CalSoc 2023

caledonian society for endocrinology and diabetes

Atholl Palace Hotel

March 3rd/4th

Meeting sponsored by

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Programme of Events

Friday 3rd March

Trainee session

Chair: Dr Laura Reid
Specialist Registrar, Edinburgh Centre for Endocrinology & Diabetes

10:00 – 12:00 Adrenal update
Dr Marie Freel
Queen Elizabeth University Hospital, Glasgow

Bone update
Professor Rachel Crowley
St Vincent's University Hospital, Dublin

Afternoon session

Chair: Dr Alex Graveling
Consultant Endocrinologist, Aberdeen Royal Infirmary

13:15 – 14:00 AIP mutations and pituitary tumours; Irish giants and Scottish connections
Dr David Carty
Consultant Endocrinologist, Glasgow Royal Infirmary

14:00 – 14:45 Balancing Bone
Professor Rachel Crowley
Consultant Endocrinologist, St Vincent's University Hospital, Dublin
Clinical Professor, University College Dublin

14:45 – 15:20 Coffee

Chair: Professor Brian Kennon
Consultant Endocrinologist, Queen Elizabeth University Hospital, Glasgow

15:20 – 16:05 Everything you wanted to know about genetic testing but were afraid to ask
Dr Paul Newey
Clinical Reader / Honorary Consultant Endocrinologist
Ninewells Hospital & Medical School, Dundee

16:05 – 16:50 Managing thyroid nodules and thyroid cancer in 2023
Professor Kristien Boelaert
Professor of Endocrinology / Consultant Endocrinologist
University of Birmingham / University Hospitals Birmingham

Programme of Events

Saturday 4th March

Morning session

Chair: Dr Sandeep Thekkepat
Consultant Endocrinologist, University Hospital Monklands

09:00 – 09:45 Functional Imaging of Pituitary Adenomas in Scotland – Choosing the Right Patients
Dr Prakash Abraham
Consultant Endocrinologist, Aberdeen Royal Infirmary

09:45 – 10:30 Trainee presentations I
Victoria Tyndall
Laura Reid
Maria Bantounou

10:30 – 11:00 Coffee

Chair: Dr Kathryn Linton
Consultant Endocrinologist, Edinburgh Centre for Endocrinology & Diabetes

11:00 – 11:45 Trainee presentations II
Kavinga Gamage
Kirsty Wood
Kirstin Griffin

11:45 – 12:30 Type 1 diabetes and technology update
Dr Fraser Gibb
Consultant Endocrinologist/ Honorary Clinical Reader
Edinburgh Centre for Endocrinology & Diabetes / University of Edinburgh

David Carty

Biography

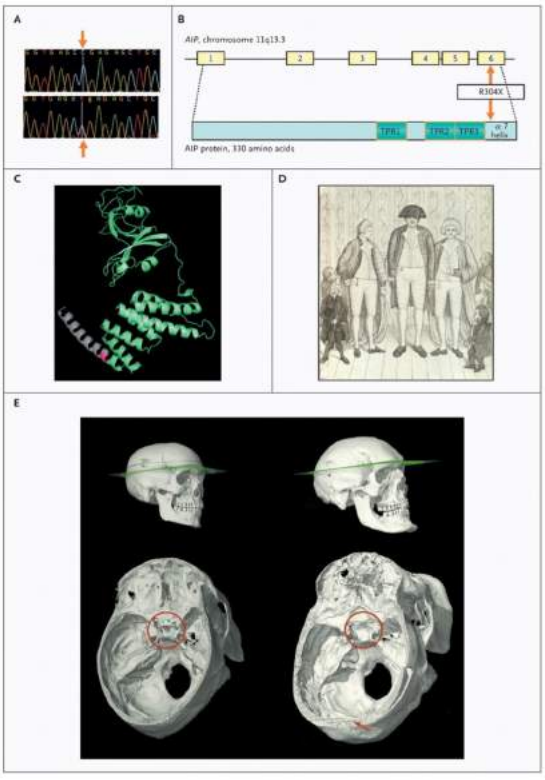
David Carty graduated from Aberdeen University in 2001. After initial training in Inverness and New Zealand he was Clinical Lecturer in Diabetes and Endocrinology at the University of Glasgow from 2010-2015. He was awarded a PhD in 2012 for his thesis entitled “Pre-eclampsia: early prediction and long-term consequences.”

He was appointed as a Consultant in Diabetes and Endocrinology at Glasgow Royal Infirmary in 2015, where he co-runs the combined diabetes & endocrine/ obstetric clinic. He has clinical and research interests in diabetes, endocrinology and medical complications of pregnancy, and was awarded an NRS Career Research Fellowship from the Chief Scientist’s Office to support his research activities. He is lead clinician for Diabetes and Endocrinology in North Glasgow and is a training programme director for Internal Medicine Training in the West of Scotland deanery.

AIP mutations and pituitary tumours; Irish giants and Scottish connections

Although most pituitary tumours arise sporadically, in around 5% of cases there is a familial presentation. Familial isolated pituitary adenoma (FIPA) is defined as pituitary tumours occurring in two or more family members, in the absence of other recognised genetic syndromes. Pathogenic variants in the aryl hydrocarbon-interacting protein gene (AIP) have been increasingly recognised since their initial description in 2006 and are reported in up to 15% of FIPA families. AIP associated tumours are most commonly growth hormone producing; presenting at a younger age with large tumours that are relatively resistant to conventional medical therapy.

In this talk I will discuss historical aspects of Irish giants and some of the initial studies examining the relationship between FIPA and germline AIP mutations. I will present 2 case series from our own clinic which further examine this relationship, as well as discussing current indications for testing.



- Familial isolated pituitary adenoma
- 4 index families in N Ire
- Tooth extracted
- Same AIP mutation
  - c.910C→T
- Common ancestor
  - 57-66 generations ago

Chahal HS et al. N Engl J Med 2011;364:43-50.

David Carty

AIP-associated pituitary tumours

- Typically male
  - presenting at young age
- GH secreting
  - Sparsely granulated
  - Relatively resistant to medical therapy
- Vast majority macroadenoma
  - Apoplexy more common

AIP-associated pituitary tumours

- Incomplete penetrance
  - 17-23% with AIP mutation clinically affected
  - FH often not elicited
- Homologous / heterologous
- Reported worldwide
  - Youngest affected patient 4 yrs

Family 1

- First reported AIP family with prolactinoma
  - IGF-1 normal in all affected patients
- High degree of penetrance
- No known Irish heritage
- Degree of DA resistance

Rachel Crowley

Biography

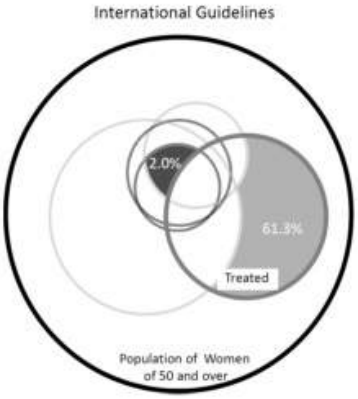
Consultant Endocrinologist at St Vincent's University Hospital Dublin, Clinical Professor at University College Dublin. Co-lead Irish centre for European Reference Network in Rare Bone Disease (ERN BOND). Co-lead rare disease clinical trials network. Interested in rare bone, adrenal, pituitary and electrolyte disorders, as well as rare disease research challenges. Reader, and capsizer of small boats.

