlotte P167
James, Lynette P12
Jane, Sanders JA5
Janecke, Andreas OP5.3
Janus, Dominika P261
Jarmasz, Jessica S. P218
Jarvis, Sheba **P319**
Javadpour, Mohsen P369
Javeed, Ali P348
Jayal, Yashoda P344
Jayasena, Channa OC4.1
Jayasena, Channa N P259, OC4.3
Jayasuriya, Anuradha OC3.2
Jayraj, Aarthi S **P247**
Jebasingh, Felix P166, P237
Jeffery, Jinny P159
Jen, Jian Ping P96
Jenkins, Kenny **CC10**
Jenkins, Rhys OP5.4
Jervis, Nikie **P49**
Jethwa, Preeti P67
Jin, Yan P218
Johan, Malm JA3
Johanna, Svensson JA4
John, Reggie **P372**
Johnson, Elspeth P205
Johnson, Gillian OP3.3
Johnson, Tom OC5.6
Johnston, Philip C **OP4.4**
Johnston, Susan P2
Jonas, Kim OC4.5, OC4.6, OP3.3
Jones, Bethany P330
Jones, Christopher P311
Jones, Derek P127
Jones, Jonathan OP8.1, P85
Jones, Karen P287
Jones, Max **P23**
Jones, Rhys **P292**
Jones, Simon W. OC1.3, P210
Jonhson, Elspeth OP2.2
Jose, Arun P237
Jose, Biju OC3.2, P370
Joseph, Aneez P237
Joseph, Jooly P370
Joseph, Neetha P27, P45
Joseph, Sonia P183, P190
Joshi, Ashwin P21
Joshi, Dr Ashwin CC3
Jourdain, Mercé P371
Jude, Edward P228, P334
Junior, Jair P352
Juszczak, Agata P183, P190, P38
Juul, Anders OP3.1

Kabat, Marek OC5.1
Kaczynski, Jakub P316
Kalaiah, Yogesh P314
Kalaria, Tejas **P324**, P378, P394
Kalenderoglou, Nikoletta **P211**
Kalogianni, Eleni P390
Kamaruddin, Shafie OP6.4
Kannappan, Vinodh OC7.1
Kapoor, Ashutosh P146
Kapoor, Nitin P166, P237
Karamat, Muhammad Ali P215
Karavitaki, Niki **HDI1.2**, OC3.2, OC3.5, OP1.3, P151, P233
Kardalas, Efstratios P306
Kardami, Elissavet P218

Karen, Forbes JA1
Kareem, Mr Jamal P325
Karim, Rehmat P303
Karkhanis, Amol **P308**
Karpe, Fredrik OC6.6, P221
Karra, Efthimia P121, P165, P308, P377, P43
Karra, Eftimia P189
Karunanayaka, Madushani P89
Kaucha Rana, Anita **P152**
Kaur, Rupinder **P82**
Kaushal, Kalpana CC5, P35
Kavvoura, Foteini P134
Kawalec, Joanna P293
Kayes, Lucy **P139**, **P285**
Kazrooni, Noor S **P295**
Kearney, Mark OP2.1
Kearney, Tara OC3.5, OP1.3, P233, P365
Keen, Fred **P251**, **P97**
Keerie, Catriona P31
Keevil, Brian P171, P380
Kelechi, Ubani P341
Kelly, Chris P133
Kelman, Alexandra OC6.4
Kempegowda, Punith OC4.1
Kennard, Matilda BSW1.3
Kennedy, Ashling P98
Kennedy, Oliver P302
Kerr, Enda OP4.4
Kersten, Christian JA4
Khadayate, Sanjay P65
Khalid, Maha P393
Khalifa, Mai P95
Khalilova, Samira P239, **P92**
Khan, Abdul Rehman P348
Khan, Danyal OC3.1
Khan, Haris P192
Khan, Hashim **P77**
Khan, Huma Humayun **P321**, P356
Khan, Irfan OP6.4, **P356**
khan, Irfan P335
Khan, Jansher **CC8**
Khan, Muhammad Athar Iqbal **P39**
Khan, Sairah P130
Khan, Shazia OC5.6, P316, **P360**
Khanam, Amina **P357**
Khoo, Bernard OC2.2, P165, P189, P43
Khot, Shreya OC6.3
Kikodze, Nino P386
Kiloh, George OP2.4
Kim, Dae P381
Kim, Jana OC2.1, OC7.1
Kineman, Rhonda D JA2
King, Aileen **BSW1.3**, OC6.3
King, Andrew P366
Kinton, Rebecca **P257**
Kircher, Stefan CC1
Kjaer, Anna Sophie L. Kjaer OP3.1
Klaucane, Katarina OC3.2
Kline, Gregory OP8.3, P309
Kneebone, Roger P339
Kocbiyik, Merve OC2.6
Kocova Vlckova, Hana P158
Koh, Timothy J JA2
Kolawole, Babatope P124
Kolias, Angelos OC3.1
Kollurage, Udeni **P42**
Komber, Ahmad P33
Kondo, Yuri P231
Konrad, Daniel P16, P161
Kooblall, Kreepa **OC1.2**
Korbonits, Marta P161, P91
Korbonits, Márta OC3.1, OC3.6, P363, P51, P80
Kostoula, Melina P391
Koulouri, Olympia OP8.1, P85, P96
Kountourides, Gabriella OP3.2
Koutoukidis, Dimitrios P53
Koysombat, Kanyada **P116**
Krishnamurthy, Roopa P228, P334
Krishnan, Amutha OC3.2
Krishnan, Leena P122
Krone, Nils **E1NS1.2**, P12
Krone, Nils P P16, P161
Krone, Ruth P161
Kumar, Anoop P72
Kumar, Mohit P41
Kumar, Narendra P82
Kumar, Niraj P90
Kumar, Santhosh P166
Kumar, Sheethal **P330**
Kurera, Isuri P22
Kurzawinski, Tom **NS1.1**, OC5.3, P126, P188, **P200**, **RET2.3**
Kurzawinski, Tom R OP7.1, P276, P125
Kushe, Manish **P368**
Kwok, T'ng Choong **OC6.4**
Kwong Fei, Eugene Leong P176
Kyaw, Khin Yadanar **P248**
Kyle, Catriona P350
Kyriacou, Alexis P286
Kyriacou, Angelos P286
Kyriakakis, Nikolaos OC3.5, OP1.3, P233, P3
Kyriakopoulos, Georgios P306

