Society for Endocrinology

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THE ENDOCRINOLOGIST

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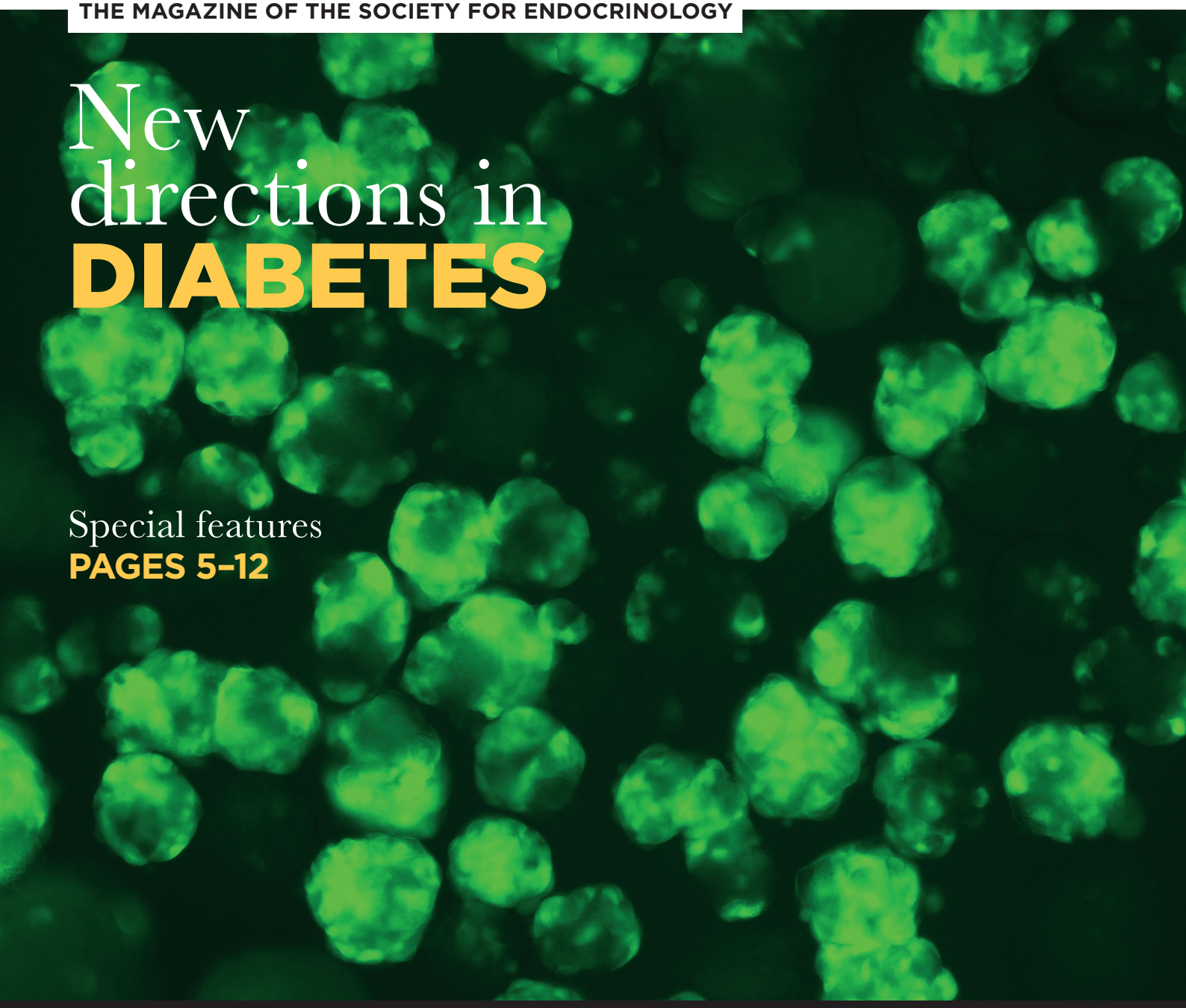

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A word from THE EDITOR...

It is my pleasure to introduce the spring issue of *The Endocrinologist*. It's a bittersweet moment (if you'll pardon the pun, in this diabetes-themed magazine!), as it is my last as Editor, and also the final one for Associate Editor Craig Doig. But fear not! Craig and I have provided a lasting legacy of **our highlights from our time at *The Endocrinologist*.**

As I mentioned, this issue is packed with diabetes-themed articles, as well as interviews and Society news. Our breadth of articles on diabetes management includes **Harshal Deshmukh's useful update** on continuous glucose monitoring methods and integration with hybrid closed-loop systems, along with their important adoption into NICE guidelines and roll out into NHS practice. Researchers at the University of Leeds provide an overview of the use of glucose monitoring and **management of diabetes during pregnancy.** They give an insight into the exciting area of research that they are undertaking, which has demonstrated that the cargo of small, secreted vesicles (extracellular vesicles) is altered in pregnancies affected by gestational diabetes. Understanding how these changes in cellular communication impact pathogenesis and long-term outcomes in child health is an important area of research. I look forward to seeing it progress over the coming years.

This spring saw the long-awaited return of the **Society for Endocrinology BES conference,** after an 18-month hiatus to reset its timing from the autumn. And what a corker it was! It was great to catch up with friends and colleagues and listen to the outstanding scientific achievements of our presenters.

It's at this point that I must sign off for the last time. It's been a pleasure and privilege to be part of *The Endocrinologist* team. I'd like to thank everyone who has contributed to the magazine – Board members, authors, and a special thanks to our Managing Editor, Jane Shepley, who steers us well. I am pleased to be leaving *The Endocrinologist* in great hands, with the current Editorial Board line-up and new incoming Editor Kate Lines, supported by Associate Editor Bhavna Sharma. I'm looking forward to reading future issues.

Over and out.

KIM JONAS

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Become a contributor...

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The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the SUMMER 2025 issue: **21 April 2025**.

Front cover image: Cryopreserved islets (see Hibbert *et al.* on **PAGE 6**)

HOT TOPICS

Hot Topics is written by Victoria Chatzimavridou-Grigoriadou, Craig Doig, Zin Htut, Edouard Mills, Gareth Nye, Bhavna Sharma and Vincent Simpson

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the **Members' Area of the Society website**. *Endocrine Connections*, *Endocrinology, Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.

JOURNAL OF ENDOCRINOLOGY

GLP-1R/NPY2R and reproductive function in mice fed a high-fat diet

A proportion of women with polycystic ovary syndrome (PCOS) are overweight or obese. PCOS affects 5–20% of women of reproductive age, and is characterised by anovulation, menstrual irregularities, insulin resistance and hyperandrogenism.

In this study, Khan *et al.* investigated the effects of exendin-4 (Ex-4) and peptide YY (PYY) on reproductive function in mice fed a high-fat diet (HFD). Both peptides reduced blood glucose and energy intake without affecting body weight. Ex-4 increased the frequency of metoestrus and decreased that of dioestrus, eliminating repeated dioestrus and acyclicity in treated mice. Luteinising hormone levels were elevated in both Ex-4 and PYY groups, compared with controls. Changes in adrenal morphology induced by the HFD, such as reduced capsule and zona glomerulosa thickness, were reversed by peptide treatments.

In the ovaries, the HFD increased atretic follicles, an effect that was mitigated by Ex-4 and PYY. Ex-4 also enhanced the formation of corpora lutea due to prolonged metoestrus. Gene expression analysis revealed altered insulin receptor and progesterone receptor expression in the adrenals, with Ex-4 downregulating the glucagon-like peptide-1 receptor (GLP-1R), and PYY affecting *Prgtr* expression in both the adrenals and the ovaries.

These findings suggest that modulating GLP-1R and neuropeptide Y2 receptor (NPY2R) can influence reproductive physiology, with potential direct effects on ovarian and adrenal function in female mice.

Read the full article in *Journal of Endocrinology* **264** e240189
https://doi.org/10.1530/JOE-24-0189

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Glucocorticoids reduce GLUT2 expression in pancreatic β-cells

Glucose transporter type 2 (GLUT2) is a well known cellular component responsible for glucose-stimulated insulin secretion within pancreatic β-cells. Low levels of this transporter are linked to development of type 2 diabetes, and it is known that glucocorticoids are involved in pancreatic β-cell destruction. However, the link between the two has not yet been uncovered.

Ono and Kataoka investigated the role of hepatocyte nuclear factor-1 (HNF1), a transcription factor normally seen regulating gene activity in the liver and pancreas, among others, in linking glucocorticoid usage and GLUT2 reduction. Using a comprehensive *in vitro* approach, they clearly demonstrated that mRNA expression of the gene responsible for GLUT2 proteins (*Slc2a2*) is reduced by the application of dexamethasone in glucose-responsive cells, and that this repression is solely due to HNF1α or HNF1β.

This study opens up the potential for understanding the progression of type 2 diabetes in some patients, whilst also providing new evidence for future studies in the area.

Read the full article in *Journal of Molecular Endocrinology* **74** e240077
https://doi.org/10.1530/JME-24-0077

ENDOCRINE-RELATED CANCER

More than a mutation: lessons from living with MEN2

While multiple endocrine neoplasia type 2 (MEN2) is well understood at a genetic level, its real-world impact on patients and families is often overlooked. In this mini-review, Brain *et al.* go beyond molecular mechanisms to explore the lived experiences of patients with MEN2A/B through four case studies.

They highlight the critical role of RET genetic screening, along with calcitonin monitoring, in enabling early diagnosis and intervention, while also revealing challenges in cascade testing, particularly in non-nuclear families. They illustrate how genotype–phenotype correlations are not always predictive, with unexpectedly aggressive cases requiring additional genetic testing, and discuss how gastrointestinal symptoms in infancy can signal MEN2B, prompting early thyroidectomy to prevent metastatic disease.

The study also underscores the under-appreciated psychosocial burden of MEN2, including anxiety, uncertainty and lifelong monitoring. Parents describe the challenges of navigating a rare, hereditary cancer syndrome, emphasising the need for holistic, patient-centred care. The case studies reinforce the need for specialist expertise in managing both medical and psychological aspects of the disease.

Overall, this review highlights the importance of addressing not just the medical complexities of MEN2, but also its impact on quality of life, offering useful insights for healthcare professionals working with hereditary endocrine disorders.

Read the full article in *Endocrine-Related Cancer* **32** e240130
https://doi.org/10.1530/ERC-24-0130


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CONTINUED ON PAGE 4

CONTINUED FROM **PAGE 3**

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CLINICAL ENDOCRINOLOGY

Higher risk of incident diabetes in primary hyperparathyroidism

Previous studies have suggested an increased prevalence of diabetes in patients with primary hyperparathyroidism (PHPT). Potential mechanisms include hypercalcaemia-related insulin resistance and decreased insulin sensitivity due to 1,25-dihydroxyvitamin D deficiency.