Balancing Bone

This talk will focus on getting the right bone treatments to patients who need them. It will explore the factors that lead to over- and under-treatment of osteoporosis both from the patient and the clinician perspective, and review the challenges in clinical decision making and engagement with treatment plans.

Treatment Decisions re osteoporosis

- Osteoporosis treatment profile Valencia



Messages

- Guidelines do not agree
- Significant number treated without obvious indication
- Small number missed

More likely to be treated if: age 65-69; menopause < 40yo; vert #; DXA OP
Less likely if BMI > 30kg/m²

Sanfélix-Gimeno PLOS One 2015

Under treatment – starting / continuing

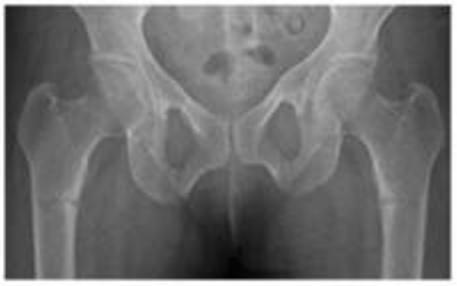
- Patient reluctance to start / non-adherence to prescription
  - only 39% of English-language OP guidelines include patient beliefs / values / preferences *Sale Osteopor Int 2019*
- HCW reluctance / concern re complications
- Failure to recognise risk

- Deferred until after investigation / investigation delay

Rachel Crowley

Over treatment

- The worried well
- Research participants / control subjects
- Non-fragility fractures
- GC replacement (rather than pharmacologic) therapy
- Treating osteomalacia rather than osteoporosis



Treatment Planning

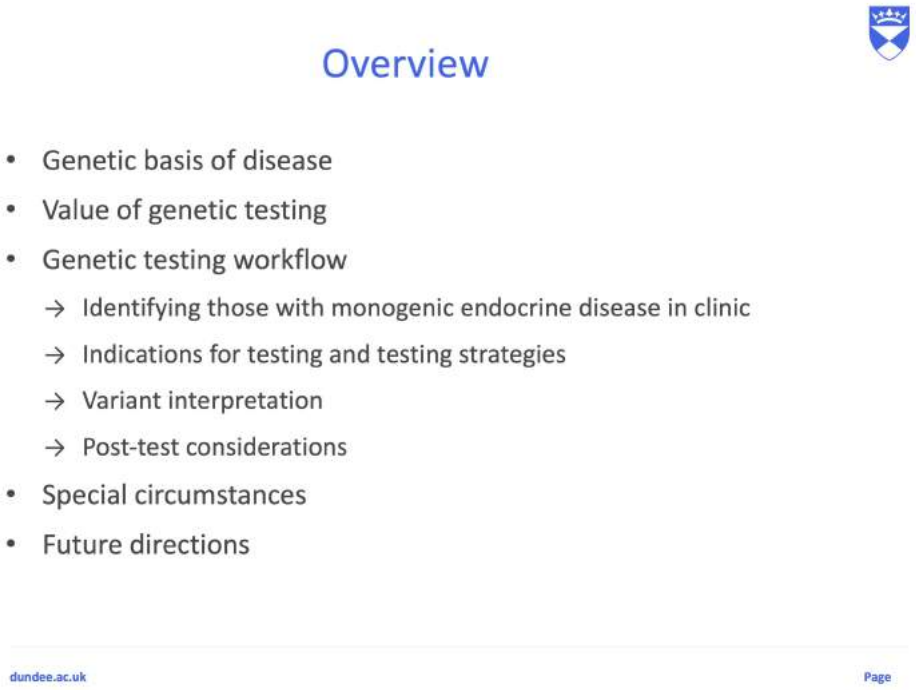
- Does this individual need osteoporosis treatment?
- What's the risk / benefit for this individual, for the proposed treatment?
- Should it be stopped / paused / when / what is needed to mitigate risk of stop?
- Monitoring plan

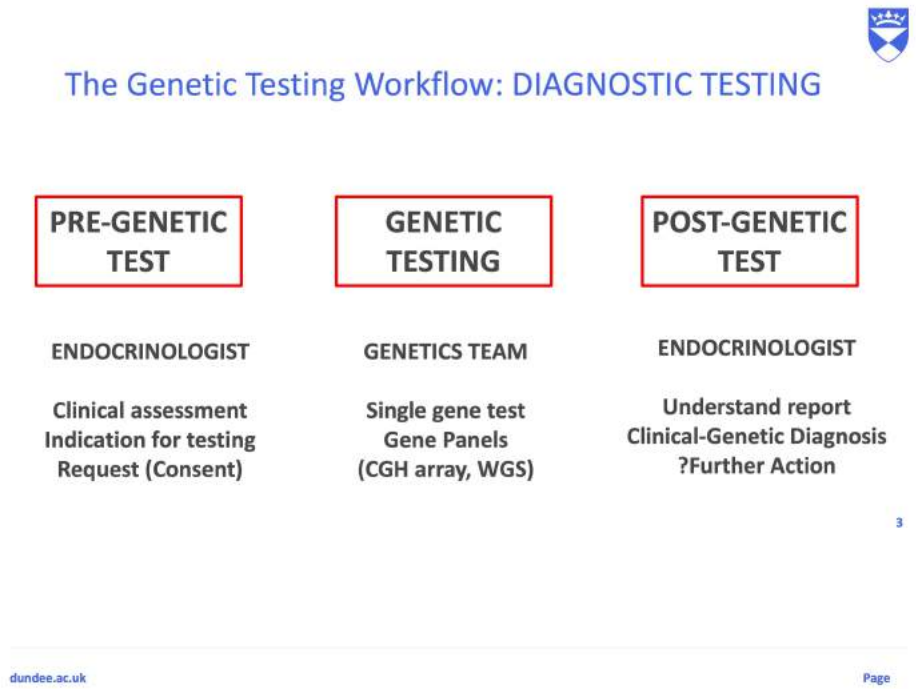
Paul Newey

Biography

Dr Paul Newey is a Clinical Reader and Honorary Consultant Endocrinologist at Ninewells Hospital & Medical School, Dundee. He undertook his undergraduate training in Edinburgh before moving to Oxford for specialist training. He moved to Dundee in 2014 and combines clinical and research activity with major interests in endocrine neoplasia syndromes, disorders of calcium homeostasis and practical aspects of genetic testing.