L. Ronchi, Cristina P7
L.W. Yau, Joyce P360
Laing, Ian P35, P88
Lajeunesse-Trempe, Fannie OC4.1
Landwehr, Laura CC1
Lang, Katharina OC5.1
Laniba, Leah P366
Lansdown, Andrew OC3.2, **P150**
Larner, Dean P64
Larsen, Casper K. OC5.1
Latif, Wajeeha **P203**, **P44**
Lavery, Gareth P156, P64
Lavrentaki, Aikaterini P306
Lawrence, Neil P12, P160
Lawson, Alexander P324
Lawton, Phillip P339
Lazaro, Nila P366
Lazarus, John P127
Lazarus, Katharine P169, **P17**, **P184**, P243, P26
Lazarus, Syndia OC1.5
Lazkani, Aida OC5.1
Le Roux, Carel P351
Lebouvier, Thibaud P371
Lecante, Laetitia L. **OP3.4**
Lee Yoong Zher, Melvin **P375**
Lee, Benjamin Yi Hoong P150
Lee, James P174, P176
Lee, Jessica **CC8**
Leese, Graham P137
Leggieri, Adele OC3.6
Leite, Nayara C P353
Leka-Emiris, Sofia P16, P161
Lenherr-Taube, Nina P16, P161
Leung, Alexander A. OP8.3
Levy, Miles OC7.6, P102, P120, P172, P173, P179, P23, P236, P263, P51
Levy, Miles J. OC3.2
Lew, Peisan P218
Lewandowski, Krzysztof **P254**, **P293**
Lewin, Michelle **P287**
Lewinski, Andrzej P254, P293
Lewis, Alexander P187
Lewis, Janet P150
Lewis, Steff P31
Li Ling, Jolene Chia **OC7.4**
Liang, Shiyi P207
Liarakos, Alexandros **P134**
Lichiardopol R, Corina P161
Lichiardopol, Corina R P16
Lightman, Stafford OP1.4
Lim, Adrian KP P259
Lim, Chung Thong P182, P229, P270
Lim, Eugenie P46
Lim, Jonathan **P194**
Lin, Nyan **P96**
Lin, YeunYi **P137**
Lin, Zhimin **P174**
Lines, Kate OC1.2

Ling, Yong P245
Litchfield, Ian P208
Lithgow, Kirstie OC3.2, OC3.5, OP1.3, P233
Littler, Dr Peter CC3
Littlewood, Gail P310
Liu, Jieruo P204, P61, **P68**
Livingston, Mark **P88**
Livingstone, Rachel **OP6.3**, **P326**
Llahana, Sofia P12, P155
Lomidze, Ketevan **P386**
Lonergan, Eibhlin **P98**
Loo, Helen P321
Lopez, Daniel Baz OC5.6
Lorentzen, Marc OC2.4
Lorigan, Paul P302
Lothe, Inger Marie B JA4
Loughrey, Paul Benjamin OC3.2, **P91**
Lovegrove, Catherine **OC1.4**
Low, Brandon Shu Huang **P58**
Lubczynska, Malgorzata Marta **P396**
Lucas-Herald, Angela **P261**
Luczay, Andrea P161
Ludgate, Marian P127, **S5.1**
Lukasiak, Magdalena **OP2.4**
Lund, Andrew P177
Lwin, Hnin P209, P216, P71
Lwin, Min Thant **P248**
Lyall, Marcus P317
Lynch, Eilidh P138
Lynch, Julie OC3.5, OP1.3, P233, P3
Lynsey, Jessica OP4.4

Maarouf, Amro **P190**
MacFarlane, James OC3.2, **OP1.2**, OP8.1
Macfarlane, James P85, P96
Machado Duque, Manuel P359
Machenahalli, C Pratibha P330
Macinerney, Ruth P95
MacKenzie, Scott OC5.5
Mackin, Sharon P138
Macklin, Andrew P393
MacLean, Jillian P336
MacLeod, Ken P340
Macriyiannis, Thrasos P374, P396
Mada, Srikanth P361
Madan, Arina **P338**
Madani, Gitta OC7.5
Madden Doyle, Lauren **P12**
Madhotra, Ruchika **P193**
Madu, Nneka M **P289**
Maenhout, Annelies P390
Magata, Fumie P231
Magid, Kesson OC3.1
Mahajan, Anubha OC1.4
Maharaj, Avinaash P15
Maher, Sean **P70**
Mai, Knut OP8.1, P85
Maitra, Saptarshi P15
Majeed, Waseem P365
Malik, Ahmed **P37**
Malik, Iqbal P137
Mamoojee, Yaasir **HDI1.1**, OC3.2
Mandair, Dalvinder OC2.2
Mandal, Sumedha **P162**, P7
Manivannan, Selvambigai OC2.1, **OC2.6**, OC7.1
Mann-Wineberg, Dania **P274**
Manna, Luiza P168
Mannan, Fahmida **P345**
Mannath, Sathia Narayanan **P149**, **P181**, **P25**, **P28**
Mannath, Sathia narayanan **P299**
Mannion, Richard OP8.1, P96
Manousou, Pinelopi P53
Manson-Bahr, David P45
Mansoor, Wasat P171
Maratos, Eleni P366
Marchetti, Piero P65
Marcus, Hani P94
Marcus, Hani J OC3.1
Margetts, Dr Jane CC3
Marginean, Otilia P16
Marjot, Thomas P53
Markosyan, Renata L P16, P161
Markou, Maria P306
Marland, Anne P155
Marroquin Ramirez, Lucia P15
Marsden, Daniel OP1.2
Marseden, Louise P304
Marselli, Lorella P65
Marsh, Joe **BSW2.3**
Marshall, Lynley V P125
Marta, Angellica P65
Martin, Carmen Sorina **P86**
Martin, Claire S. P66
Martin, Hilary S4.3
Martin, Niamh OC3.2, P17, P240, **P339**
Martin, Sorina P100
Martinez-Chantar, Maria P371
Martins da Silva, Sarah **S4.1**
Massalha, Hassan **EC1.4**
Mateen, Abdul **CC4**
Mathara Diddhenipothage, Shani A D **OP3.1**
Mathara Diddhenipothage, Shani A D Mathara Diddhenipothage **P110**
Matheou, Michael OC6.6
Matheou, Mike OC3.2
Mathew, Susan OC3.2
Matsuda, Fuko P231
Matsuyama, Shuichi P231
Matthews, Alexandra **P183**
Matthews, Sarah **P278**
Mattot, Virginie P371
Maurage, Claude-Alain P371
Mavilakandy, Akash OC3.2
Maxwell, Melanie P45
May, Caroline **P257**
May, Christine P321
Maybin, Jacqueline **OP3.2**
Mazen, Inas P161
Mazzoleni, Adele P90
Mc Ilmoyle, Jim OP4.4
McArdle, Nicholas P45
McCabe, Chris OC2.6
McCabe, Christopher OC2.1, **OC7.1**, PL7.1
McCormick, Peter OC4.5, OC5.2
McDonald, Neil Q OP7.1
McDonnell, Tara OC4.1
McEleny, Kevin P123
McGlacken-Byrne, Sinead **P126**
McGovern, Andrew P159
McGowan, Barbara OP7.2
McGowan, Barbara M OP7.1
McGregor, Alison P339, P340
McHugh, Joseph P70
McIlroy, Marie OC2.5, **S3.2**
McKenna, Jordan OP4.4
McLaren, David OC3.5, P3, OP1.3, P233
McLaren, David S. OC3.2
McLean, Joanne P198
McLoughlin, Katie OC3.5, OP1.3, P233
McNabb, Carolyn P127
McQuibban, Nicholas A. R. P281
McTaggart, Malcolm **P380**
McTernan, Philip P219
McVeigh, James OC4.3, OP8.4
Meeran, Karim P105, P130, P147, P169, P17, P184, P26, P30, P75
Mehta, Anku P391
Melrose, Rachel P185
Melson, Eka **OC4.1**, **P209**, P216, P71
Melton, Douglas A P353
Meng, Xin **OC3.4**
Menon, Ravi P142
Merete, Krogh JA4
Mercado-Gómez, Maria P371
Mes, Steven P96
Metherell, Louise OP5.3, P15
Methlie, Paal OP1.4
Meyer, Leah P204, **P61**, P68
Michael, Sylvia P155
Michaelidou, Maria **CC5**, **P35**
Middleton, Morag P135