To characterise the association further, Zhang *et al.* undertook a population-based retrospective cohort study involving 2,749 patients with PHPT and 13,745 age-, sex- and index year-matched individuals without PHPT. In their series between 2000 and 2019, patients with PHPT had 15% higher risk of incident diabetes compared with matched individuals without PHPT. In patients with PHPT, a 44% higher risk of incident diabetes was found in subjects with serum calcium concentrations above the median value (2.63mmol/l), compared to those with levels below the median value. Amongst patients with PHPT, there was a positive linear relationship between serum calcium concentration and the risk of incident diabetes.

Based on these findings, the authors demonstrate that patients with PHPT have a higher risk of incident diabetes compared with individuals without PHPT. Hence, they advise regular screening for dysglycaemia in patients with PHPT.

Read the full article in *Clinical Endocrinology* **101** 605–613
https://doi.org/10.1111/cen.15118

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Palmoplantar keratoderma – a rare complication of type 2 diabetes

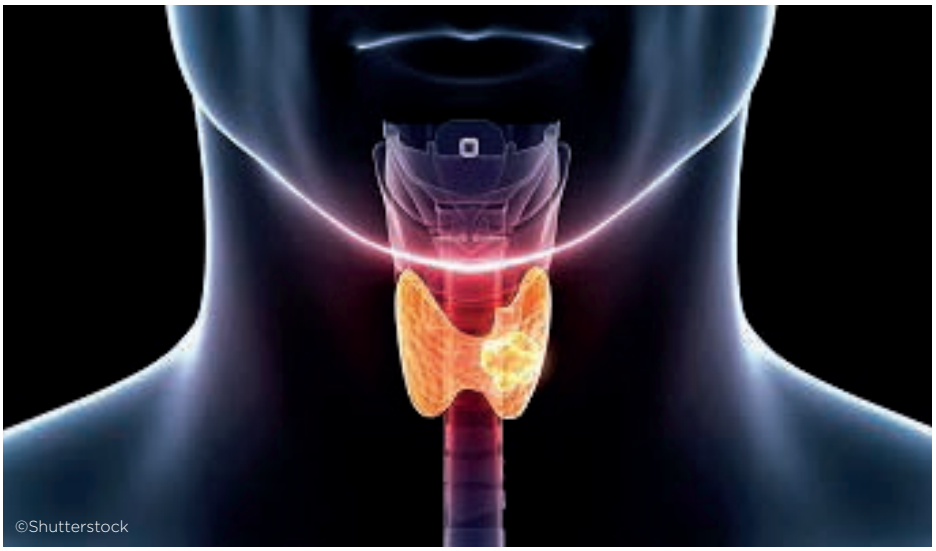
Acquired palmoplantar keratoderma (PPK) is a rare dermatologic condition associated with systemic diseases, including uncontrolled diabetes mellitus.

Iqbal *et al.* report the case of a 53-year-old woman with suboptimally controlled type 2 diabetes who presented with diabetic ketoacidosis (DKA; glucose 40mmol/l, ketones 7mmol/l) and septic shock, secondary to a methicillin-sensitive *Staphylococcus aureus* necrotising soft tissue infection. Her history included intellectual impairment and long-standing, poorly controlled diabetes managed with insulin. On examination, she was found to have severe plantar keratoderma and onychogryphosis, which had progressively worsened over 2 years. Glycated haemoglobin was raised (10.4%, 90 mmol/mol) with negative diabetes antibodies (anti-insulin and anti-glutamic acid decarboxylase), consistent with poorly controlled type 2 diabetes. Magnetic resonance imaging confirmed a necrotising back wound, which was managed with i.v. antibiotics and debridement.

She was managed for DKA and switched to twice-daily mixed insulin and metformin on discharge. For her PPK, she was prescribed 40% urea cream, resulting in gradual improvement. This case highlights the importance of regular dermatologic assessments in diabetes care to detect and manage rare complications such as PPK.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports*
EDM-24-0088 https://doi.org/10.1530/EDM-24-0088

ENDOCRINE CONNECTIONS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Thyroid disorders and type 2 diabetes: do we need to screen?

This long cohort study, conducted over a decade, studied the relationship between thyroid disorders and type 2 diabetes in Germany. Sarabhai and Kostev compared more than 150,000 patients who had thyroid disorders with matching controls, making this a sizeable study.

The study provides novel insights into the complex bidirectional relationship between thyroid dysfunction and type 2 diabetes. The authors highlight the importance of metabolic monitoring, age-specific screening and preventive strategies in patients with thyroid disorders for primary prevention of type 2 diabetes.

This work has the potential to impact local practice, making it an interesting read for everyone.

Read the full article in *Endocrine Connections* **14**
e240554 https://doi.org/10.1530/EC-24-0554

ENDOCRINE ONCOLOGY

Rare bladder paraganglioma treated with robotic surgery

Bladder paragangliomas are exceptionally rare neuroendocrine tumours, accounting for just 0.05% of all bladder cancers, often resulting in delayed diagnosis.

Shekhda *et al.* present the case of a 36-year-old woman with a 10-year history of post-micturition palpitations, headaches and episodic hypertension. Biochemical tests revealed elevated urinary normetanephrines, and imaging identified a ^{123}I-MIBG-avid bladder mass, which, interestingly, was non-avid on ^{68}Ga-DOTATATE positron emission tomography/computed tomography. She was optimised with preoperative alpha-blockade, and underwent a successful robotic partial cystectomy without complications.

This case highlights the importance of early recognition of bladder paragangliomas in patients with unexplained post-micturition symptoms. A multimodal imaging approach is crucial for precise localisation, while preoperative alpha-blockade remains essential to prevent intraoperative hypertensive crises. The successful outcome also highlights the value of a multidisciplinary team – including expertise in endocrinology, urology, radiology and pathology – in ensuring optimal management. Although no genetic mutations were identified, ongoing surveillance is vital, due to the potential risk of recurrence.

As awareness increases, this case emphasises the need to refine diagnostic strategies and perioperative protocols for these rare, but clinically significant, tumours.

Read the full article in *Endocrine Oncology* **5** e240044
https://doi.org/10.1530/EO-24-0044

GETTING IN THE LOOP: REVOLUTIONISING DIABETES CARE WITH CGM AND HYBRID CLOSED-LOOP SYSTEMS

WRITTEN BY HARSHAL DESHMUKH

Continuous glucose monitoring (CGM) has transformed the landscape of diabetes care, providing patients and clinicians with unprecedented insights into glucose dynamics. From its early days as a supplementary monitoring tool, CGM has evolved into a cornerstone of advanced diabetes management, particularly with its integration into hybrid closed-loop (HCL) systems. This evolution, coupled with new NICE guidelines on adoption of HCL systems,[1] signals a paradigm shift in the treatment of type 1 diabetes, paving the way for a more automated and personalised approach.

TRANSFORMING DIABETES MANAGEMENT WITH CGM

CGM technology continuously measures interstitial glucose levels, providing real-time feedback on trends and variability. Data from the Association of British Clinical Diabetologists audit show that patients using CGM experience improved glycaemic outcomes, reduced episodes of hypoglycaemia, and better quality of life.[2] This innovation has shifted the focus from static glycaemic control metrics, such as glycated haemoglobin (HbA1c), to dynamic measures, such as time-in-range[3] and time-below-range[4] glycaemic variability, which better reflect daily glucose patterns. Furthermore, CGM data empower clinicians to personalise interventions by identifying patterns that traditional methods of self-monitoring of blood glucose often miss.

HYBRID CLOSED-LOOP SYSTEMS: THE NEXT FRONTIER

The real-world data from the NHS England closed-loop pilot[5] have shown us that HCL systems are associated with improvements in HbA1c, time-in-range, hypoglycaemia, diabetes-related distress and quality of life in people with type 1 diabetes. The NICE Technology Appraisal Guidance TA943[1] (published 19 December 2023) recommends the use of HCL systems for managing blood glucose levels in adults, children and young people with type 1 diabetes.

These systems are suitable for individuals with an HbA1c of 58mmol/mol (7.5%) or higher, or those experiencing disabling hypoglycaemia despite optimal management using continuous subcutaneous insulin infusion or CGM. HCL systems are also recommended for pregnant individuals or those planning pregnancy. However, their use is contingent on being procured at a cost-effective price, as agreed by NHS England, and must follow the NHS implementation plan. The systems should be used with the support of a trained multidisciplinary team and only by individuals or carers capable of using them, with access to structured education programmes.

CHALLENGES AND FUTURE DIRECTIONS

Despite their benefits, CGM and HCL systems face barriers to widespread adoption. Cost remains a significant limitation, particularly in resource-limited settings. While initiatives such as the NHS provide subsidised access, global efforts are needed to ensure equitable availability. Education is another critical factor. For many patients, the wealth of data generated by CGM can be overwhelming. Structured education programmes are essential to help users interpret and act on CGM data effectively, maximising its potential. Finally, clinicians must navigate the learning curve associated with these advanced systems. Integrating CGM and HCL systems into practice requires familiarity with the technology and its implications for patient care.

CONCLUSION

CGM, particularly when integrated into HCL systems, has revolutionised diabetes care, marking a transformative shift comparable with the discovery of insulin. The recent NICE guidelines signify a critical milestone, providing a robust framework for the widespread adoption of HCL systems.

However, as we advance this new standard of care, it is imperative to address challenges related to accessibility, ensuring these ground-breaking technologies are available to all individuals, regardless of socioeconomic status or geographical location. By fostering innovation, promoting education, and championing equitable access, we can unlock the full potential of CGM and HCL systems, significantly enhancing quality of life for people living with diabetes.

HARSHAL DESHMUKH
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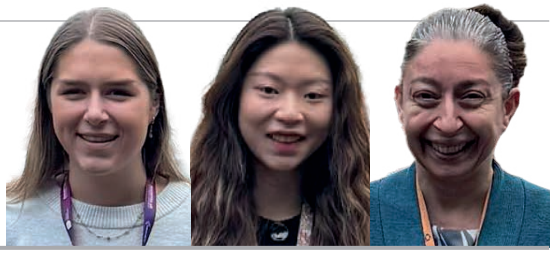
THE UK'S ROLE IN THE FUTURE OF THERAPY FOR TYPE 1 DIABETES

WRITTEN BY JESSICA E HIBBERT, JUNYUE HUANG AND ILDEM AKERMAN



Diabetes was first recorded in the 5th century BCE, recognised by the characteristic 'sweet urine' of affected individuals. However, it wasn't until 1922 that the discovery of exogenous insulin transformed type 1 diabetes (T1D) from a fatal diagnosis into a manageable condition.[1] More than a century later, we now understand that the disease is driven by an autoimmune attack on pancreatic β-cells, leading to the loss of endogenous insulin and the lifelong need for insulin replacement.