Everything you wanted to know about genetic testing but were afraid to ask





Paul Newey

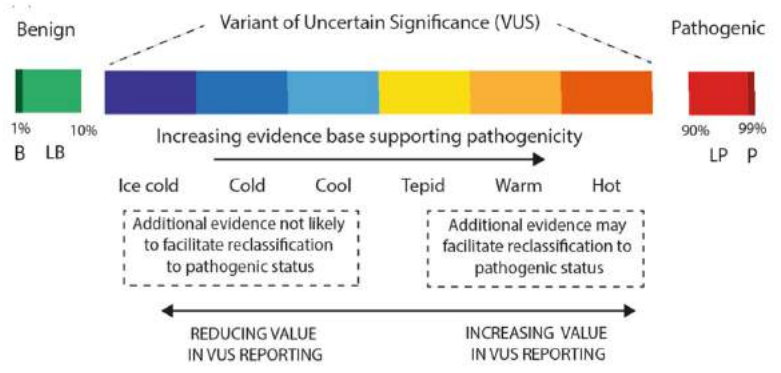
Selecting the optimal genetic test

- Determining the optimal diagnostic genetic test will be determined by:
  - The clinical phenotype
  - The likely type of genetic abnormality responsible for the phenotype (e.g. SNV, indel or larger structural/chromosomal abnormality)
  - The extent of genetic heterogeneity (i.e. how many different genes could give rise to the clinical phenotype)
  - The availability of DNA samples from additional family members

Germline genetic testing: DNA sequencing

	Next-Generation Sequencing (NGS)		
Sanger Sequencing	**Disease-targeted gene panel**	**Whole-Exome Sequencing (WES)**	**Whole-Genome Sequencing (WGS)**
1-10 genes	5-100 genes	30,000 genes	Everything (coding and non-coding)
• labour intensive • low content • interpretation simple • cost/base high	• low content • interpretation simple • cost/base medium	• high content • interpretation challenging • high risk VUS/IFs • cost/base low	• Very high content • interpretation challenging • high risk VUS/IFs • cost/base very low
e.g. 1-10kb (1000-10,000bp)	e.g. 5-100kb (5000-100,000bp)	e.g. 30Mb (30,000,000bp)	e.g. 3Gb (3,000,000,000bp)

Variants of Uncertain Significance



Newey, Clin Endocrinol 2022

Kristien Boelaert

Biography

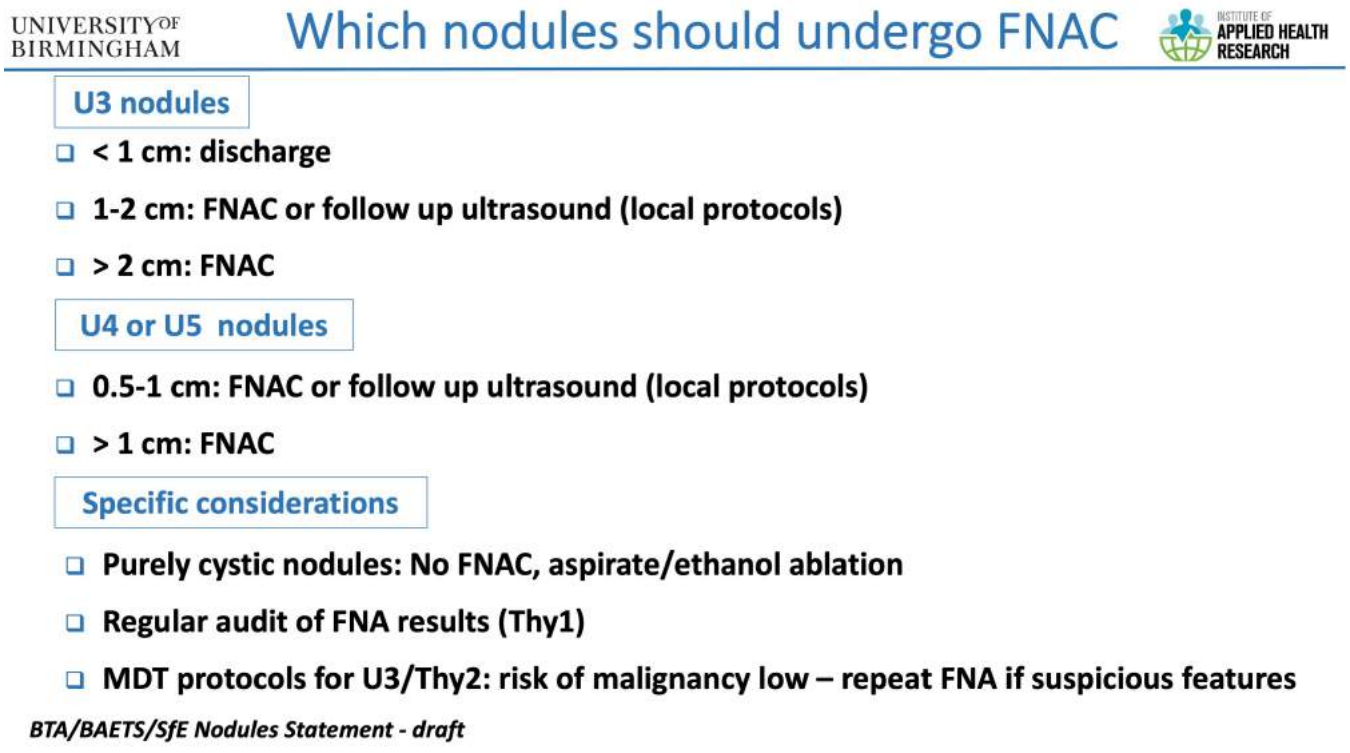
Kristien Boelaert is a Professor of Endocrinology at the University of Birmingham and a Consultant Endocrinologist at University Hospitals Birmingham. She is an active researcher in the field of thyroid diseases. She has published more than 160 papers (H-index 47) and has received more than £8 million in grant funding. She was the Clinical Lead for the NICE Guidelines on Thyroid Diseases and leads the National Consensus Statements on Management of Thyroid Cancer. She is a member of the RCOG Green-Top and the American Thyroid Association guideline panels on Thyroid Diseases in Pregnancy. Kristien is Senior Editor for Endocrine Connections, BMC Endocrine Disorders and the Journal of the Endocrine Society. She serves on the Editorial Boards of several endocrine journals including Lancet Diabetes & Endocrinology, Thyroid and Clinical Endocrinology. She is President-Elect of the British Thyroid Association, Chair of the Clinical Committee of the Society for Endocrinology and member of the SfE Council, The ATA Awards Committee, the Endocrine Society Annual Steering Meeting Committee and the RCP Specialist Certificate Examination Board.

Managing thyroid nodules and thyroid cancer in 2023

Thyroid nodules are common and may be found in around 50% of the population on high resolution ultrasound. Increasingly they are detected on cross-sectional imaging for non thyroid-related indications. The vast majority (>90%) of thyroid nodules are benign and it is important to identify those that are potentially malignant for further management.

The incidence of thyroid cancer has increased significantly over the last 4 decades, although this is largely due to increased detection of low-risk thyroid cancers and mortality rates have not changed significantly. The majority of differentiated thyroid cancers are low risk and their current management involves significant de-escalation of treatment and reduced follow-up. In addition, several targeted treatments have been identified for advanced and metastatic differentiated and medullary thyroid cancer.

This symposium will summarise the latest evidence and guidelines in the contemporary management of thyroid nodules and cancer.