Mihai, Gabriela **P232**
Milenkovic, Tatjana P161
Miler, Emma OP6.2, **P118**
millar, robert **LOE1.2**
Miller, Ben P183
Miller, Hamish P53
Miller, Kieran OP8.4
Miller, Madelaine **P169**
Millership, Steven **P65**
Mills, Edouard G P371
Mills, Edouard. G **OC4.4**
Mills, Nicholas OC5.6
Milne, Alison P135, **P153**
Milner, Annabelle **P62**
Minhas, Raisa **P245**
Minhas, Sukhbinder OC4.3
Minhas, Suks P259
Miras, Alexander P207
Missbrenner, Cornelia OC4.1
Mistry, Anisha P363
Mitchell, Anna L P17
Mitchell, Catherine P245
Mitchell, Dr Anna L CC3, P234
Mitchell, Kirsten OC3.2
Mitchell, Rod T. OP3.4
Mitelpunkt, Daniel OP8.4
Mizuno, Tooru P218
MJ, Paul P166
Mladenova, Irina P43
Moakes, Richard J. A. P66
Modalavalasa, Harsh P90
Modi, Manish P267
Mohamed, Ahmed P134
Mohamed, Einas **P142**
Mohammed, Al-Amin **P119**
Mohammed, Bushra T. **P47**
Mohammed, Kamrudeen P253
Mohammed, Zainab Taha P47
Mohideen, Shifaniya Banu P138
Mohindra, Sandeep P82
Mohnike, Klaus P161
Mohora, Alexandra P50
Mon, Hla Myat **P24**, **P315**, **P397**
Monaghan, Philip P171
Monaghan, Phillip CC5, P302
Mongolu, Shiva P303
Monticone, Silvia OC5.1
Moonim, Mufaddal OC7.5
Moorwood, Catherine OC1.2
Morelli, Annamaria P371
Morgan, Stuart P64
Morganstein, Daniel P281, P381
Morley, Elizabeth P42
Morrin, Martina P18
Morrison, Amy **P102**, **P172**, P23, P236
Morrison, Patrick J P91
Morton, Nicholas P352
Mouchtouris, Panagiotis P306
Moulik, Probal P136
Mueller-Fielitz, Helge P371
Muhammad, Fakhraddeen **P223**
Muhammad, Zubair P128
Mukherjee, Annice P116
Mukherjee, Neil P67
Mukhtar, Ghazel **P353**
Mulatero, Paolo OC5.1
Mullan, Karen P139, P285
Mullan, Karen R P91
Mulligan, Lois **RET2.1**
Mundell, Natasha **P193**
Mung, Sai Man CC5
Munir, Alia P241
Munir, Alia CC9, P83, P89
Murphy, Alice **P219**
Murphy, Kevin P204, P232, P340, P52, P68
Murphy, Kevin G P213, P344, P61
Murphy, Niamh P114
Murphy, Noel P332
Murray, Anna S4.3
Murray, Lynne P135
Murray, Robert OP1.3, P233, P3
Murray, Robert D OC3.5, OC3.2
Musa, Salwa P15
Myint, Khin Swe P10, P27, P45
Myint, Swe **P297**
Müller, Lisa M. OC5.1