Today, approximately 400,000 people in the UK live with T1D,[2] and its incidence continues to rise. While insulin therapy has evolved far beyond the days of cow pancreas-derived insulin and urine dipsticks, people living with T1D remain entirely dependent on exogenous insulin for blood glucose control. Yet, insulin's narrow therapeutic window presents challenges: fluctuations in blood sugar levels increase the risk of both hypoglycaemia and hyperglycaemia, contributing to serious complications, such as retinopathy and neuropathy,[3] highlighting the urgent need for alternative therapies.

NOVEL APPROACHES TO MANAGEMENT

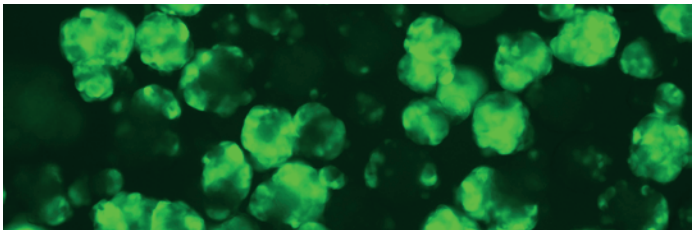
Preventative strategies have shown promise: teplizumab, a drug approved by the US Food and Drug Administration, is able to delay the onset of T1D by up to three years.[4] However, preventative drugs must be administered during T1D onset, limiting their use to those still within the 'honeymoon period' post-diagnosis.

For others living with T1D, replacing lost β-cells presents a potential solution to eliminate insulin dependence and its associated risks. In 2000, islet transplantation gained traction when James Shapiro's team improved outcomes using steroid-free immunosuppression.[5] However, donor shortages remain a challenge.

In the last decade, cell-replacement therapies that use stem cell-derived islets (SC-islets) have become a reality. Notably, Douglas Melton and Timothy Kieffer's teams independently pioneered protocols to generate insulin-responsive β-cells *in vitro*. Melton's protocol was commercialised, with the refined cells used in Vertex's clinical trials: VX-880, which delivers SC-islets via hepatic infusion with ongoing immunosuppression, and VX-264, which uses an encapsulation device to protect transplanted SC-islets from immune attack.[6,7] Justifiably, Melton, a father of two children living with T1D, was named one of *Time* magazine's 100 most influential people in 2009.

Yet, significant challenges remain for cell-replacement therapies. How can we reliably generate these cells at a scale that can help thousands? How can we protect them from the immune system? How do we ensure that they can integrate into the body and efficiently vascularise?

Cryopreserved SC-islets produced by BetaCell Birmingham display insulin promoter-driven green fluorescent protein expression.



Addressing these challenges will require integration of cell engineering, immunomodulation, vascularisation and encapsulation, needing collaboration from specialists across the breadth of UK scientific research. Non-specialised laboratories face significant challenges in generating quality-controlled SC-islets, due to the labour-intensive nature of these protocols and a lack of the specialised expertise that is required.

PROGRESS IN THE UK

Across the pond, Canada and the USA lead cell-replacement therapies for T1D. Despite its powerhouse status in research, the UK is somewhat falling behind. Nevertheless, there is much reason to remain optimistic. In the past decade, Francesca Spagnoli and Rocio Sancho's teams at King's College London pioneered the production of SC-islets in the UK. This was soon followed by the Akerman lab, and the establishment of BetaCell Birmingham, an academic facility that aims to produce SC-islets for UK researchers, enabling them to overcome the fundamental barriers faced by cell-replacement therapies.

BetaCell Birmingham is already shaping the landscape of cell-replacement therapies in the UK, through its strategic interdisciplinary collaborations with bioengineers and islet biologists at Imperial College London and Oxford University. Having developed its own 3D organoid protocol, BetaCell Birmingham is now set to produce up to 10 billion SC-islets simultaneously with the purchase of a new bioreactor funded by **NC3Rs (National Centre for the Replacement, Refinement and Reduction of Animals in Research)**, aiming to position UK researchers on a par with their North American peers.

What's next for the UK? Vertex has already invested $0.5 billion in its cell-replacement therapies – a sum that will need to be recouped within the lifespan of its intellectual property (IP) licence. Can the NHS afford to cover the cost of cell-replacement therapy? Unless Wes Streeting performs a miracle, the UK will need to step up and produce its own SC-islets, either by patenting new technology, or by swiftly acquiring the capacity to produce SC-islets once they become 'generic medicine', following the expiration of IP. This is no easy feat, as the cells must comply with all relevant guidelines while being produced at a large scale – trillions at a time – something that is currently only achievable at a single Catapult facility in the UK.

Thankfully, the Steve Morgan Foundation has recently given the T1D therapy field in the UK a much-needed boost with a £50 million injection. Let's hope this enables more UK researchers to study SC-islets, sparks more patents in the field, and supports the UK's capacity to supply SC-islets for the NHS when the time comes…

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MANAGING DIABETES FOOT: STEPS TOWARDS A BETTER FUTURE

WRITTEN BY WING MAY KONG

Over my career, diabetes foot disease has evolved from a 'Cinderella' subject to a subspecialty in diabetes and endocrinology. This increased recognition is long overdue. The cost of managing foot ulcers in diabetes has been estimated at £1 billion annually in England alone,[1] and accounts for 450,000–900,000 hospital bed days per year.[2]

Among the thousands of amputations performed each year, the five-year mortality following major amputation is over 70%.[3] A longitudinal study found a hazard ratio for death of 2.2 post-amputation, after adjusting for known risk factors, including cardiovascular disease, chronic kidney disease and co-morbidities.[4]

While much of the focus has been on amputation rates, the impact of foot ulcers is often neglected. The five-year mortality for someone with a diabetes foot ulcer is greater than for most major cancers.[5] Most of us are aware that diabetes is associated with a higher mortality rate. However, a recent study of 12,000 people with type 2 diabetes in Salford, UK, found that most of this excess mortality was amongst those with a history of diabetes foot disease, with a standardised mortality ratio (adjusted for deprivation) of 1.13 for those with no history of a foot ulcer, compared to 2.6 for those with a history of foot ulceration.[6]

When looking at these stark population data, it can be easy to forget the huge impact on the person living with a diabetes foot complication. Having a diabetes foot ulcer is associated with a lower quality of life than being on haemodialysis or having a diabetes macrovascular complication.[6] Foot ulcer management carries the burden of frequent clinic visits and restrictions on activity and work, which in turn create financial insecurity, loss of self confidence, and stress, as well as the stigma of a chronic wound and anxiety about amputation.

THE UNDERLYING BIOLOGY

Our feet are amazing pieces of engineering, with 26 bones, 30 joints and over 100 muscles, tendons and ligaments maintained by a sophisticated vasculature. The foot is an ecosystem of interconnected anatomy and physiology that maintains foot health and allows most of us to take our feet for granted. Infected foot wounds need 5–10 times more blood flow than intact skin. Diabetes neuropathy not only leads to loss of protective pain sensation, it also disrupts the autonomic autoregulation of arteries and capillary beds. This, combined with macrovascular disease, means infection and necrosis can establish rapidly.

ADVANCES IN MANAGEMENT

There have been major advances in our approach to diabetes foot disease. Osteomyelitis is recognised as an important cause of chronic foot ulcers and amputation, which can often be treated successfully with targeted antibiotics.[7] Tibial angioplasty and stenting are commonplace, with high success rates, and developments in offloading and orthopaedic reconstruction are able to address ulcers secondary to foot deformity, including Charcot's. However, major variation in foot outcomes persists. Between 2018 and 2021 there was a fourfold variation in major amputations and an eightfold variation in minor amputations across Clinical Commissioning Groups in England.[8]

The National Diabetes Foot Care Audit (NDFA) has shown that seamless integration of foot services with strong collaborative relationships across community and hospital teams significantly improve outcomes for people with foot complications.[2] These data are supported by a recent analysis of clinical negligence claims for diabetes foot complications.[9] Sadly, overstretched budgets and current commissioning arrangements mean such integration and collaboration are becoming increasingly difficult.

IMPROVING DATA COLLECTION

High-quality data are essential to improving outcomes. However, we still do not even know how many people have foot ulcers. Case ascertainment for the NDFA remains low and this will continue to be a problem while data collection remains manual.

Counting foot ulcers presents challenges, with individual patients often having multiple ulcers – some healing, some relapsing. However, the real challenge is making foot disease a sufficient priority, so that the resources are found to create the foot templates in our electronic patient records, and the algorithms to count ulcers reliably from these data.

AVOIDING STIGMA IS IMPORTANT

Foot complications happen because the ecosystem has failed. Yet healthcare professionals often criticise the individual for not taking better care, wearing the wrong shoes or simply walking too much. For many, taking sick leave is not an option, and resting their foot would mean income or even job loss. Wanting to take your grandchildren to the park should not be equated with not caring about one's health.

The stigma and judgement projected by health professionals are internalised by patients. However, the huge regional variations in foot outcomes show that it is our healthcare structures and ourselves, as health professionals, that need to do better. The Language Matters movement[10] has made huge strides in changing the way health professionals think and talk about diabetes, and is a must for all doctors working in diabetes.

The burden of diabetes foot disease remains too high. High-quality research and innovation are essential, but we need to be much smarter in collecting and using data, with strong leadership at local and national levels, to ensure integration of foot services across community and secondary care. We need to recognise the huge individual burden of diabetes foot disease, and ensure we respond with kindness and empathy.