Kristien Boelaert

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FU of conservatively managed nodules

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- **U2 nodule > 1 cm with high-risk clinical features – discharge if no progression on repeat scan**
- **U3 nodule > 1 cm with Thy2 cytology – discharge if no progression on FU scan**
- **U3 nodule > 1 cm without cytology – consider follow up for at least 2 years**
- **U3 nodule > 1 cm and with repeated Thy1 cytology – consider follow up for at least 2 years or diagnostic hemithyroidectomy**
- **U4 or U5 nodule < 1 cm – consider follow up for at least 2 years**
- **Any nodule with Thy3a, Thy3f, Thy4 or Thy5 cytology not treated surgically – consider follow up for at least 5 years**

BTA/BAETS/SfE Nodules Statement - draft

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Extent of surgery for DTC

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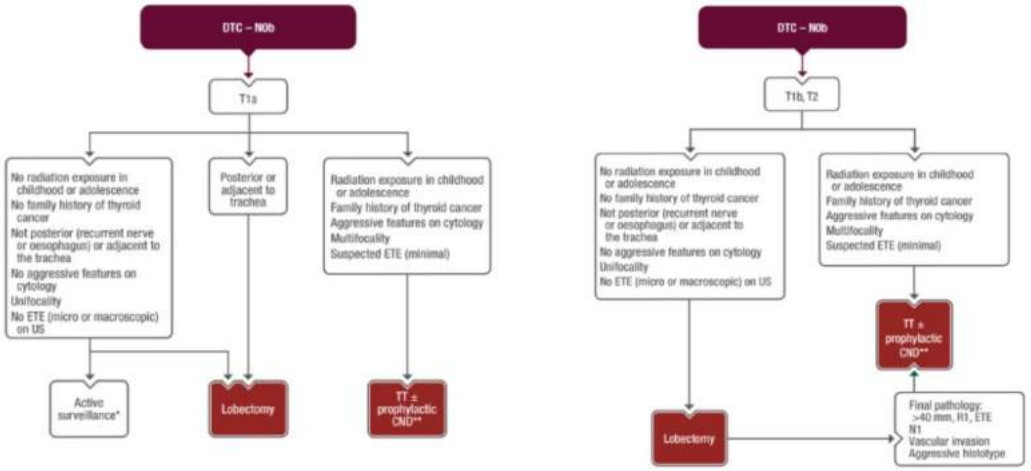

Filetti et al. ESMO Thyroid Cancer. Annals Onc 2019; 30: 1856-1883

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No 131-I in low risk DTC

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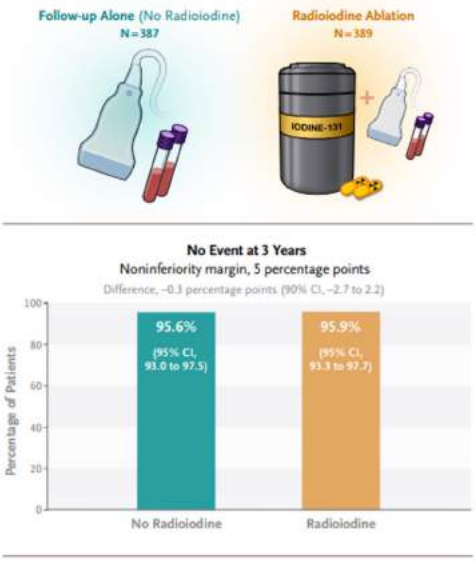

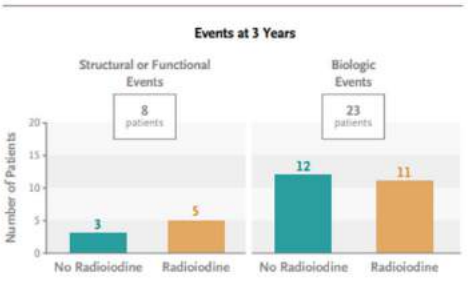

CONCLUSIONS

In patients undergoing thyroidectomy for low-risk differentiated thyroid cancer, follow-up alone without radioiodine therapy was noninferior to radioiodine therapy in terms of events at 3 years.

Leboulleux et al. NEJM 2022, 386: 923-932

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Proposed algorithm for DTC

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	Neck ultrasound	Serum Tg measurement	TSH target	DRS	Specialist follow up
Lobectomy	6-12 months* 3 years^	Not recommended	0.3 – 2.0 mIU/L indefinitely	Not applicable	3 –5 years
Total thyroidectomy no RRA	6-12 months* 3 years	Recommended for 3 – 5 years	0.3 – 2.0 mIU/L indefinitely	Optional	3 –5 years
Total thyroidectomy with RRA	6-12 months Nil further if negative	Recommended for 3 – 5 years	< 0.1mIU/L until DRS / then reassess	9-12 months	3 –5 years

UK Consensus Statements for low risk thyroid cancer, 2023, draft

Prakash Abraham

Biography

Prakash Abraham has been working as a Consultant Endocrinologist at the Aberdeen Royal Infirmary since 2002. He is the Clinical Lead for Endocrinology since 2015 where he is active in several areas of Endocrinology.
He has an interest in clinical Pituitary disease and in collaboration with colleagues in Cambridge was instrumental in setting up a 11C-Methionine PET CT scan service in Aberdeen for functioning pituitary adenomas. He is involved in setting up pathways for this scanning to be used by pituitary centres across Scotland and has been involved in health economics research of this modality.

Functional Imaging of Pituitary Adenomas in Scotland – Choosing the Right Patients

Abstract:
11C-methionine (11C-Met) positron emission tomography co-registered with MRI is a new imaging technique used for functioning pituitary adenomas, permitting targeted intervention (Transphenoidal Surgery (TSS) or Radiotherapy). The C-Met PET-CT scan has been available in Aberdeen since Dec 2016 – with a break from 2019-2022 due to cyclotron refurbishment.

We now have availability for one day a month – potentially 2 per day (or about 20 patients across Scotland a year) and can offer this scan for suitable patients with Acromegaly, Cushing's disease, TSHoma and Prolactinomas. We continue to develop our pathways for this scan and continue to collaborate closely with Cambridge – the only other centre in UK doing this scan presently.

Prevalence figures of these rare endocrine conditions (Aberdeen ABZ extrapolated)
Acromegaly - 7-8 per 100000 (ABZ 40, Scotland 400)
Cushing's - 3 per 100000 (ABZ 15, Scotland 150)
TSHoma - 0.5 per 100000 (ABZ 3, Scotland 30)
Prolactinomas - 40-50 per 100000 (ABZ 200, Scotland 2000)

How many would benefit from the scan in Scotland?
Acromegaly - Aberdeen - perhaps about 10 would benefit from the scan, so extrapolate to Scotland, up to 100 could potentially benefit (but will plan to roll out gradually according to our prioritisation strategy to maximise cost benefit).
Cushing's & TSHoma even rarer and mainly for primary diagnosis - perhaps about 3-5 new patients per year across Scotland who would not have a clear target on their MRI Pituitary.
Prolactinomas - we have not had any scan experience here yet, but Cambridge doing the scan for some difficult cases prior to surgery.

Patients with acromegaly will be invited to participate in a health economic evaluation of the scan. Impact of MOREAPT (Management Of REsidual Acromegaly following Primary Therapy) strategy on acromegaly management following primary therapy.

Our initial experience of about 20 patients, shows that this imaging modality can be transformative in a small subset and choosing the right patients will maximise the benefit.