Nabi, Syed Assad **P131**
Nacu, Miruna Viorela P86
Nadeem, Sajjad P328
Nadia, Amin P161
Naeem, Ammara **P165**, P189
Nag, Sath CC10, **P247**, P272, P273
Nagarajah, Kalyani **P195**
Nagarajan, Shilpa ECS1.1, P205
Naidoo, Jarushka P18
Naik, Mitesh P130
Nakamura, Sho P231
Nampoothiri, Sreekala P371
Napier, Catherine P21
Narayanan, Deepa P185
Narayanan, Ram Prakash P14
Narendran, Parth P208, P58
Narula, Kavita P17, P184, **P243**, **P26**
Narunsky, Rachel **P121**, **P377**
Naserzadeh, Parvaneh P379
Natesh, Basavaiah P330
Naughton, Aoife P279
Navalkissoor, Shaunak OC2.2
Nawaz, Asif P140
Nayar, Dr Rahul CC3
Naziat, Auditi P388
Neelam-Naganathan, Dharshan **P33**
Neumann, Uta P16, P161
Newbold, Kate P125, P381
Newby, David P316
Newell-Price, John OC3.2, OP5.1, P160
Newey, Paul P137, P198, P51
Newsome, Philip P53
Newton, Eric P139
Ngiam, Kee Yuan P174
Nguyen, Nini OP5.2
Nicolaou, Marina **P283**
Niculescu, Dan P84
Niedzela, Marek P16, P161
Nieto, Hannah OC2.1, OC2.6, OC7.1
Nijith, Lakshmi **P182**, P229, P77
Nikolaou, Nikolaos **OP2.4**, **P56**, P63
Njue, Faith P112
Nogueiras, Ruben P371
Nonaka, Daisuke OP7.1
Nordenstrom, Anna P161
Norris, Jonathan P279, P282
Norton, Mariana P204, P61
Novaes, Olivia P258
Novakova, Lucie P158
Ntali, Georgia **P306**
Ntshangase, Sphamandla **P316**
Nwokolo, Muna P189

o Connor, Christine OP4.4
O′ Shea, Triona P232
O′Connell, Ian P41
O′Connell, Jean P70
O′Connell, Michele P261
O′Halloran, Domhnall P98
O′Leary, Thomas OC1.1
O′Mahoney, Samantha P281
O′Reilly, Michael P12, P18
O′Rourke, Paige OP2.2, P205
O′Sullivan, Lisa P114
Oakey, Rebecca J OP1.1, P337
Obeid, Mariam P35
Obermayer-Pietsch, Barbara OC4.1
Obuobie, Kofi P362
Odeniyi, Ifedayo P275, P76
Ogunbiyi, Olumide K OP7.1
Ogunko, Arthur P373
Oh, Han Boon **P276**
Ohkura, Satoshi P231
Ojeda, Laura P352
Ojo, Olalekan P69
Ojo, Olubukola P69
Okafor, Emeka P79
Okoro, Grace P154
Okosieme, Onyebuchi OC7.2, P128

Olaniyi, Kehinde P109, P119, P235
Olaniyi, Kehinde S. **P260**
Olaniyi, Kehinde S. Olaniyi **P217**
Olaogun, Idowu **P19**, **P288**
Olaremi, Japhet **OP4.3**
Olatunji, Lawrence A. P217
Oleksii, Nikolaienko JA4
Oliveira, Larissa RET2.1
Oliver, Nick P30
Oliver, Samuel OC1.1
Olopade, Oluwarotimi **P275**, P76
Olszewska, Zuzanna OP3.2
Omer, Tahir **CC6**
Onishi, Ami P352
Ooi, Chia Soon **P300**
Oommen, Suresh **P79**
Orchard, Elizabeth OP3.1, P112
Orme, Steve OC3.5, OP1.3, P233
Orozco Escobar, Andrea P359
Oshimo, Yukina **P231**
Osman, Basheir P333
Osman, Omer **P123**
Otulana, Olatoye P341, P347
Oustabassidis, Eva P279, P282
Ovadia, Caroline P168
Owen, Bryn **P340**, P68
Owen, Bryn M P344
Owens, Lisa P114, P258, P264, P351
Owens, Martina OC1.2, OP7.3
Owles, Henry P197
Oyibo, Samson O P289, P295, P73
Ozanne, Susan OC6.5
Ozoran, Hakan **OC6.6**
O′Brien, Odharnaith P18
O′Reilly, Michael W. OC2.5, OC4.1
O′Shaughnessy, Peter J. OP3.4

Page, Karen OC7.6
Pai, Rekha P166
Pain, Simon P191
Paisey, Richard P54
Pal, Aparna OC3.2, P321
Palani, Raghavendar **P178**
Palazon, Asis P371
Palazzo, Fausto OC7.5, OP4.1
Pallai, Shillo P95
Palma, August **MTE3.1**
Pambinezhut Kunjumohaned, Fathima **P252**
Pambinezhut, Fathima **P143**, **P145**
Pan, Shwe P141, P392
Pana, Monica P29
Panagiotou, Grigorios P195
Panay, Nick P116
Pandanaboyana, Mr Sanjay CC3
Panicker, Janki OC3.2, **P242**, P287, P291
Panourgia, Maria P197
Pantaleao, Lucas OC6.5
Panteliou, Eleftheria **P96**
Papadopoulou, Deborah **P130**, P17, P184, P26, P267
Papaleontiou, Giorgos **P107**
Parameswaran, Rajeev OC7.4, P174, P176, P200, P284
Park, Rachel Huei-Sook **P284**
Parker, Richard P53
Parkin-Crawshaw, Jessica P162, P7
Parry, Sion P205
Parry, Sịn OP2.2
Parthasarathy, Prabha P340
Partsalaki, Eirini P306
Parvanta, Laila P175
Parveen, Nazia P65
Pasaliu, Andreea P157
Pascu, Raluca P29
Pasieka, Janice OP8.3, P309
Pasquier, Florence P371
Patel, Bijal OC4.4, P267
Patel, Dipesh P189, P43
Patel, Kashyap OP7.3
Patel, Nishchil P159
Patel, Tabassum **P236**
Patel, Vinod OP8.2
Paterson, Rachel P135, P163
Pathmanaban, Omar P365
Patil, Aashutosh P144
Patrikios, Ioannis P286
Patterson, Cathy OP4.4
Paul, Sanders JA5
Paul, Thomas P166, P237
Pawlak, Tadeusz P106, P348
Pearce, Simon P123, P21
Pearson, Ewan **PL9.1**
Pecori, Alessio OC5.1
Pedder, Hugo P116
Pedersen, Anette Tønnes OP3.1
Perbet, Romain P371
Perez-Ternero, Cristina **OP5.2**
Perren, Aurel JA4
Perry, John S4.3
Perumal, Samundeeshwari P329
Peters, Debbie P169
Phan-Hug, Franziska P16, P161
Phelan, Niamh P258, P351
Philip, Sam P163
Philips, Sam P90
Phillips, Ben **P35**
Phillips, Benjamin **CC5**
Phillips, Jonathan P31
Phylactou, Maria OC4.4, P267
Picolos, Michalis P286
Piec, Isabelle **OP6.1**, **OP6.2**, P31
Pigny, Pascal P371
Pillai Syam, Kaushal **P170**
Pineda-Torra, Ines OP2.1
Pinnick, Katherine P221
Pintilie, Hannah P10
Pinto, Diluka OC7.4, P284
Pittaway, James P175
Piya, Milan P219
Plachka, Katerina P158
Plowman, Christina P175
Pofi, Riccardo P321
Poiana, Catalina P50, P84, P87
Poissy, Julien P371
Ponder, Bruce **RET1.1**
Ponsford, Mark James P140
Poologasundarampillai, Gowsihan OC1.3, P210
Popat, Dillon CC1, **OC5.2**, OP5.2
Portilla Pinzón, Alfredo P359
Potter, Tom **P63**, P64
Powlson, Andrew P318
Poyrazoglu, Sukran OP3.1, P16, P161
Poznansky, Mark C P353
Prabhu, Krishna P237
Pradeep, Anjali OC4.3
Prehn, Jochen S3.2
Premawardhana, Lakdasa OC7.2, P128
Prete, Alessandro **OC5.1**, P1, P162, P7
Prevot, Vincent OC4.4, P371
Priestley, Julia **NS2.3**
Pritchcard, Dylan OC5.3
Probst, Ursina P16, P161
Probst-Scheidegger, Ursina OP3.1
Proctor, Ian P125
Prouten, Jennifer CC6
Pruar, Troy P176
Przybojewski, Stefan OP8.3
Puente, Nuria P78
Purewal, Tejpal OC3.2