WING MAY KONG
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UNDERSTANDING EARLY-ONSET TYPE 2 DIABETES

WRITTEN BY SHIVANI MISRA

Type 2 diabetes has typically been a condition affecting middle-aged or older adults. In recent years, however, there has been an increase in younger people presenting with type 2 diabetes. Early-onset type 2 diabetes is associated with a faster progression to microvascular[1] and macrovascular[2] complications than later-onset type 2 diabetes, and has a significantly reduced life expectancy.[3]

EPIDEMIOLOGY

The term early-onset type 2 diabetes is defined as a diagnosis at under 40 years of age. It includes children and adolescents, though younger adults, aged 18–39 years, account for most cases.[4]

The English National Diabetes Audit (NDA) has found approximately 150,000 people currently living with early-onset type 2 diabetes in England. In the last five years, there has been an increase of about 18% in the cross-sectional prevalence of type 2 diabetes in those aged under 40 years, compared with an 11% increase in older age groups. Although the incidence of early-onset type 2 diabetes is still comparatively low compared with typical, older-onset type 2 diabetes, this rapid increase (observed both in the UK and globally) is concerning.[4]

The risk factors are similar to later-onset type 2 diabetes, but appear to be amplified. Certain populations are at particular risk, including those living with obesity at young age and people from ethnic groups including South Asian, East Asian, African–Caribbean, Middle Eastern and First Nation populations. In the UK, the rising prevalence is predominantly driven by an increase in young adults of White British ethnicity, and South Asian and African–Caribbean ethnicities are also disproportionately affected.[5] There appears to be a female preponderance at younger ages, but this balances out as the age of onset approaches 40 years. There is a strong association with socioeconomic deprivation.

'In the last five years, there has been an increase of about 18% in the cross-sectional prevalence of type 2 diabetes in those aged under 40 years…'

The adverse outcomes associated with early-onset type 2 diabetes are stark. In an analysis across 19 high-income countries, life expectancy was significantly reduced, with a diagnosis at the age of 30 years leading to around 15 years' loss of life expectancy.[3] Women with early-onset type 2 diabetes also experience adverse pregnancy outcomes, including higher rates of perinatal death compared with pregnancies in women with type 1 diabetes.[6]

WHAT UNDERLIES THE ADVERSE OUTCOMES?

The higher burden of complications could simply be a result of a longer duration of diabetes. Better studies are needed to investigate this. However, a meta-analysis showed that, when adjusted for current age (or duration), each one-year decrease in age at diagnosis was associated with a 3% increase in macrovascular disease and a 5% increase in microvascular disease.[7]

Another explanation might be exposure to multiple cardiometabolic risk factors from young age. Studies have shown that younger individuals with type 2 diabetes have a higher body mass index (BMI), a more adverse lipid profile and a higher glycated haemoglobin (HbA1c) at diagnosis, compared with patients with later-onset type 2 diabetes.[8]

'Importantly, there may also be individual patient factors, such as socioeconomic deprivation, that affect engagement with self-management and, in turn, impact risk of adverse outcomes.'

The trajectory of early-onset type 2 diabetes also appears to be different, with several studies demonstrating a rapid worsening of β-cell function and a rapid progression to insulin treatment.[9] Importantly, there may also be individual patient factors, such as socioeconomic deprivation, that affect engagement with self-management and, in turn, impact risk of adverse outcomes.

RECOGNISING THE NEED FOR TARGETED CARE

The NDA has shown that people with early-onset type 2 diabetes are least likely to receive diabetes care processes – the nine diabetes checks that all people with diabetes should receive annually. In the National Pregnancy in Diabetes Audit, two-thirds of women with pre-existing type 2 diabetes did not have HbA1c <48mmol/mol at conception, and only 5% received folic acid.[5,6] We need to deliver better care, but what does good care look like?[10]

Classification

It is important to consider alternative diagnoses, including type 1 diabetes and monogenic diabetes. Some have argued that type 2 diabetes should be a diagnosis of exclusion in younger age groups. Some ethnic groups, for instance South Asian and East Asian, may not be significantly overweight when they present with early-onset type 2 diabetes. A leaner BMI in any young person labelled with type 2 diabetes should prompt diabetes classification tests.

HbA1c target

Once diagnosis is established, the HbA1c level should be reduced to tight targets. Guidelines recommend dual treatment with metformin and SGLT-2 inhibitors from diagnosis in high-risk groups.

Weight management

Currently, glucagon-like peptide-1 (GLP-1) agonist therapy remains fourth-line in NICE guidelines, but clearly a focus on sustainable weight reduction is necessary in addition to targeting glycaemia. Options include weight management programmes, GLP-1 agonist treatment, very low-calorie diets via the NHS Path to Remission Programme, and bariatric surgery for those eligible.

Cardiovascular risk reduction

There is a need to proactively screen for and treat hypertension and dyslipidaemia, recognising that cardiovascular risk engines underestimate life-time cardiovascular risk in those under 40 years of age.

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Pregnancy
Women of child-bearing age should be encouraged to start contraception if they are not planning a pregnancy, so that medications can be used safely. For those planning pregnancy, preconception counselling is imperative.

SUMMARY

Early-onset type 2 diabetes presents a growing public health challenge, with a more aggressive disease trajectory and significantly worse outcomes when compared with later-onset cases.

Addressing this requires a multifaceted approach, including early and accurate diagnosis, tighter glycaemic control, structured weight management, and proactive cardiovascular risk reduction. Additionally, improving access to essential diabetes care processes and targeted preconception counselling for women is crucial. Prevention must also be a priority, with stronger efforts to reduce obesity and metabolic dysfunction in young people, if we are to reduce the rising incidence of early-onset type 2 diabetes.

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PREGNANCIES COMPLICATED BY MATERNAL DIABETES: RECENT ADVANCES

WRITTEN BY ABIGAIL R BYFORD, ELEANOR M SCOTT AND KAREN FORBES

Maternal diabetes in pregnancy increases the risk of pregnancy complications, including stillbirth, pre-eclampsia and pathological fetal growth, where as many as 50% of infants can be born large-for-gestational age (LGA).[1–3] Pregnancies with infants that are LGA can result in preterm birth, shoulder dystocia and stillbirth, as well as an increased risk of developing cardiometabolic complications later in life.[2]

Whilst much of the literature to date has focused on management of these conditions in women with gestational diabetes (GDM) or type 1 diabetes, a recent systematic review highlights that adverse pregnancy outcomes, particularly increased rates of perinatal mortality and pathological fetal growth, are also a concern in type 2 diabetes, which is increasing in prevalence.[1] Measures to predict at-risk pregnancies and to reduce adverse outcomes in pregnancies complicated by maternal diabetes are paramount.[4,5]

USE OF DIABETES TECHNOLOGIES TO PREDICT AND IMPROVE OUTCOMES

Continuous glucose monitoring (CGM) technology, which provides detailed information on glycaemic control over the 24-hour day,[2] can improve pregnancy outcomes[6,7] and detect temporal changes in glucose profiles associated with LGA in pregnancies complicated by type 1 diabetes and GDM.[2,8,9] This has proved particularly important in type 1 diabetes, where these findings have led to new clinical guidelines recommending that CGM is offered to all women with type 1 diabetes in pregnancy, to improve glycaemic control and reduce neonatal complications.[10,11]

More recently, another advancement in diabetes technology has led to further recommendations aimed at improving outcomes in pregnancies complicated by type 1 diabetes. The AiDAPT (Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes) trial assessed 'pregnancy-specific' hybrid closed-loop therapy, which utilises real-time CGM measurements to automatically adjust insulin delivery from an insulin pump. It was found to improve maternal glycaemic control, including an increase in time spent within the pregnancy glucose target range, and a reduction in time in a hyperglycaemic state, without increasing periods of hypoglycaemia.[12] This was associated with lower rates of LGA, reduced

'Adverse pregnancy outcomes, particularly increased rates of perinatal mortality and pathological fetal growth, are also a concern in type 2 diabetes, which is increasing in prevalence.'

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maternal weight gain and reduced burden for mothers. It has now been incorporated into NICE guidance and is being implemented nationally.[13,14]

It is clear that diabetes technologies are important for both prediction and prevention of adverse outcomes in type 1 diabetes. However, this technology's potential in other types of diabetes in pregnancy needs to be determined, particularly in GDM, where screening is currently only offered to women with risk factors, at 24–28 weeks of gestation. Ongoing clinical trials are currently being conducted to determine if early-pregnancy CGM metrics can be used to predict adverse outcomes in pregnancies at risk of GDM and in those complicated by type 2 diabetes in the MAGiC[15] and PROTECT[16] studies respectively. The results of these studies will provide important data to inform the management of GDM and type 2 diabetes.

In parallel, other alternative or complementary diagnostic and therapeutic strategies for improving outcomes in pregnancies complicated by maternal diabetes should also be considered. Recent advances in understanding the molecular mechanisms linking a diabetic maternal environment to fetal growth may aid in this.

'Other alternative or complementary diagnostic and therapeutic strategies for improving outcomes in pregnancies complicated by maternal diabetes should also be considered.'

MECHANISMS LINKING HYPERGLYCAEMIA TO ADVERSE PREGNANCY OUTCOMES

The placenta is essential for normal fetal growth. In pregnancies complicated by maternal diabetes, there are several alterations that occur, including changes to the placental vasculature, growth and ability to transfer nutrients, including glucose, to the fetus.[17]

Studies have investigated the impact of glucose on the placenta, but often these studies have utilised supraphysiological glucose concentrations. We have shown that subtle fluctuations in maternal glucose, that mimic *in vivo* levels detected by CGM in pregnancies complicated by GDM and LGA, directly impact the placental transcriptome (unpublished observations). Functional enrichment analysis suggests that these transcriptomic changes may affect placental lipid metabolism and vascular development, which may explain why subtle fluctuations in glucose impact fetal growth and other adverse outcomes, although further work is required to confirm this.

In addition to direct effects of glucose, it is also important to understand the impact of other components of a diabetic environment on the placenta. These include extracellular vesicles (EVs), small lipid-bound vesicles released by cells and tissues, which have been shown to change in both concentration and microRNA content in the maternal circulation in pregnancies complicated by gestational diabetes.[17,18]

Recently, work in our team has established that specific microRNAs contained within EVs are altered in pregnancies with GDM, prior to the onset of LGA.[19] Thus, they may have the potential to serve as biomarkers for the prediction of adverse outcomes. Additionally, EVs have been shown to traffic to and enter distal tissues, including the placenta, where they influence events by delivering their functionally active cargo.[17,20] Many microRNAs are altered in the placenta in GDM.[17]

'Molecular studies are beginning to improve our understanding of the events linking a diabetic environment to altered fetal growth through actions on the placenta.'

The focus of our current work is examining whether these changes could be attributed to EV delivery of microRNAs from the maternal circulation, and if maternally derived EVs and their microRNA cargo contribute to LGA by impacting placental function.