Prakash Abraham

Who to refer for molecular imaging of functioning pituitary adenomas?

Email for referrals and Met PET scan: gram.metpetscan@nhs.scot

Acromegaly:
Primary Localisation:
New diagnosis, No clear pituitary target. IGF1 >1.3 (persistent)
Secondary Localisation:
Willing for surgery or RT if target found.
Higher Priority: IGF1 >1.3 on current medications (likely to rise to >1.5 on discontinuation)
Lower priority: Patient controlled with SSA wishing to consider surgery – due to SSA side-effects or a chance to see if surgical cure is possible.
Willing to stop medication for 3 to 5 months (SSA 3 months, DA 1 month, Can continue Pegvisomant).
Scan booking will be based on IGF1 levels on medications (IGF1 >1.5ULN, scan booked at 3 months, IGF1 between 1.3-1.5, scan booked for 4 or 5 months off medication (SSA))

Cushing's
Primary Localisation
New diagnosis, No clear pituitary target or adenoma <6mm, Likely Pituitary driven
Secondary Localisation
Recurrent Cushing's.
Willing for surgery or RT if target found.
Willing to stop medication for 3 to 5 months (SSA 3 months, Can continue Metyrapone /Ketoconazole/Osilodrostat) including morning of test

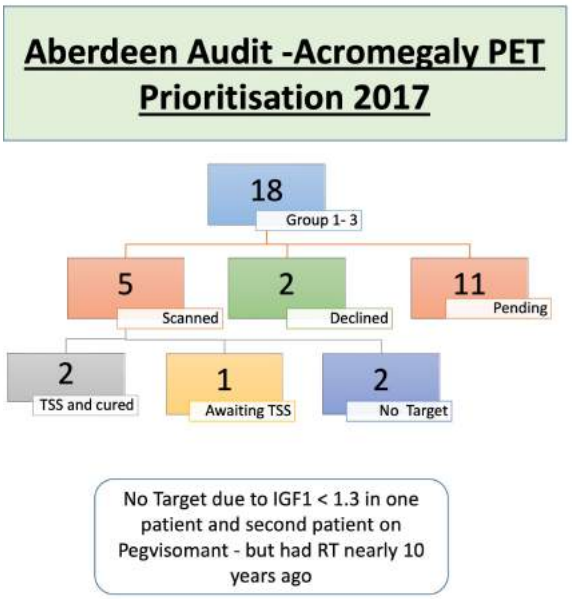
TSHoma
New Diagnosis, No clear pituitary target or adenoma <6mm?
Willing for surgery or RT if target found.
Willing to stop medication for 3 to 5 months (SSA 3 months, Can continue antithyroid medications). Avoid overtreatment resulting in hypothyroidism.

Prolactinoma
Resistant or Intolerant of Dopamine Agonists
No clear pituitary target
Willing for surgery or RT if target found

Prevalence and potential metPET patients (ABZ-Aberdeen, 10% population of Scotland)

- Acromegaly - 7-8 per 100000 (ABZ 40, Scotland 400)
  - Potential benefit from metPET scan - 10-15(ABZ); 100-150(Scotland)
  - Aberdeen Audit – upto 18 patients identified
- Cushing's - 3 per 100000 (ABZ 15, Scotland 150)
  - 3 to 5 new patients per year, across Scotland, where adenoma <6mm and needs either BIPSS or metPET
- TSHoma - 0.5 per 100000 (ABZ 3, Scotland 30)
  - 1 to 3 patients per year across Scotland where adenoma not visualised on scan
- Prolactinomas - 40-50 per 100000 (ABZ 200, Scotland 2000)

Prakash Abraham



Group	Acromegaly Treatment Status	2017	2020
1a	Poor control on SSA/pegvisomant	7*	0*
1b	Poor control, SSA intolerant/unsuitable (may have tried DA)	0	2
1c	Suboptimal control on SSA	2	2
2	Good control, very high-cost medication pegvisomant/pasireotide	1	1
3	Good control, high-cost medication SSA	8	12
4	Poor control DA – switch to SSA	4	0
5	Good control on DA	2	3
6	Good control on no medication	27	29
7	Deceased/Lost to follow-up	0	2
	Total	51	51

Functioning assessment prior to scan

- Confirmation of functional activity 6 weeks prior to scan date- if not active enough , will need to remain off medication for longer and recheck parameters monthly and defer scan
- Acromegaly - IGF-1 ratios>1.5 ULN and ideally GH >1.5mcg/l on day of scan (Off SSA for atleast 3 months and Cabergoline for 1 month).
- Cushing's – consistent hypercortisolism (no evidence of cyclicity) - can remain on metyrapone/ketoconazole/osilodrostat. ACTH done in last 2 months (and on day of scan)
- TSHoma- hyperthyroid bloods – can remain on ATD (off SSA for 3 months). Avoid overtreatment resulting in hypothyroidism.

Health Economics

- The surgical cure in 3 patients (two acromegaly and one TSHoma, on Pegvisomant and Lanreotide) has resulted in a cost saving of ~£60,000 per annum .
- Since 2017, the cost saving to our endocrine drug budget from these three patients would have been about £300,000 – with ongoing savings, since two of the patients are under 35 years.
- Research project
  - Clinical and Health Economic impact of using **MOREAPT** (**M**anagement **O**f **RE**sidual/ **RE**current **A**cromegaly following **P**rimary **T**herapy) strategy by using 11C-methonine PET CT/MR scanning in the management of partially treated and symptomatic acromegaly following primary therapy .

Victoria Tyndall

We present a case of severe Amiodarone Induced Thyrotoxicosis (AIT) in a 41 year old Ukranian refugee with significant underlying cardiac disease (AF, mechanical AVR with leak, reduced ejection fraction 48% and severe MR).

The patient was initially routinely referred to Cardiology while resident in a refugee ship in Leith Docklands, alongside his wife and two children. He later presented to the emergency department with palpitations and a pulse in AF of 170-180bpm while taking Amiodarone 200mg daily which was switched to Bisoprolol and Digoxin rate control. Thyroid function tests (TFTs) were normal with a fT4 24pmol/L and TSH of 1.9 at that time.

He re-presented one month later with worsening palpitations, fatigue and weight loss. Repeat TFTs showed new thyrotoxicosis and T4 >100 pmol/L and T3 of 25pmol/L. Thyroid storm was likely with a Burch-Wartofsky score of 55. Propylthiouracil 200mg six hourly was commenced alongside Prednisolone 40mg OD. Bisoprolol was switched to Propranolol 40mg QDS.

At follow up three weeks later, PTU therapy was switched to Carbimazole 60mg OD. A thyroid ultrasound was consistent with thyroiditis and a diagnosis of Type 2 AIT was made. Cholestyramine 4g BD was also initiated shortly thereafter. Despite 60mg Prednisolone, 60mg Carbimazole and Cholestyramine 4g QDS, severe thyrotoxicosis persisted with fT4 >100 and fT3 4.3nmol/L. A thyroidectomy was therefore planned in a final attempt to render him euthyroid prior to a redo AVR and new MVR.