Qamar, Imran **P192**
Qamar, Younus P15
Qayum, Ambreen P116
Qian, Jiani OC2.4
Qin Xian Quah, Nicole P390
Quigley, Ann-Marie OC2.2
Quilang, Rachel C JA1
Quinn, Lauren **P208**
Quinn, Lauren Marie P58
Quinn, Mark P337
Quinton, Richard **OCP1.1**, P123
Qureshi, Sheharyar P256
Qureshi, Sheharyar P24, P290, P315
Radermacher, Peter P111
Radia, Florika P391

Radian, Serban P84
Radotra, Bishan D OC3.1
Radzikowski, Jakub P339
Rahim, Asad P183, P190
Rai, Ashutosh **OC3.1**, P363, P80, P82
Rai, Pareekshith **P266**
Raja, Touqeer **P177**
Rajan, Remya **P166**, P237
Rajanbabu, Anupama P247
Rajeeve, Vinothini P80
Rajesh, Mariya CC6
Rajesh, Shradha **P131**
Rajpar, Hiba **P256**, **P290**
Raju Paul, Susan P353
Rakovac, Ana P351
Ralston, Stuart P31
Ramachandran, Hari OP6.2
Ramage, Lynne E OC6.4
Ramalingam, Ramanan P227
Ramburuth, Vivek **P73**
Ranathunga, Ishara P143, P145, P252
Randell, Matthew P208
Randell, Tabitha P16, P161
Randeva, Harpal S. OC4.1
Rangan, Srinivasa P136
rani, Shuchi P72
Rasheed, Hira P373
Rashid, Rajeeb P58
Rashid, Razan Ali P247
Rasika, S P371
Rathi, Kiran **P328**
Ravat, Zahra **P355**
rayanagoudar, Girish P142
Raza, Karim P66
Raza, Mohammed Mansoor P44
Razvi, Salman OP4.3, P278
Read, Jordan P15
Read, Martin **OC2.1**, OC2.6, OC7.1
Rebekah, Grace P237
Reddy Velma, Ganga P319
Reddy, Narendra OC3.2, OC7.6, P120, P172, P173, P263
Rees, Aled **CMW1.2**, **ENS1.1**, OC4.1, P12, P127
Reeves, Patrick P353
Rehman, Abaid Ur **P23**
Reimann, Frank P204
Reimer, Kai P52
Reincke, Martin OC5.1
Reisz, Zita P366
Reng, Rifkatu P132
Rengarajan, Lakshmi P215
Renshaw, Derek P214, P59
Reyes-Alvarez, Eduardo RET2.1
Reynolds, Saira OP7.4
Rhiannon, Berkeley **P255**
Riancho, Julien OC5.1
Rice, Thomas OC3.1
Richardson, Douglas RET2.1
Richter, Alex P58
Riva, Antonio OC6.1, P207
Rix, Beatrice OP7.1
Rizos, Evangelos P286
Robb, Cara OP3.2
Roberts, Anna P61
Roberts, Gerallt OP4.4
Roberts, Rita E JA2
Robertson, Douglas **ESD1.2**
Robil, Cyril P371
Robinson, Chloe OP2.4
Robinson, Lynne OC4.1
Robinson, Robert P298
Robinson, Stephen OC7.5, P296
Robles, Juan Pablo P111
Rocha, Thais P. OC4.1
Rochester, Mark P45
Roncaroli, Federico P365
Ronchi, Cristina CC1, OC2.3, P162
Ronchi, Cristina L. P157
Ronneberger, Ruth P288
Rorsman, Patrik **MTE1.1**
Rosenthal, Miranda P121, P377
Ross, Emma P125
Ross, Richard P160
Rossi, Gian Paolo OC5.1
Rostom, Hussam OC3.4
Rowe, Matthew P159
Roy Chowdhury, Sharmistha P167, P292, P97
Roy, Noémi B A P271
Roy, Sabyasachi **P22**
RoyChowdhury, Sharmistha P99
Rubin, Katrine EC1.3
Ruent, Sigrid OC6.3
Ruggles, Oliver P157
Rui, Lee P176
Russo, Gianni P16, P161
Ruth, Katherine OP7.3
Rutter, Guy P65
Ryan, Cliona P18