IN SUMMARY

Maternal diabetes increases the risk of complications for both the mother and the fetus. We have described how advancements in diabetes technology have led to improvements in maternal glycaemic control and perinatal outcomes, particularly in pregnancies complicated by type 1 diabetes. However, with rates of diabetes in pregnancy rising, there is a clear need to develop further complementary therapeutic strategies. Molecular studies are beginning to improve our understanding of the events linking a diabetic environment to altered fetal growth through actions on the placenta. Exploiting these findings may lead to further improvements in pregnancy outcomes and the long term health of infants exposed to diabetes *in utero*.

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SHARED SPECIALIST NURSING ROLES: FINDING YOUR FEET, LEARNING TO JUGGLE

WRITTEN BY AMY GLOVER

I had been a Diabetes Specialist Nurse for 20 years or so, including a stint working as a Clinical Nurse Manager in New Zealand for 12 years. Then the opportunity to learn and grow in a new specialty presented itself, and I decided I was ready for a new challenge.

The trust I was employed by had had their first Getting It Right First Time (GIRFT) review in endocrinology. The clinical lead was asked by the review team/deep dive visitors what the first item was on the wishlist for the service and, without hesitation, his answer was an endocrine specialist nurse. With that, a part-time position was created, and I was the successful applicant.

With a very new position, and learning a new specialty within the confines of part-time hours, it has been quite daunting and, at times, a steep learning curve. However, the opportunity to specialise in a diverse and interesting field has meant that every day is a learning day, which most definitely provided the challenge I was looking for, and the next step in my career.

FINDING YOUR FEET

New endocrine nursing roles, in discussion with other nurses, tend to consider what the local service needs are in order to support direct patient care. From a nursing perspective, I was able to start the service from scratch, as it was a new position, and I have been fortunate to have been able to influence and shape the service.

Two of the priority areas identified for the service were to establish dynamic function testing in the absence of a planned investigation unit, and to provide patient education for emergency administration of hydrocortison (see Figure 1).

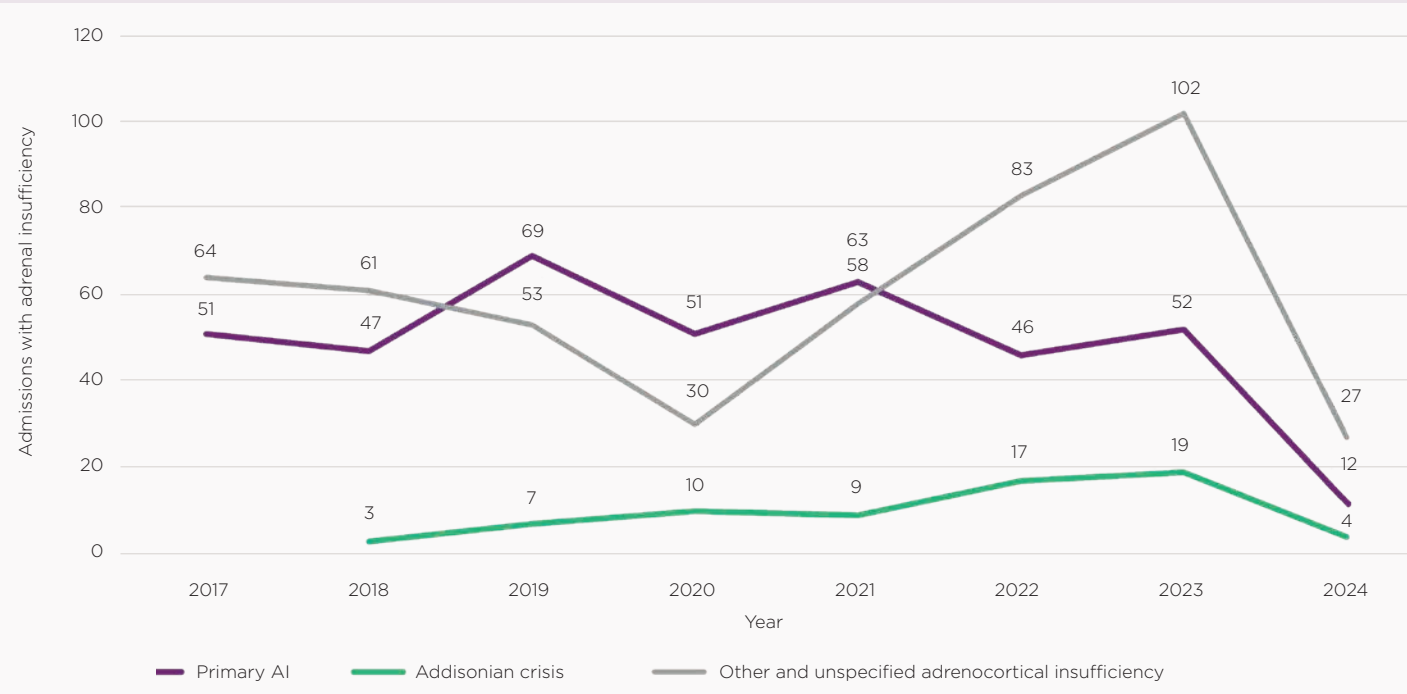
My candid first recollection (and somewhat naïve thoughts) regarding undertaking function testing was that I didn't consider this to be part of my role. However, I have learnt a great deal about various conditions as a result. Slowly, some of the jigsaw puzzle pieces started to fit into place. It has also ensured that the journey of referral and investigation starts sooner, with improved patient satisfaction, based on our friends and family responses. I am able to help provide a diagnosis, including a timely discharge where appropriate, with the development of a defined pathway (see Figure 2).

Referrals to endocrine services have been growing over the past five years, with a 31% increase compared with a 17.5% increase for general outpatient referrals, based on hospital data (GIRFT).

Straight-to-test involves proceeding straight to an appropriate investigation without a prior clinic appointment. The aim is to improve time to diagnosis, provide earlier reassurance, improve access to services and avoid unnecessary clinic appointments. This concept is well utilised in suspected cancer pathways. The GIRFT report (2021) highlights the importance of providing more pre-testing: increasing efficiency by making better use of pre-consultant appointments, the suggested target for services being at least 30%. As a result, endocrine specialist nurses can significantly improve the efficient running of departments. Time to treatment can also be improved and, as a result, so can patient satisfaction (Figure 3).

From a practice perspective, it has also developed my clinical skills. I understand the principles of investigations and have learnt to interpret results, including the next stage of the diagnostic journey to next stage investigations, including imaging. With time, I am learning how fascinating and exciting endocrinology is.

Figure 1. Reduction in hospitalisations for adrenal crisis following implementation of patient education programmes and emergency hydrocortisone kits.



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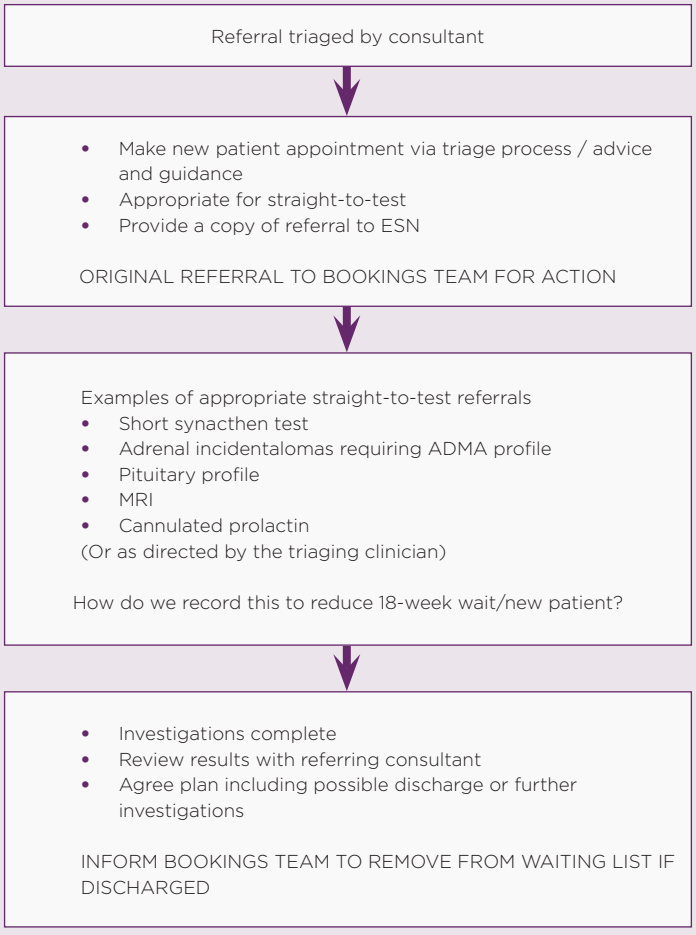
I have welcomed support from local services and endocrine specialists, with whom I have been fortunate to spend time. I know that if I drop them an email or a call they will provide support and offer encouragement, and they have been generous with their time. The endocrine community (who are fewer in number than the diabetes fraternity) are a friendly bunch, and I found it easy to contact colleagues through WhatsApp or the Facebook endocrine nurse group.

The Society has recognised the situation faced by many new endocrine nurses, as they tend to be singular roles, particularly in tertiary services. Support from the Society by means of the early-career nursing scheme has allowed me access to the online platform Qooper (**www.qooper.io**), where I can track my competency development, and remain in touch with my clinical supervisor, Lisa Shepherd, who encouraged me to undertake the Masters Level Module in Endocrine Nursing.

LEARNING TO JUGGLE

My half-time share with diabetes has meant that I could continue in the lead nursing role for inpatient care. This, on occasions, has been quite puzzling for staff who sought an inpatient consultation on the day I was wearing the endocrine hat. Conversely, when there are deadlines looming or reports to consider, something (and it's usually endocrine time) has to give.

Figure 2. Straight-to-test pathway, based on experience gained from a pilot run. ADMA, adrenal mass; ESN, endocrine specialist nurse; MRI, magnetic resonance imaging.