He was commenced on Lugol's Iodine two weeks prior to thyroidectomy and underwent surgery in December 2022. Perioperatively, he received hydrocortisone cover. Post operatively, his Carbimazole and Colestyramine were stopped and a reducing regime of Prednisolone alongside Levothyroxine was implemented on discharge.

At Endocrine follow up, he felt much improved with TFTs showing a T4 of 11pmol/L and TSH of 18. His Levothyroxine dosage was adjusted up to 125mcg. Atrial fibrillation was rate controlled though he is still experiencing occasional runs of fast palpitations. He awaits cardiothoracic surgery and has been admitted in the interim with decompensated heart failure in the context of gastroenteritis.
This rare case highlights the various medical treatment options for severe thyrotoxicosis. It also shows that cessation of Amiodarone therapy does not prevent the occurrence of thyrotoxicosis after the drug has been stopped.

Laura Reid

Impact of CSII therapy on diabetic retinopathy in Type 1 diabetes

Introduction: Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide and affects almost all adults with Type 1 diabetes within 20 years of diagnosis. It is well established that optimising glycaemic control reduces DR risk, however little is known about the impact of individual Type 1 diabetes treatment modalities on the incidence and progression of DR.

Study Question: How does intensification of glycaemic control with insulin pump therapy affect DR incidence and progression?

Methods: Retrospective cohort study using the SCI – Diabetes database, assessing retinal screening outcomes and HbA1c changes in people with Type 1 diabetes within NHS Lothian. Comparative analysis of 204 adults commenced on CSII therapy between 2013 and 2016, and 211 adults eligible for CSII during the same period but who continued on MDI therapy.

Results: DR progression occurred in a smaller proportion of adults following commencement of CSII vs continued MDI therapy over mean 2.3 year follow-up (26.5% vs 18.6%, $p = 0.0097$). High baseline HbA1c (>75 mmol/mol [9%]) was associated with DR progression in the MDI group ($p = 0.0049$) but not the CSII group ($p = 0.93$). Change in HbA1c at follow-up, irrespective of baseline glycaemic status, did not significantly affect DR progression in either group.

Study conclusions:

- No evidence of early DR worsening following the introduction of CSII therapy in those with no or mild baseline DR
- Change in HbA1c not associated with DR progression
- Reduced DR progression in adults treated with CSII compared with MDI

Maria Bantounou

A Systematic review of drug exposure as a predictor for diabetic retinopathy risk modelling

Introduction

Diabetic retinopathy (DR) is an important cause of avoidable vision loss in working-age people. Many models have been developed to predict the risk of developing DR utilising routinely collected clinical information including a commercially available application RETINARISK1. NHS Grampian and the University of Aberdeen have developed a DR progression risk prediction algorithm that uses automated imaging markers as predictors of retinopathy in addition to clinical variables. As changes in DR have been linked with glucose-lowering therapies, antihypertensives and lipid-lowering drugs (LL)2, drug exposure is being investigated as an additional predictor in this algorithm. However, modelling drug exposure is challenging as drug dose, duration of exposure, frequency of administration and compliance require consideration. To identify and evaluate drug modelling techniques utilised in DR prediction models, we performed a systematic review of the literature.

Methods

This search was undertaken from 24/07/2022 to 28/07/2022, using the EMBASE, MEDLINE and SCOPUS databases. Record screening, data extraction, risk of bias (ROB) assessment using the Prediction model ROB Assessment Tool (PROBAST)3 and certainty of evidence assessment following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)4 were performed by two independent reviewers. Quantitative analysis was undertaken in R version 4.1.1. The protocol for this review was registered on the PROSPERO database (CRD42022349764).

Results

19 DR risk prediction modelling studies (figure 1) that included drug exposure as a predictor were identified; 14 were at high, 2 were unclear and 3 were at low ROB. Due to high ROB and heterogeneity, outcomes of this review were of low certainty according to the GRADE assessment.

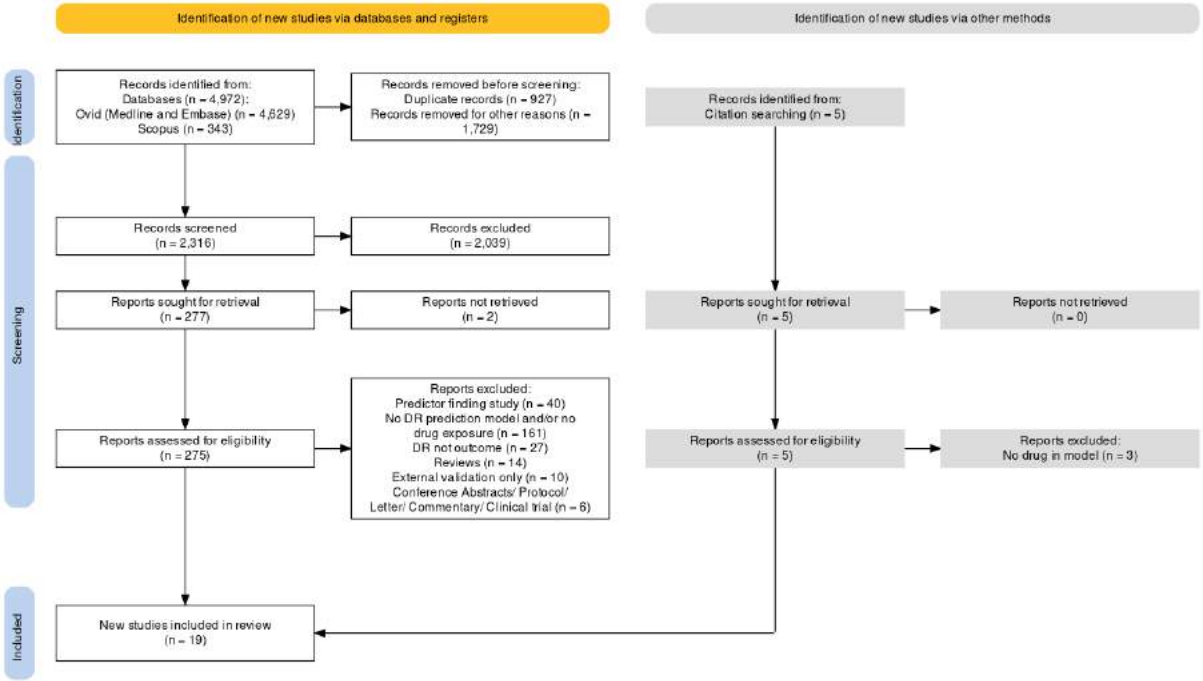


Figure 1: Prisma flowchart of selected studies. Records removed for other reasons at identification; N=121 not in English language, N=270 animal studies, N=1338 not an article. Abstract screening exclusion reasons; N=929 DR not outcome, N=98 review, N=882 no DR risk prediction model, N=85 irrelevant, N=21 no drug exposure, N=9 preclinical study, N=11 guideline, N=2 Case reports, N=1 Clinical trial (no model), N=1 commentary. DR; Diabetic retinopathy.