Saad, Muhammad P296
Saada, Janak P45
Saada, Louis P27, P94
Saadulla, Agink **P6, P9**
Saeed, Mohamed P263
Saeed, Sadaf P209, P216, P71
Safdar, Nawaz OC3.5, P233
Safdar, Nawaz Z **OP1.3**
Sagar, Rebecca P6, P9
Sagi, Satyanarayana V P73
Sagmeister, Michael OC1.3, P210, P346, P66
Saha, Pratyusha P162, P7
Sahay, Nikita **P372**
Sahoo, Saroj **P189**, P43
Saket, Priyadarshi OC4.3
Sakthivel, Pavithra **P246**
Salem, Victoria P61
Salema, Valmiki **P331**, P338
Salerno, Maria Carolina P16
Sam, Amir P340
Sam, Amir H. OP8.4
Samarasinghe, Suhaniya P207
Sammut, Eva OC5.6
Samuel, Miny OC7.4, P284
Samuelson, Clare P8
Samyraju, Manjula P295
Sander, Kerstin OC5.3
Sandu, Andreea P87
Sankar, Adhithya **P41**
Sanpawithayakul, Kanokporn **P363**
Santhosh, Abraham P106
Santucci, Catherine P312
Saqib, Aaisha P312
Saravanan, Ponnusamy OP2.3, P212
Sarwani, Aysha **P18**
Sas, Theo C.J. OP3.1
Sathanam, Prisca P166
Sathyanarayan, Sheela **P338**
Sathyapalan, Thozhukat OC3.5, OP1.3, P108, P233, P303
Sato, Marimo P231
Sauer, Sascha OC2.3
Saunders, Philippa **P48**
Sauve, Florent P371
Sayda, Mariwan **P1**
Sbiera, Silviu OC2.3
Scawn, Richard P390
Schauer, Marc OC2.3
Schini, Marian P33
Schoenmakers, Inez OP6.1
Schoenmakers, Nadia EC1.4
Scholz, Anna **P127**
Schurmans, Stephane OP2.1
Schwaninger, Markus P371
Scotucci, Jacopo **P318**
Searell, Catrin P104, P13, P255
Sebastian, Sonia P363
Secener, Kerim OC2.3
Seejore, Khyatisha P186, P3
Sellers, Stephanie P316
Semenovykh, Dmytro **OC4.2**
Semenovykh, Kateryna OC4.2
Semple, Robert K OC6.4
Sen, Supriya P166
Seneviratne, Sumudu Nimali OP3.1
Sengupta, Shyrea OP4.4
Sennik, Devesh P96
Serban, Laura P96

Servin-Recio, Renee P319
Seshadri, Shyam P297
Shafiq, Nauman **P37**
Shafiq, Shahriar P23
Shah, Preet **P186**, **P249**
Shah, Syed OC3.2
Shah, Vikas P172, P179
Shaheen, Fozia OC4.1, **P1**
Shaikh, Sheeba **P144**, **P93**
Shakher, Jayadave P333
Shanker, Arjan **OC1.3**
Shapey, Jonathan P366
Sharif, Ariane P371
Sharma, Bhavna P170, P243, P277
Sharp, Gemma OP3.2
Sharrocks, Katie **OC3.3**
Sharrod-Cole, Hayley P378
Shaw, Jacqui OC7.6
Shawcroft, Thomas OP8.4
Shears, Debbie P271
Shears, Deborah P110
Shehzad, Muhammad Umair **P115**, **P20**, **P269**
Sheikh, Anum P391
Sheikh, Katrina P333
Sheikh, Usman P79
Shekari, Saleh S4.3
Shekhda, Kalyan P189, P43
Shekhda, Kalyan Mansukhbhai OC2.2
Shepherd, Lisa P155, P183, P190, P4
Sheridan, Bethan A P138
Sheridan, David P53
Sherlock, Mark P18
Shine, Brian P321
Shinwari, Shah Khalid OC3.2
Shipley, Alexandra **P265**
Shirgadwar, Shubhendu Madhavrao **P212**
Shirran, Sally S3.2
Shiyao, George He **OC7.4**
Shnorhavorian, Margarett P16, P261
Shoaib, Khalisah **P90**
Shortman, Robert OC5.3
Shuaibu, Ramatu **P132**
Shukla, David P58
Siddiqui, Mohammad Asim P224
Sigamani, Elanthenral P166
Silva, Mauro SB OC4.4
Silverwood, Clare P189
Simbi, Bigboy OC7.3
Simpson, Helen P17, P188, P4
Singh, Ainesh **OC7.5**
Singh, Ashish P166
Singh, Nidhi **P72**
Singh, Prashant P136
Singh, Trisha OC5.6
Singh, Vinita P121, P377
Single, Katherine P17
Sirbu, Anca P100, **P29**
Sirbu, Anca Elena P86
Sirindil, Fatih OC5.3
Sitch, Alice J. OC4.1, OC5.1
Skinner, Catherine P289
Skordilis, Kassiani P18
Skurok, Philip **P194**
Slater, Deborah P301
Sládek, Martin OC4.2
Small, Benjamin OC7.1
Smeeton, Fiona P251, P336
Smith, Alison **P67**
Smith, Bernard Rees JA5
Smith, Chris **OP5.3**, **P15**
Smith, Christopher P199
Smith, David P180
Smith, Ellen OP3.4
Smith, Karen P2
Smith, Paul **P262**
Smith, Robert **P304**
Smith, Vick P154
Smith, Vicki OC2.1, OC2.6, OC7.1
Smurthwaite, Hannah **P294**
So, Benny OP8.3, P309
Soare, Iulia **P100**
Sobti, Manvi P390
Soffientini, Ugo OP3.4
Soghal, Shamanth P215
Soh, Bennet P174
Sohail, Sara **P332**
Solanki, Sam P89
Solomon, Alexandra P215
Solomon, Andrew P274
Solomou, Antonia P363
Soong, Elaine P94
Soran, Handrean P345
Soruna, Omolayo **P175**
Soyoye, David P124
Spalding, Kirsty **S2.2**
Spivey, Alan P339
Spooner, Muirne P70
Spranger, Joachim OP8.1, P85
Spurgeon, Laura P199
Srinivas-Shankar, Upendram P40, P244
Srinivasan, Balasubramanian T **P250**
Srinivasan, Shari P18
Srinivasan, Venkataramanan P372
Srirangalingam, Umasuthan P188
Srivastava, Rajeev P138
Srnic, Nikola **OP2.2**
Stacey, Mike OP5.4
Stankovic, Stasa **S4.3**
Starbrook, Lauren P378
Stechman, Michael P140
Stedman, Michael **OC7.2**
Stedman, Mike P128
Steichen, Elisabeth OP5.3
Stepien, Karolina P78
Stergiadis, Sokratis P139
Stevenson, Mark OC1.2
Stewart, Sarah OP5.3
Stian Knappskog, Halfdan Sorbye JA4
Stimson, Roland H OC6.4
Stirling, Claire **P135**
Stoneham, Sara P125, P276
Storme, Laurent P371
Strasburger, Christian P85
Strasburger, Christian J OP8.1
Su Khin, Kyaw Linn **P38**
Subbiah, Kasi **P329**
Suchacki, Karla J OC6.4
Sudarshanan, Aditya P149, P181, P28, P299
Sugathan, Navin **P228**
Sule, Zakary **P23**
Suleiman, Mara P65
Suleyman, Oniz OC3.1
Sultana, Shakila P218
Sumová, Alena OC4.2
Sunassee, Kavitha OC2.1, OC7.1
Sundlöv, Anna JA4
Suntornlohanakul, Onnicha OC5.1, P162, **P7**
Surendran, Aarthi **P357**
Sureshkumar, Sumetha OC4.6, OP3.3
Sutcliffe, Robert CC1
Svec, Frantisek P158
Svingen, Terje OP3.4
Swapnil, Asif Mahbub **P374**
Swarbrick, Katherine OP7.1
Swedrowska, Magda OC4.4
Swinton, Paul OC1.1
Swords, Francesca P94
Syed, Akheel P345
Syed, Akheel A P286
Syed, Ateeq P355
Syed, Zubair UL Hassan P79
Sylvia, Lui JA1
Syme, Harriet OC7.3