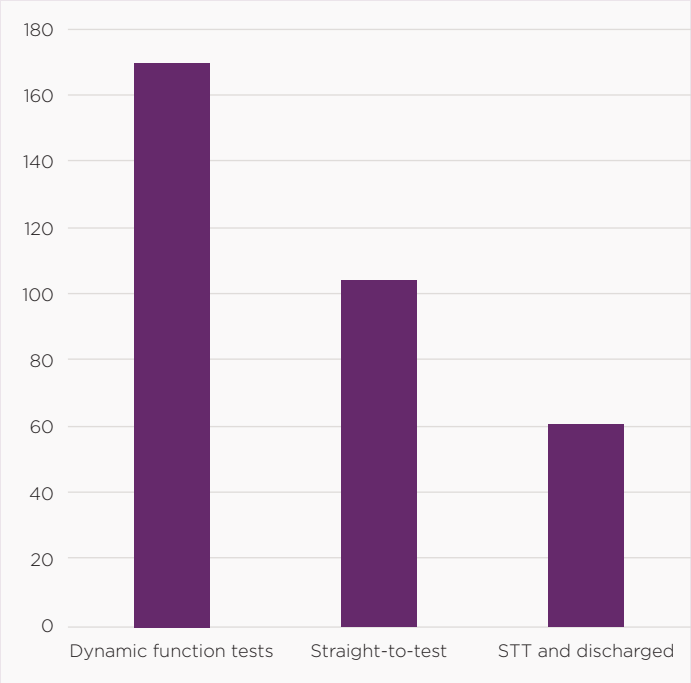


Figure 3. Dynamic function tests, straight-to-test (STT) investigations and subsequent nurse discharges, 2024.

The diversity in my current position means there are unlimited opportunities for me to learn from and share experiences with coworkers. I remain in awe of my very knowledgeable consultant colleagues who have to wear various hats, sometimes more than one hat at the same time! I enjoy the mixture of acute care and outpatient activity that my current, occasionally hectic, job provides.

Anecdotally, there may be an increase in dual roles. Discussion with my colleagues has indicated that, as well as my role in Bolton, examples of services adopting this dual-role approach, covering both diabetes and endocrinology, may be found in Northumbria, Shrewsbury and Telford. Possible motives could be financial, rather than employing a full-time endocrine specialist nurse, or taking a more considered approach to cross-cover services or increase professional development. There is little information within the literature with regard to dual roles and responsibilities, and how this may impact service provision. Further research or questionnaires would be welcomed.

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FURTHER READING

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An interview with…
GABRIELA DA SILVA XAVIER
NEW JOURNAL CO-EDITOR-IN-CHIEF

Gabriela da Silva Xavier is an Associate Professor in Cellular Metabolism at the University of Birmingham, and a team member in the Women's Metabolism Health Theme at the NIHR Birmingham Biomedical Research Centre. We caught up with her to learn about her career in endocrinology, her roles in the Society for Endocrinology and her new position as Co-Editor-in-Chief of two Society journals: *Journal of Endocrinology* and *Journal of Molecular Endocrinology*.

Tell us about the focus of your current research
My research for the past 20+ years has mainly been on pancreatic islet function, trying to elucidate how variations in the genome impact upon the function of the endocrine pancreas and, therefore, the risk of developing diabetes. The genomic variations were identified via genome-wide association studies in humans, and frequently also impact upon the function of other tissues that are important in metabolic regulation. So, perhaps unsurprisingly, the work led me to take a more systemic lens to diabetes research, moving beyond the pancreas and looking at the impact upon or of other tissues, e.g. adipose tissue.

Since moving to the University of Birmingham, I have become more involved in research on rare metabolic conditions in which diabetes and obesity are part of the pathology. This is due to our close links with the University Hospitals Birmingham NHS Foundation Trust, where some of these conditions are managed. I am a member of the NIHR Birmingham Biomedical Research Centre's Women's Metabolic Health Theme. Gestational diabetes is one of the areas in which we are currently developing work packages, together with our patient and public involvement and engagement groups. As a result of these connections, my work has taken on a more translational slant.

What inspired you to choose a career in endocrinology?
I chose to work on diabetes because it is a condition that was common amongst people I know, so I was aware of it from an early age. I have always been interested in science, because I enjoy finding out how things work. So, it seemed logical to marry the love for science and the desire to do something that could be helpful to people I know.

Once I started, I very quickly became hooked. The endocrine system is a very beautiful thing. For example, the control mechanisms within, and exerted by, the islets of Langerhans are so very clever and elegant. Then there are the additional layers of control exercised by tissue cross-talk to achieve some sort of best-possible balance within the system. This makes for a really complex control module that constantly adjusts with input from multiple sources, but which, at its most basic, is essentially just made up of bags of chemicals.

Things do go wrong but, considering how much work is done, I find it a wonder that things don't (noticeably) go wrong a lot more. There is much to learn from studying such a system. Work is a lot of fun (usually), also because I have the good fortune to work with really lovely, engaging people. This is a good career choice and I would recommend anyone with an enquiring mind to explore it as an option.

Have you found any recent advancements in your field particularly exciting?
The ability to generate islet cells from stem cells is a very exciting development. The implications for treatment – increasing the availability of islet cells for transplantation – is huge. However, there is also substantial potential to use such stem cell-derived cells/organoids for research purposes. For example, this could include drug testing and to help us gain a better understanding of how human pancreatic endocrine cell development could be impacted by different factors during fetal development, and what that may mean for the long term metabolic health of the offspring.

How has the Society played a part in your career?
As a researcher, the annual conference and the journals run by the Society for Endocrinology have been really helpful in acquiring and exchange of knowledge. I have had the opportunity to take on different roles within the Society, through which I have learnt a lot, met a lot of interesting people, and had the space to develop my leadership skills.

Up until very recently, I was a member of the Science Committee. As part of the committee, I had the privilege of working within interest groups to look at how the Society could support and develop education in endocrinology, or a career framework for research scientists in endocrinology. Being involved in such work gave me a better understanding of what the community needs, what tools/levers are already there and what is missing, and how we can work together to meet those needs.

That gave me the impetus to apply for the role of Deputy Chair of the Society's newly formed Grants Committee, because I believe that helping to set up an effective grant award system would enable us to meet some of those needs. I get a real sense of support and community within the Society for Endocrinology, and this positive culture helps to drive research.

What motivated you to become Co-Editor-in-Chief of two Society journals?
The exchange of ideas and information is key to scientific research and progress. Scientists need safe spaces in which to communicate their ideas and to obtain information, and *Journal of Endocrinology* and *Journal of Molecular Endocrinology* have provided this. We currently face many (new) challenges in publishing – which makes the job interesting – and I wanted to be involved in helping to meet these challenges. I would also like to see young scientists more involved in scientific discourse; I see being involved with these journals as a potential means to this.

What advice can you give early-career researchers looking to publish their work in a journal?
The best piece of advice I got was to put figures together as the work develops. It may involve moving figure panels around over the course of weeks, months and years – and some might question if that is the best use of time. However, I found that doing that allowed the narrative to evolve in a visual manner as the data came in. It helped me spot holes in the logic/story, which I could then try to address with experiments. It also helped with the writing, as the narrative is developed over time with the experimental work and the figures.

I think it is important to start writing early on in one's career, to develop writing skills, with support from mentors and colleagues. Journal reviews are exchanges of ideas and opinions. Thus, the review–revision process is a learning opportunity (especially for early-career researchers), provided by the wider research community beyond the immediate laboratory team and collaborators, if it is conducted in an open and fair manner. Thus, a good learning experience is more likely when publishing in journals with a robust and supportive editorial process, such as *Journal of Endocrinology* and *Journal of Molecular Endocrinology*.

SfE BES 2025
BACK IN HARROGATE

We were thrilled to host our annual SfE BES conference in the charming town of Harrogate from 10 to 12 March 2025. The event was a vibrant celebration of the latest and greatest in clinical and scientific research.

It was truly inspiring to see our community come together, share knowledge, and ignite our collective passion for endocrinology.

Thank you to all our exhibitors and sponsors for supporting this amazing event.

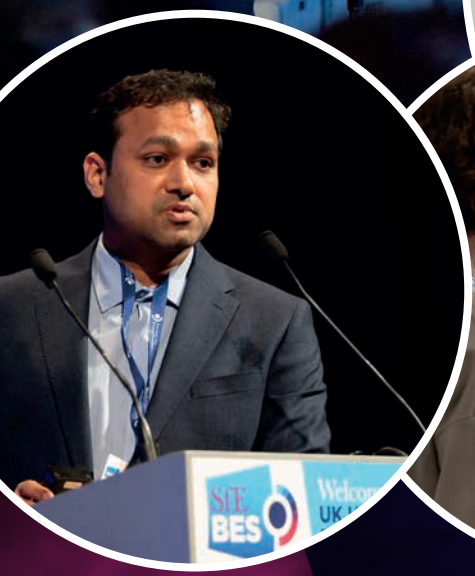
Congratulations to all our medal and prize winners. Look out for them in the next issue of *The Endocrinologist*.

1,072
attendees

499
abstracts

388
from the UK

111
international



Your Society in 2024

Supporting careers, championing inclusion, advancing research and patient care

Society for Endocrinology

Supported our community by...

Creating a new **Events & Training Committee** to ensure the Society meets changing training needs

Awarding **161 grants**

Webinars

Holding **6 webinars** and **5 virtual coffee chats** to share best practice

Inspired the next generation of endocrinologists by...

Encouraging students to develop their science communication skills through our **Student Video Awards**

Holding our Endocrinology and Diabetes Taster Sessions for **325 people**

Re-launched our programme of **awards and prizes** to better showcase the incredible diversity of talent across endocrinology

Advanced clinical practice by...

Launching 2 real-world data registries, **NSAT & PROMMIS**

Contributing significantly to the **NICE guidelines on adrenal insufficiency:** identification and management

Releasing two clinical guidelines on understanding, diagnosing and treating **female hypogonadism** and diagnosis and management of **post-bariatric hypoglycaemia**

Sharing **best practice** between centres through interdepartmental peer review in...

Dublin **Edinburgh** **Glasgow**

Shared high-impact endocrine research...

257 abstract submissions and a total of **231 posters** at the Joint Irish-UK Endocrine meeting

Welcoming NEW PERSPECTIVES

We encourage members from all career levels, backgrounds and specialties to join the Society's Council of Management and committees. This ensures that we remain aware of the external challenges that our members face, maximise our Society's positive impact and continue to support a thriving future for endocrinology. Here are the members who will take up Council and Committee Chair positions, following our 2025 Annual General Meeting. We welcome them and everyone else who is taking up a new role following last autumn's open call for applications to join our team.

KRISTIEN BOELAERT
President-Elect

ALED REES
General Secretary

KEVIN MURPHY
Events and Training Officer

ALEX COMNINOS
Council Member

VICKI SMITH
Council Member

RUTH CASEY
Clinical Committee Chair-Elect

SOFIA LLAHANA
Corporate Liaison Committee Chair-Elect

HELEN LOO
Nurse Committee Chair-Elect

In conversation with…
KIM JONAS AND CRAIG DOIG
OUR RETIRING EDITOR AND ASSOCIATE EDITOR

This issue of *The Endocrinologist* was the last for Kim Jonas and Craig Doig as Editor and Associate Editor respectively. They served on the magazine's Editorial Board for a combined total of around 14 years, and took up their current positions in spring 2022. Since then, they led the Board in coming up with ideas for, commissioning, reviewing and promoting over 100 feature articles across 13 issues.