Maria Bantounou

The drug classes that were identified as predictors in the model included insulin (15/19, 79%), diuretics (1/19, 5.26%), anti-hypertensives (5/19, 26.3%), oral glucose lowering medication (7/19, 36.8%), LL (5/19, 26.3%), antiplatelets (1/19, 5.3%). Drug exposure was modelled as a categorical (n=14), as a combination of continuous (dose) and categorical (frequency, treatment duration) (n=3) or as a continuous (dose) variable (n=2). Aspirin (n=1), OAD (metformin; n=1, OAD; n=1) and LL (fenofibrate; n=1, LL; n=1) were associated with reduced risk of DR. Insulin (n=11) and antihypertensives (n=2) were correlated with an increased risk of DR.

Five studies reported calibration, 14 discrimination and 17 classification methods used. Four studies externally validated their models. Concordance measures of the models during internal validation ranged from 0.55 to 0.96 with the pooled C-statistic=0.79 (CI:0.77-0.82). In external validation, concordance ranged from 0.57 to 0.84 with the pooled C-statistic=0.78 (CI:0.71-0.83). Models with insulin, antihypertensives and LL (C-statistic=0.83; CI:0.74-0.92) had the highest C-statistic in internal validation (table 1); in external validation, higher concordance was noted for models including insulin (C-statistic=0.81; CI:0.77-0.82).

Table 1: Tabulated results of internal and external validation concordance statistics by drug exposure meta-analyses. CI; Confidence Interval

	Medication(s) in the summary model	No of other variables in the summary model *	C-statistics summary	95% CI	Weight
Internal validation Summary models					
1	Antihypertensive and oral anti-diabetic drug	4	0.61	0.54-0.68	6.2%
2	Insulin	10	0.81	0.78-0.84	42.3%
3	Insulin, oral anti-diabetic drug, antihypertensive, lipid-lowering drug	6	0.70	0.66-0.73	12%
4	Insulin and antiplatelet drug	15	0.79	0.74-0.85	15.6%
5	Insulin and oral anti-diabetic drug	10	0.7	-0.14-1.55	3.1%
6	Insulin and lipid-lowering drug	14	0.80	0.77-0.83	7%
7	Insulin, antihypertensive, lipid-lowering drug	5	0.83	0.74-0.92	10.9%
External validation Summary models					
1	Insulin	15	0.81	0.64-0.98	23.5%
2	Insulin and lipid-lowering drug	14	0.79	0.79- 0.82	64.8%

**coefficient > ±0.1 and/or p-value <0.05 and/or feature importance analysis F score> 200 : Variable in the models ranged from age, sex, BMI, past medical history, blood glucose/ HbA1c, kidney function, lipid levels, blood pressure, diabetes duration, smoking status*

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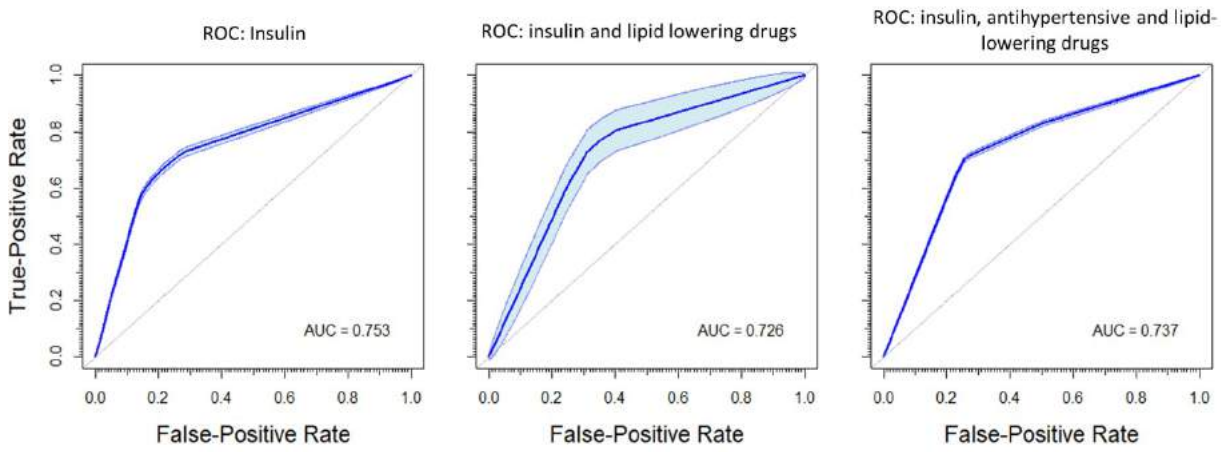
The Area Under the Curve (AUC) of the summary Receiver Operating Curves (ROC) for internal validation was 0.745. Insulin models had the highest summary AUC=0.753 (figure 2). Insulin was the only drug associated with DR development/progression (logOR=0.74, CI:0.37-1.12, p-value<0.01).

Figure 2: Internal validation summary ROC curve for models with available data according to drug(s) included as predictor(s) in models. The area under the summary ROC curve (AUC) is shown.



Conclusion

Drug exposure was handled as a categorical variable in most diabetic retinopathy prediction models, reflecting the challenges in modelling large-volume drug data derived from electronic health records. Insulin was consistently correlated with improved model concordance and had a significant subgroup effect on DR progression. Future work is needed to improve the standardisation of drug information recording using SNOMED to enable the development of better models to understand the impact of drug exposure on diabetes complications.

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Kavinga Gamage

Cushing disease presenting as osteonecrosis of the femoral heads…

Introduction

Non traumatic osteonecrosis of the hip is commonly seen with exogenous steroid treatment and may rarely be associated with exogeneous hypercortisolism.

Case presentation

A 64-year-old female with background history of hypertension presented with left sided hip pain which was worse with movement. There was no preceding history of fever. Examination revealed a BMI of 20.2kg m-2, central obesity with thin extremities. There were round facies and thin skin. She had hyperpigmented nails and extremities. Blood pressure was 150/90mmHg. Examination of the hips revealed painful hip movements on left hip as well as right hip. Proximal myopathy was noted on neurological examination. Laboratory investigations were significant for hypokalemia (serum Potassium 3.3 mmol/L) and overnight dexamethasone test was not suppressed (416nmol/L). X-ray hips showed left sided crescent sign. Magnetic Resonance Imaging of bilateral hips were done after orthopedic opinion which showed bilateral T1 hypo intensity and T2 heterogeneous hyperintensity and double line sign at the femoral heads. Further evaluation revealed an ACTH of 23.2 ng/dL suggestive of ACTH dependent Cushing. Inferior petrosal sinus sampling confirmed pituitary dependent ACTH hypersecretion, unfortunately lateralization was not possible. MRI pituitary revealed a left sided pituitary microadenoma. She underwent transsphenoidal hypophysectomy which demonstrated pituitary adenoma in histology with Ki index of 40%. Post operative cortisol values remained elevated, and radiotherapy planned.

Conclusion

Endogenous Cushing syndrome should be considered in patients presenting with osteonecrosis of the hip, especially in those without prior history of steroid use.

Kirsty Wood

Title: Desmopressin Test – any use in Cushing's disease?

Identifying the cause of hypercortisolism is vital in ensuring the correct treatment plan for a patient. I present the cases of two patients in whom the desmopressin test, used as an adjunct to the CRH test, proved helpful in determining the cause.