Tabasum, Maria **P244**, **P40**
Tailor, Aishwariya **P57**
Taiwo-Ola, Dorcas **P341**, **P347**
Talaulikar, Vikram P116, P117
Talbi, Neila OP5.3
Talla, Maria P326
Talwar, Divreena P264

Tam, Joseph OC2.4
Tam, Trevor P118, **P27**, **P94**
Tan, Garry OC6.6, P53
Tan, Lok Yi Joyce P98
Tan, Qinyuan P52
Tan, Tricia OP4.1, P169, P17, P184, P243, P26
Tandl, Veronika OC4.1
Tang, Jonathan OC1.1, **P31**
Tang, Meng-Xing P213, P259, P52
Tao, Yuxuan P61, P68
Taqi, Muhammad P253, **P303**
Taracatac, Paolo **P202**
Tarigopula, Giridhar P245
Tarr, Charlotte P364
Tauni, Rahat P356
Tavoukjian, Vera **P201**
Taylor, Angela P1, P5
Taylor, Angela E. OC4.1, OC5.1
Taylor, Carla G. P218
Taylor, Peter OC7.2, P127, **P128**, P140
Teli, Vaishali P349
Tellier, Genevieve **P104**, **P13**, P255
Ternier, Gaetan OC4.4, P371
Tetti, Martina OC5.1
Thakali, Sonu P337
Thakkar, Simran **P224**, **P266**
Thakker, Rajesh OC1.2, OC1.4
Than Yu, Kyi Pyar **P370**
Thanda, Hnin P335
Thangaratinam, Shakila CC1
Thankamony, Ajay P161
Thant, Aye Aye **P187**
Thatcher, Gregory P319
Thayaparan, Kunaratnam P77
Thayyil, Sheena **CC6**
Theodoridou, Katerina P139
Theran, Juan P323, P342, P376, P385
Thirkettle, Sally CC5, P171
Thomas, Anu P209, **P216**, P71
Thomas, Julia P304
Thomas, Nick P366
Thomas, Nihal P166, P237
Thomas, Shawn P166
Thomas, Tessy P16
Thornton, Caitlin OC7.1
Thottungal, Kevin P209, P216, P71
Thulaseedharan Pillai, Rakesh P77
Thurston, Layla OC4.4, **P277**
Timamy, Abdulmalik P197
Timmers, Henri J.L.M. OC5.1
Tinker, Andrew P363
Tino, Peter OC5.1
Tipping, William P206
Tiwari, Swasti P72
Todd, Diane P102
Toledo-rodriguez, Maria P262
Tolley, Neil OC7.5, OP4.1
Toma, Iustin P50
Toma, Iustin-Daniel **P84**
Tomlinson, Jeremy **HDI1.4**, P12, P265, P53, P56, P63, P64
Tomlinson, Jeremy W OP3.1
Toogood, Andrew P151, P246
Topping, Anne Elizabeth P151
Tough, Jillian P133
Toumpanakis, Christos OC2.2
Tourigny, David **OC2.3**
Touska, Philip OP7.2
Tran, Hanh OC4.6
Tresoldi, Alberto OC3.5, OP1.3, P233
Triebel, Jakob **P111**
Trifanescu, Oana P50
Trifanescu, Raluca **P50**, P84
Trinh, Mi EC1.4
Tripathi, Gyanendra P219
Tripathi, Manjul OC3.1, P82
Trojani, Giampaolo OP8.4
Trottein, FranÓois P371
Truong, Vi **P301**
Truran, Peter P21
Tsatsanis, Christos JA3
Tseretopoulou, Xanthippi **P16, P161**
Tsoutsouki, Jovanna **P267, P322**
Tun, HayMar P209, P216, P71
Tun, Nyo Nyo P395
Turcu, Adina **MTE6.1**
Turki, Mohanad P241
Turner, Helen **P112**, P154, P265, **P279**, P282
Turner, Helen E OP3.1, P110, P271
Turner, Jeremy P191
Turner, Mark **P214**, P59
Tuthill, Antoinette OC1.2
Twyman, Frazer OC5.3
Tymms, James P41
Tyrrell, Jess **S2.3**
Tzanela, Marinella P306
Tzanninis, Stamatios **P383**
Tzoulis, Ploutarchos P225