We're extremely grateful to Kim and Craig for their incredible service and, before they stepped away from their roles, we asked them to reflect on their time with the magazine.

How and why did you first get involved with *The Endocrinologist*?

KIM I was approached by a couple of the people who were on the Editorial Board, and I thought it sounded fun and a good way of getting involved in communicating endocrinology, with a greater reach than we can achieve with journal articles.

CRAIG I was always aware of *The Endocrinologist*, and I'd seen how broad endocrinology was within each issue. I viewed getting involved as a way of widening my exposure within the field.

KIM Yes – it's definitely opened up the opportunity, because I don't think that Craig and I knew each other properly before we worked together on the magazine, and now we're collaborating in research too!

CRAIG It's really benefited both of us.

Why is *The Endocrinologist* important for UK endocrinology?

CRAIG I think the community that the magazine creates binds us together. Because it is largely generated by the readership, it feels familial in a way. You recognise names and faces and think, 'Let's see what they've been doing recently.'

KIM I think it's a good way of showcasing our breadth as a community, to members and beyond.

What have you enjoyed most about your time on the Editorial Board?

KIM It's definitely been about meeting people. Getting to know other members of the Board whom I didn't know and who aren't in my field has been my biggest highlight.

> ***'…I thought it sounded fun and a good way of getting involved in communicating endocrinology, with a greater reach than we can achieve with journal articles.'***

CRAIG I agree – it's been professionally and personally beneficial. I do recall one lovely moment, when I went to do a student's viva and there wasn't a room booked, so they put us in a very important person's professorial office. The only publication on that very important person's desk was the latest copy of *The Endocrinologist*. That was really cool.

Finally, what advice would you give to your successors?

KIM Commission authors to write articles early, to give people the best chance of saying yes, and come to the Board meeting prepared with some ideas. No idea is silly, and you can work them up as you chat through things with the Editorial Board.

CRAIG Yes, don't be afraid to put ideas out there and bounce them off your colleagues on the board. Also, get to know people – say hello at conferences to people doing interesting work – that can be your 'in' to inviting them to write. But, even if you don't know someone at all, just ask them – they might say no, but that doesn't matter.

Broadening horizons IN BELFAST

The joint meeting of the Irish Endocrine Society and the Society for Endocrinology took place on 14–15 October 2024 in Belfast. Here, two attendees share their perspectives on the conference.

RACHEL CROWLEY

Consultant Endocrinologist, St Vincent's University Hospital and School of Medicine, University College Dublin

I had contributed to the programme planning, so I was nervous coming to the meeting, hoping it had all come together in an appealing format for the members of both societies. I was really pleased, as I soon saw great talks and interaction with speakers. I must give a particular shout-out to Caroline Gorvin for her work in the bone session (which was attended, with great feedback, by colleagues without a background or interest in bone).

I thought there was huge engagement with patient groups and network representatives between presentations. I enjoyed presenting in the hypothalamic disease session myself, and we followed it up with detailed case discussions. I was delighted with the prize winners, particularly seeing Julie Martin-Grace being awarded the O'Donovan Medal for work in rare endocrine disease.

Rachel Crowley, AJ van der Lely and Niamh Phelan at the Belfast City Hall disco. ©M Hannon

One of the best parts about going to these events is meeting with old friends and colleagues, and we had a wonderful dinner at Belfast City Hall. This was followed by a disco – fortunately I had brought my runners with me, for the walk back to my hotel, so I shed my heels and had a great time on the dance floor!

The meeting was a good showcase for the members of both societies, to see what was happening in the other group. Some of us who hold dual membership felt very valued in the competition for numbers at the morning AGMs! There was also a lot of networking between members, with trainee fellowships, grant applications and even a friendly rugby match scheduled at the meeting.

I am looking forward to the SfE BES conference in Harrogate and the Irish Endocrine Society meeting in Portlaoise in 2025.

Rachel Crowley and Suzanne McCormack. ©RDCTN

ALANNA SILKE

Endocrinology Registrar, St Vincent's University Hospital, Dublin

This was the first time I had attended an endocrinology conference and, coincidently, my first time in Belfast. Upon arrival, I noticed how the conference spread over a very large area. However, once I got my bearings, I appreciated the organised nature of the layout. Going through the various posters and getting a flavour of what my peers are researching was thought-provoking and gave me good inspiration for future poster designs.

The number of talks on offer was almost overwhelming, and I did have to make some tough choices about what to attend. Particular stand outs included the 'How Do I…?' series of talks on diabetes, which covered many common issues that crop up in both inpatient and outpatient settings. It was pitched at a very approachable level, and I felt more confident after attending. I also found the sessions on clinical case studies in Cushing's syndrome really interesting. The panel of experts and consultants in the audience had a lot of insight to give.

It was a pleasure to discuss the talks with other registrars who, like me, are at the beginning of their careers. I found this helpful, as we often took away different learning points due to the variety of our experiences. Talking with the trainees in the NHS system was a good opportunity created by the joint nature of this meeting.

FEMALE HYPOGONADISM: MULTI-DISCIPLINARY GUIDANCE FOR A MULTI-FACETED CONDITION

WRITTEN BY CHANNA N JAYASENA AND RICHARD QUINTON

Female hypogonadism (FH) is a common cause of period loss in women of reproductive age, but there are significant uncertainties and wide variation in its management.

Its treatment has hitherto been shaped by a combination of custom, clinical experience and study data relating to older, postmenopausal women. Existing clinical guidance on FH has largely focused on gynaecological practice, typically for specific conditions, such as premature ovarian insufficiency (POI).

However, the diagnosis and management of different forms of FH have long remained a challenge for clinicians. The Society for Endocrinology commissioned new guidance to provide a multidisciplinary perspective on managing all forms of FH. Input was gathered from endocrinology, primary care, reproductive medicine/gynaecology and patients. As with the Society guidance for male hypogonadism, our aim was to produce a document that would be enjoyable to read, while being informative and evidence-based. We also chose to consider broader evidence encompassing transgender women, and to provide specific considerations for key forms of FH, such as Turner syndrome and functional hypothalamic amenorrhoea. The guidance is free-to-read in *Clinical Endocrinology*, and this article highlights some of its findings.[1]

DIAGNOSIS

The diagnosis of FH is not always straightforward. Women with POI frequently suffer for two years prior to diagnosis and treatment, despite multiple medical consultations. Diagnosis in women with central hypogonadism may take even longer, due to GPs' poor awareness of its characteristic biochemistry. Although oligo-amenorrhoea is a prerequisite for the diagnosis of hypogonadism, there are other more common causes of menstrual disturbance, such as polycystic ovary syndrome and progestogenic contraceptives, and women with hypogonadism may instead be initially assumed to have one of these as the primary disturbance.

We no longer recommend progestogen challenge testing during the FH diagnostic pathway. We instead emphasise that a low serum oestradiol (E_2) concentration (<200pmol/l) and/or thin endometrium (≤4mm) on ultrasound are consistent with FH when a woman has not experienced menstruation for several months. Alternative causes of a thin endometrium include systemic or intrauterine progestogen exposure, and following menstrual bleeding. Polycystic ovarian morphology on sonography should not distract clinicians from making a primary diagnosis of hypogonadism when the endometrium is thin, the uterus appears immature, or serum E_2 is low (<200 pmol/l) in a woman without a recent period.

Previous reviews and guidelines have carefully avoided committing to any specific serum E_2 threshold, perhaps due to concerns about assay variability, the focus of gynaecological practice on ultrasound findings, and the fear that it might distract from careful clinical phenotyping. However, consensus within our guideline group highlighted the pragmatic need to help steer generalists, as well as specialists, using serum E_2 levels. Normative reference ranges for serum E_2 are detailed yet unhelpful for diagnosing conditions such as FH. Therefore, we conducted a literature search for what might constitute an abnormally low E_2 level in the context of prolonged amenorrhoea. An E_2 threshold level <200pmol/l was agreed upon as an approximate threshold for women with lactational and hypothalamic amenorrhoea. Future studies may better define the biochemical threshold(s) for diagnosing FH.

MANAGEMENT

We strongly recommend that hormone replacement therapy (HRT) should be based on 17β-E_2 rather than equine-derived oestrogens or ethinyloestradiol-based combined oral contraceptives (COCs). E_2-based HRT allows monitoring of E_2 levels if desired, minimises thrombotic risk (especially if transdermal), and optimises bone density and blood pressure compared with COCs. However, if contraception medication is required, then a modern E_2-based (rather than ethinyloestradiol-based) COC is recommended.

We also note that many younger women require doses significantly higher than the maximum licensed doses for older, postmenopausal women. The specified minimum E_2 doses for FH are 2mg orally or a 75µg transdermal patch, but higher doses may be required.

It is commonly advised that higher E_2 doses should prompt an equivalent rise in progestogen for women with a uterus. This seems intuitively sensible, but we could find no evidence to support it. We recommend using a bioidentical neutral progestogen (micronised natural progesterone or its stereoisomer dydrogesterone), or a levonorgestrel-releasing intrauterine system which minimises systemic progestogen exposure.

The authors could not reach agreement on whether measuring serum E_2 should also form part of routine monitoring. If serum E_2 is checked, we recommend a target range as per most UK transgender women (300–600pmol/l) or the latest international Turner syndrome guidance (350–550pmol/l).

We recommend continuing HRT to at least the median age of menopause (51 years), but to consider continuing for longer when diagnosis and treatment were delayed, when there were prior frequent or prolonged gaps in therapy, or if bone density is concerning. Thereafter, the decision to continue HRT becomes a matter of informed patient choice as per menopausal HRT. Crucially, as HRT has fracture prevention data, we do not recommend adding any bone-specific drugs, except perhaps in exceptional circumstances. The guideline discusses special circumstances where concerns about HRT might be greater, and how these can be shared with patients and mitigated by adjustments to treatment, such as obesity, venous thromboembolism, ischaemic heart disease and meningioma.

For women with functional central hypogonadism (hypothalamic amenorrhoea) due to relative energy deficit, opiates or hyperprolactinaemia, first-line treatments are lifestyle measures, analgesic dose-titration and prolactin-lowering measures respectively. However, we recommend starting HRT in the event that these measures are unsuccessful within 6–12 months or, indeed, without any delay if there is low probability that these approaches would be successful (e.g. in an athlete).