Patient 1

A 27 year old man who initially presented with weight gain, abdominal striae and sweating was admitted to the psychiatric hospital with low mood, anxiety and suicidal ideation. He was found to have elevated 24 hour urinary cortisol (1446 nmol/24 hours), random cortisol (624 nmol/L) and ACTH (98 ng/L). His cortisol did not suppress after low dose (625 nmol/L) or high dose (cortisol 259 nmol/L and ACTH 50 ng/L) dexamethasone suppression test (DST). MRI pituitary showed a 5mm adenoma and CT head, thorax, abdomen and pelvis was normal. He commenced on Metyrapone. Variable cortisol and ACTH results in the following months and delays in methionine PET availability led to the need for further biochemical localisation with desmopressin test and CRH test. These were both consistent with pituitary Cushing's disease and he proceeded to transphenoidal surgery (TSS), achieving biochemical cure with day 2 morning cortisol of 46 nmol/L.

Patient 2

A 44 year old man with a background of Crohn's disease, osteoporosis and hypertension presented with low libido. Pituitary function testing showed low testosterone 3 nmol/L, inappropriately low LH 1.7 u/L. He was admitted to hospital with reduced mobility and significant peripheral oedema. On examination, he had plethoric facies, purpura and abdominal striae. 24 hour urinary cortisol was elevated at 3890nmol/24 hours and cortisol was unsuppressed at 860nmol/L after low dose DST with elevated ACTH at 148 ng/l. CT thorax, abdomen and pelvis showed no malignancy but old rib fractures and collapsed L1 vertebra. MRI pituitary showed a likely 8x7mm adenoma. He was commenced on Metyrapone. Desmopressin and CRH tests were both consistent with pituitary Cushing's disease and he proceeded to TSS. His morning cortisol on day 2 post pituitary surgery was 102 nmol/L and subsequent morning cortisol a month later was 70 nmol/L.

Discussion

It is imperative to identify the cause of ACTH dependent hypercortisolism before proceeding to TSS. MRI fails to identify a surgical target in up to 40% of patients with Cushing's disease and may incorrectly implicate an incidentaloma. Bilateral inferior petrosal sinus sampling is invasive and can lateralise a corticotroph adenoma in approximately 50% of patients. Methionine PET has been shown to locate a corticotroph adenoma with high sensitivity but is not yet widely available.

The Endocrine Society Guideline written in 2008 advises confirming endogenous hypercortisolism with screening tests and then proceeding to a CRH test but advised against the use of the desmopressin test until additional data validates its utility. Since then, several studies have established an adjunctive role of desmopressin in the diagnostic workup of Cushing's syndrome. In the two presented cases, the combination of CRH and desmopressin tests, both consistent with pituitary Cushing's disease provided the confidence with proceeding to TSS, resulting in cure.

Kirstin Griffin

SGLT2-inhibitors in CKD: What it means for patients with type 2 diabetes?

Introduction

SGLT-2 inhibitors are an important therapy in improving glycaemic control in patients with type 2 diabetes and have been available for use in diabetes for some years now. The DAPA-CKD trial showed that these medications slow disease progression in proteinuric chronic kidney disease (CKD) as well as reduce mortality from cardiovascular and renal causes [1]. Updated NICE diabetes guidelines have recommended that an SGLT-2 inhibitor should be considered (ACR 3-30mg/mmol) or offered (ACR>30mg/mmol) in addition to an ACE-inhibitor or ARB to treat CKD in patients with type 2 diabetes and an eGFR over 25ml/min/m2 [2]. The aim of this audit was to determine how many patients with type 2 diabetes are already prescribed SGLT-2 inhibitors within two health boards, NHS Borders and NHS Lothian, and to identify how many patients, who fulfil the CKD criteria, are not on treatment but would potentially benefit.

Methods

Two database searches of SCI-diabetes in NHS Borders and NHS Lothian were undertaken to identify all patients within primary and secondary care with type 2 diabetes. Within each health board, these patients were then divided into two groups: those who were prescribed an SGLT-2 inhibitor and those who were not. Within each group, patients were then stratified according to stage of CKD and quantification of proteinuria (based on ACR and PCR recording since January 2021).

Results

The database search identified 4143 patients with type 2 diabetes within NHS Borders and 44002 within NHS Lothian. Overall, 12% (n=513) of patients with type 2 diabetes were prescribed an SGLT-2 inhibitor in NHS Borders and 20% (n=8773) in NHS Lothian. Of those prescribed an SGLT-2 inhibitor, the majority had an eGFR >60 in both health boards (Borders, 85%, n=436; and Lothian, 88%, n=7752). In NHS Borders, of the 1406 patients with an eGFR <=60 (CKD Stage 3 or above), only 5% (n=77) patients were on a SGLT-2 inhibitor. A search for patients with an eGFR 25-60ml/min/m2, and therefore could be recommended for an SGLT-2 inhibitor based on CKD criteria, identified 27% (n=982) of CKD patients within NHS Borders who had not yet been offered this therapy. NHS Lothian had a similar proportion of their CKD patients (19%, n=6558) who were not yet prescribed an SGLT-2 inhibitor.

Both PCR and ACR were poorly recorded within both groups. Measurements from January 2021 onwards were included only to ensure results were recent. In total, only 18% (n=763) of patients had a PCR, and an additional 2% (n=58) patients had an ACR recorded in NHS Borders. NHS Lothian had a recent ACR recorded for 21% (n=9109) of their patients, and an additional 2% (n=97) had a PCR. Despite poor proteinuria recording, the study identified that 94% (n=162) who had a recent PCR>50 were not yet prescribed an SGLT-2 inhibitor in NHS Borders despite meeting the criteria. In NHS Lothian, 52% (n=287) of patients with an ACR >30 were not yet prescribed this therapy.

Kirstin Griffin

Discussion

This study showed that SGLT-2 inhibitors are currently not a widely prescribed therapy for patients with type 2 diabetes in NHS Borders and NHS Lothian. Most patients currently on this treatment do not have CKD and are prescribed this for glycaemic control. This study identified a significant population of patients with CKD who would potentially benefit from this treatment. Limited documentation of proteinuria is impacting clinicians' ability to identify patients with higher levels of proteinuria who would benefit most from the addition of this therapy. Despite this, 162 patients within NHS Borders and 287 within NHS Lothian were identified with significant proteinuria who would benefit from the addition of an SGLT-2 inhibitor to their diabetes and CKD management in line with the updated NICE guidance. There is likely a much larger cohort of patients who would be recommended for this therapy if there was a record of their proteinuria. Local laboratory policy within NHS Borders has restricted the testing of PCR and ACR measurements due to cost implications. This study highlights the need for proteinuria measurement to bring NHS Borders in line with national guidance. Furthermore, as most patients with type 2 diabetes are managed within primary care further work needs to raise awareness around SGLT-2 inhibitor prescribing and updated guidance for this high-risk patient population.

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Fraser Gibb

Biography

Dr Fraser Gibb is a Consultant Endocrinologist at the Edinburgh Centre for Endocrinology & Diabetes and Honorary Clinical Reader at the University of Edinburgh. He has research interests in type 1 diabetes and a range of endocrine conditions. He can give himself speaking slots at CalSoc because he organises it.

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