U-King-IM, Jean-Marie P366
Ubani, Kelechi P347
Uddin, Mohammad P106
Uddin, Mohammad Salah **P253**
Udo, Chinyere P275
Uduku, Chukwuma P146
Ul-Hassan, Fahim P338
Ul-Hassan, Naeem P183
Ullah, Hafiz Zubair OC3.2
Umer, Reham P73
Upton, Thomas **OP1.4**
Urwyler, Sandrine OC3.5, OP1.3, P233
Usman, Khwaja Mohammed P224

Vaidya, Bijay OP7.3
Vainieri, Erika P245
Valine, Laura P353
Vamvakopoulos, Joannis OC3.2
van Beek, Edwin JR OC6.4
van den Akker, Erica P161
van der Kamp, Hetty P161
van Eck, Judith P16, P161
van Faassen, Martijn OP1.4
van Waes, Charlotte OC1.2
Vanka, Ramesh P335
Vankayalapati, Praveena **P24**, **P315**, **P397**
Varadhan, Lakshminarayanan P131
Varela-Carver, Anabel P319
Veen, Roland J. OC4.1
Vegesna, Ram PV P73
Velusamy, Anand OP7.2, P312, P337, P338
Venizelos, Andreas JA4
Vento-Tormo, Roser EC1.4
Venu, Maya P307
Venugopalprabhu, Vimal P374
Vie, Clotilde P213
Vieites, Ana P16, P161
Vignola, Maria Lillina P363
Vinogradova, Yana P116
Viola, Juilianne P339
Virdee, Simran **P164**
Visser, Jenny P63
Viswanath, Aditya **P179**
Vlachopapadopoulou, Elpis P16
Von Kriegsheim, Alex P352
Vradi, Eleni OC4.1
Vryza, Paraskevi **P286**

Waddell, Tom P93
Wadsley, Jonathan P280
Wadsworth, Charles P6
Waheed, Unaiza P345
Wahid, Alam **P191**
Wai Kit, Clement Wong **P176**
Wakelin, Sonia J OC6.4
Walker, Abigail **OC4.5**
Walker, Brian OC5.6
Walker, Catherine OP3.2
Walker, Leanne P171
Walker, Tim RET2.1
Waller, Christiane P111
Walls, Risheka **OP8.4**
Walsh, Jennie **HDI2.4**
Walsh, Neil OC1.1
Wang, Aurora OP8.4

Wang, Vera OC5.4
Wang, Weiguang OC7.1
Wang, Wenya P207
Wang, Xian **OC3.6**
Wang, Yuqin P360
Wangnoo, Subash Kumar P224
Ward, Emma P249
Warner-Levy, John P230
Wasniewska, Malgorzata P16
Wasniewska, Malgorzata G P161
Wass, John **ENS7.4**
Watson, Wendy P310
Watters, Marianne **OP3.2**
Webb, Emma OP6.2
Webster, Craig P324
Webster, Scott OC5.6
Weekes, Joanne P394
Wei, Deng JA4
Went, Richard P95
Wernig, Florian **CC7**, OC7.5, P17, P170, P245, P277, P81
West, Courtney **OP7.3**
Westcott, Felix **P205**
Whilding, Chad P65
White, Ann P171
White, Anna P133
White, Gemma **P337**
White, Katherine **P152**
White, Thomas OP8.4
Whitelaw, Ben **P366**
Whitelaw, Benjamin C OP7.1
Whittaker, Andrew OC5.6
Whyte, Martin P230
Wiggam, Ivan OP4.4
Wijewickrama, Piyumi **P188**
Williams, Bryan OC5.3
Wilton, Anthony P104, P13, P255
Wiltshire, Ryan P345
Winfield, Jessica P190
Winkler, Mathias OC2.4
Wirestrand, Elin JA3
Wiselka, Martin P173
Witczak, Justyna Karolina OP3.1
Withers, Dominic P65
Wittemans, Laura B. L. OC4.1
Wong, Anson **P246**
Wong, Kee P125
Wong, Kee Howe P381
Wood, Ffion P104, P13, P255
Woods, David OP5.4
Woodside, Jayne P139, P285
Work, Lorraine OC5.5
Working group, DEKODE P215
Wragg, Andrew P175
Wren, Alison **P390**
Wright, Josh P8
Wright, Michael P123
Wu, Xilin P320
Wunna, Wunna OC3.2
Wyatt, Rachael P157
Xu, Ruijuan **OC4.6**
Xu, Ruoyan OC5.2, OP5.2
Xu, Yiwang OC2.2

Yan, Jipeng P213, P259
Yan, Tianhai P139
Yang, Jun OC5.4
Yang, Li JA5
Yang, Lisa CC7, OC4.4
Yang, Qian P67
Yang, Wei **OP4.1**, P243
Yap, Pui San P153, **P163**
Yee, Sharlei P115, **P20**, P269
Yi Rong, Eugene Tan P284
Yin, Win Lei **P140**
Yin, Yin **P373**
Yong, Fiona P65
Young, Elaine P35
Young, Megan P267, OC5.4
Younis, Awais **OC6.2**, P211
Yousaf, Saira P141, **P392**
Youssef, Jozef P339
Yousseif, Ahmed P121, P165, P189, P308, P377, P43
Yu, Christina P296
Yu, Dominic OC2.2
Yu, Thinn P175
Yu, Vanessa P65
Yuldasheva, Nadira OP2.1
Yutuc, Eylan P360

Zafar, Sadia **P99**
Zafar, Sadia **P97**
Zahradka, Peter P218
Zaki, Beenish P331
Zaman, Sajnin P23, **P263**, **P374**
Zamora, Magdalena P111
Zarén, Peter JA3
Zarif, Nadia P232, P383
Zavala, Eder OP1.4
Zdravkovic, Dragan P345
Zeitoon, Sa′ed P272, P273
Zelinska, Natalia P16
Zennaro, Maria-Christina OC5.1
Zha, Ling OC2.1, OC2.6, OC7.1
Zhang, Jiabai P204
Zhou, Zijing P344
Zou, Zhiyong OP2.3, P212
Zubair Ullah, Hafiz Muhammad **P310**, **P327**
Zuckerman, Benjamin P312

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