Fertility options are discussed in detail, but perhaps the most important take-home message is that gonadotrophin ovulation induction confers cumulative fertility rates approaching those of fertile couples when given to women with central hypogonadism.

FH is a diverse group of conditions affecting young women, the aetiology of which influences their management. We hope this guideline helps non-specialists to distinguish FH from menopause, and supports specialists in current multidisciplinary practice for affected women.

CHANNA N JAYASENA
Section of Investigative Medicine, Imperial College London

RICHARD QUINTON
CNTW NHS Foundation Trust, Newcastle upon Tyne, and Department of Metabolism, Digestion and Reproduction, Imperial College London

REFERENCE

1. Jayasena *et al.* 2024 *Clinical Endocrinology* https://doi.org/10.1111/cen.15097.

IN SEARCH OF GIANTS FINDING THE GENETIC GIANTS OF NORTHERN IRELAND

WRITTEN BY COLLEEN SNYDER

In Search of Giants is a newly released book which brings to life research into the genetic gigantism related to an *AIP* genetic mutation found in Northern Ireland. Written by Colleen Snyder and Brendan Holland, it combines stories about modern-day giants, coping with the effects of their medical condition, with cutting-edge molecular genetic research, to reveal how science and the legends of Irish giants intertwine.[1]

The book was launched at the Royal College of Surgeons' Hunterian Museum in London on 10 September and in Belfast at the Joint Irish–UK Endocrine Meeting on 14 October 2024. Here, author Colleen Snyder explains more.

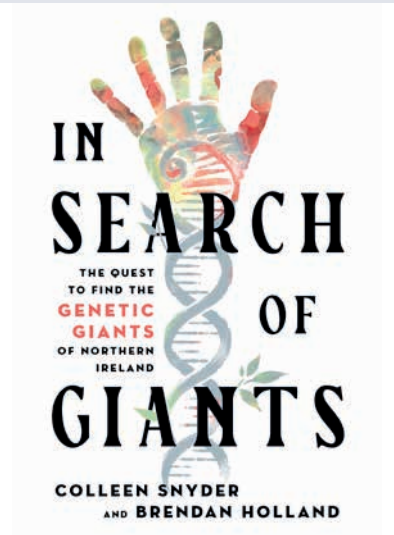
TESTING POSITIVE FOR THE *AIP* MUTATION

Even though I am Irish-American, I knew nothing about the small area in mid-Ulster in Northern Ireland that is steeped in giant lore and legends of giants.

I had a pituitary tumour and acromegalic gigantism when I was a child, but I wasn't diagnosed until 1976 when I was 20 years old. Although my transsphenoidal surgery was a success, I had a lot of psychological problems related to the changes in my body and the fact that I knew no one else with the same condition.

My life changed one boring afternoon 40 years later, during the Covid-19 pandemic, when I did a Google search about childhood acromegaly. Up popped Professor Márta Korbonits' paper about genetic gigantism in Northern Ireland, entitled 'The *AIP* mutation in pituitary adenomas in the 18th century and today'.[2]

I did some digging and found out that my great-great-grandfather had come from the area, so I asked my endocrinologist to test me and, much to my surprise, I had the *AIP* gene mutation that Professor Korbonits had linked to that region.



DEVELOPING A COLLABORATIVE BOOK PROJECT

I emailed Professor Korbonits at the William Harvey Research Institute in London, who told me that I was the first person in the USA that she knew with this *AIP* mutation. I was surprised to find out that I was actually related to the well known 18th century Irish giant Charles Byrne, who came to London from that area.

She put me in touch with my co-author, fellow patient and historian, Brendan Holland, who has lived in the geographical hotspot for the gene mutation his entire life. Brendan and I hit it off immediately and decided to work together on the book project, which had been started by Brendan and Márta some years before. I am a professional writer, and Brendan is a historian in the area, so his encyclopaedic knowledge and deep connections in mid-Ulster were invaluable.

We first met through a video chat, followed my many others, and were fortunate to have the guidance of Professor Korbonits and Dr Ben Loughrey, of Queen's University Belfast. A great deal of serendipity brought this manuscript together, detailed in the book, and the whole project took about three years.

FOCUSING ON MÁRTA KORBONITS' RESEARCH

My primary goal in this book was to tell the story behind the genetic discoveries about Irish giants, and to have stories about patients who have benefited from this research work.

Brendan first encountered Márta's research in 2009, during the making of the BBC documentary 'Charles Byrne: the Irish Giant'.[3] Art and science come together in this documentary, which combines the tragic tale of Charles Byrne with Professor Korbonits' research, and Brendan's realisation that he has the genetic mutation.

The book includes the story behind the 2013 community screening for the *AIP* mutation in the local supermarkets of mid-Ulster. This brought local volunteers together with endocrinologists from around the world in two towns in the geographic hotspot for the mutation.[4] More than 40 people were credited in the resulting paper, 'Increased population risk of *AIP*-related acromegaly and gigantism in Ireland'.[5]

THE GOAL OF *IN SEARCH OF GIANTS*

Having a rare disease such as gigantism is very isolating, often entailing a lengthy diagnostic odyssey. Patients ache to find others who share their experience and understand. The goal of this book is to find others with similar diseases, in the hope of heading off the pain, blindness, infertility and life-threatening challenges that having gigantism can bring. We hope that the stories of those with gigantism can serve as inspiration for anyone with a rare disease.

For more information about the book, or to place an order, visit **www.insearchofgiants.org**. For details of Márta Korbonits' research and for extensive information about familial isolated pituitary adenomas, consult the FIPA website at **www.qmul.ac.uk/fipa-patients**.

COLLEEN SNYDER

Colleen Snyder is an Irish-American writer whose ancestors came from mid-Ulster. She was the first person in the USA to be identified with the Northern Ireland variant of the AIP *genetic mutation, which caused her gigantism. Her work has appeared in* The Washington Post *and* Destinations *magazine.*

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1. Snyder C & Holland B 2024 *In Search of Giants* Fairsing Publishing https://www.insearchofgiants.org.
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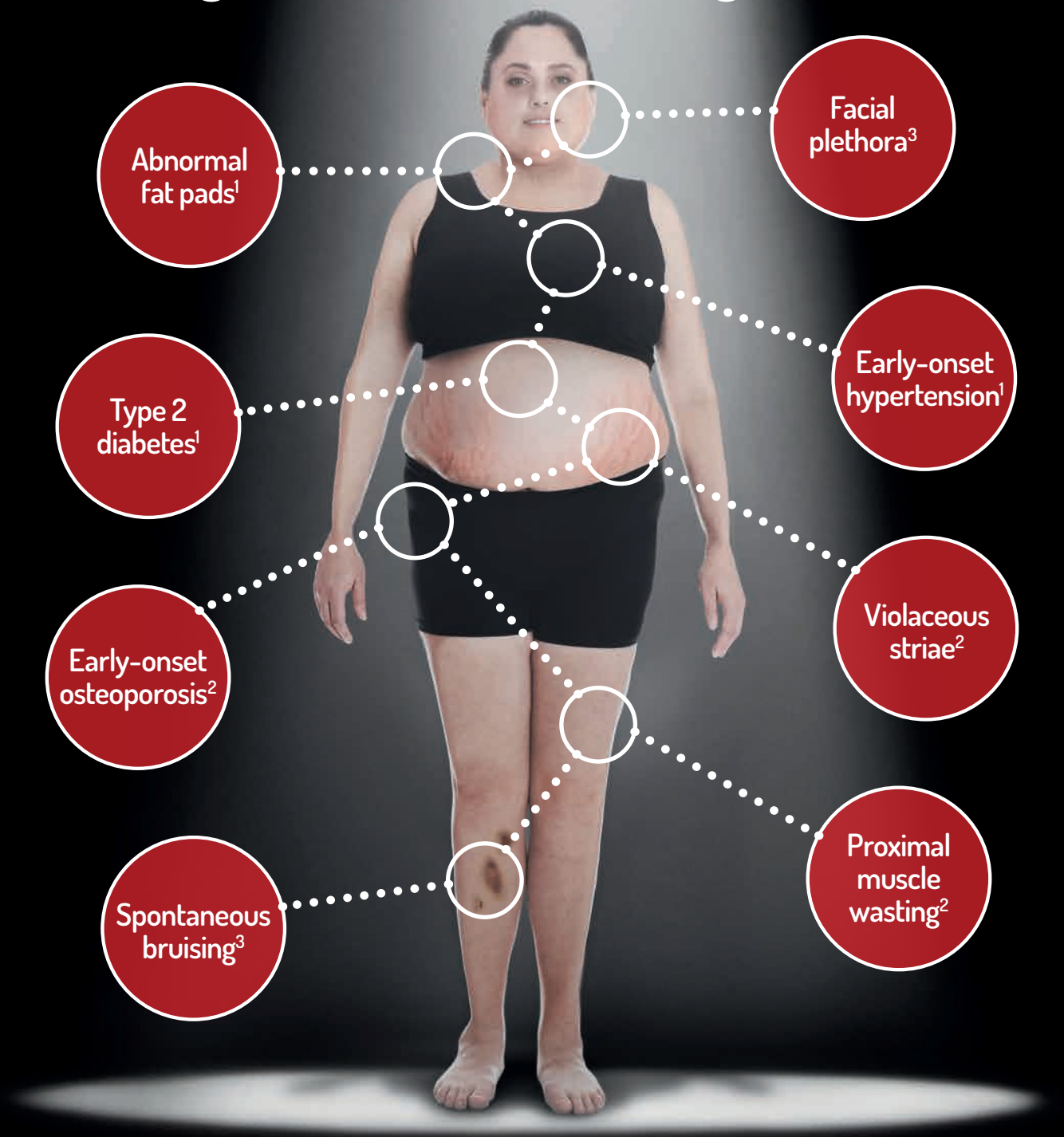
3. BBC (dir. Ronan McCloskey) 2011 *Charles Byrne: The Irish Giant* https://www.youtube.com/watch?v=xLA-KZ7sBLg.
4. Radian S & Herincs M 2013 *The Endocrinologist* **108** 24 https://www.endocrinology.org/media/1276/108.pdf.
5. Radian S *et al.* 2017 *Human Mutation* https://doi.org/10.1002/humu.23121.

Although the condition might be rare...



...the features are common

Perhaps it's Cushing's syndrome, perhaps it's something else? If you connect any of these dots within a patient, consider referring them to a specialist endocrinologist.

For a clinician's guide to recognising Cushing's syndrome's signs and features, email **cushings@connectthedots.health** and help shine a light on this rare condition.

ESTEVE
Advancing health together

Connect the dots

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