CalSoc 2019

caledonian society for endocrinology and diabetes

Dunkeld House

February 1st / 2nd

@CalSocEndo

www.calsoc.org

@CalSocEndo

#CalSoc2019

Contents

Programme of Events

Friday 1st February

13.00 – 14.30 Arrive

13.15 – 14.00 **Meet the Expert– Trainee session – Cushing's disease**
Prof John Newell-Price

Session 1

Chair: Dr Robert Lindsay
Reader
University of Glasgow

14.30 – 15.15 **Graves' Disease – optimising treatment**
Dr Fraser Gibb
Consultant Endocrinologist
Edinburgh Centre for Endocrinology & Diabetes

15.15 – 16.00 **Cushing's update**
Professor John Newell-Price
Professor of Endocrinology
University of Sheffield

16.00 – 16.15 Coffee

16.15 – 17.00 **The year in diabetes and endocrinology**
Professor Mark Strachan
Consultant Endocrinologist / Honorary Professor
Edinburgh Centre for Endocrinology & Diabetes / University of Edinburgh

17.00 – 17.30 **Endocrine genetics update / Endocrine IT system**

19.30 Dinner

Programme of Events

Saturday 2nd February

09.00 – 09.30	CalSoc Annual General Meeting

Session 2

Chair:	Dr James Boyle Consultant Endocrinologist Glasgow Royal Infirmary
09.30– 10.15	**The clinical utility of C-peptide measurement in the care of patients with diabetes** Dr Angus Jones Clinical Senior Lecturer University of Exeter
10.15 – 11.00	**Abstract Presentations** Dr Sharon Mackin Dr Maroria Oroko Dr Anne Sillars
11.00 – 11.15	Coffee
11.15 – 11.45	**Abstract Presentations** Dr Rob Gifford Dr Adeeb Naasan
11.45 – 12.30	**Update in phaeochromocytoma** Dr Colin Perry Consultant Endocrinologist Queen Elizabeth University Hospital, Glasgow
12.30	Lunch

Welcome to CalSoc 2019

Welcome to Dunkeld for the 38th winter meeting of the Caledonian Society for Endocrinology. This year's meeting promises to cover a wide range of clinically relevant topics across both diabetes and endocrinology, delivered by internationally recognised experts in their field.

In addition to the educational remit of CalSoc, the goal since the revival of the annual meeting has been to explore how the society can support improvements in endocrine care in Scotland. For several years, the possibility of a national IT system to support clinical care and research has been proposed. In the past few months progress has been made in navigating a route towards this and we will provide an update at the meeting.

Many thanks to our supporters from the pharmaceutical industry: MSD, Sanofi, Novo Nordisk, Napp and Ipsen. The meeting could not take part without their contribution and I would encourage you to visit their stands between sessions.

Dr Fraser Gibb
On behalf of the CalSoc Committee

CalSoc Committee

Dr Sam Philip
Consultant Physician and Honorary Clinical Lecturer
Aberdeen Royal Infirmary / University of Aberdeen

Dr Louise Clark
Consultant Physician
Hairmyres Hospital

Professor Graham Leese
Consultant Physician and Honorary Professor
Ninewells Hospital / University of Dundee

Dr Russell Drummond
Consultant Physician and Honorary Clinical Associate Professor
Glasgow Royal Infirmary / University of Glasgow

Dr Fraser Gibb (Secretary-Treasurer)
Consultant Physician and Honorary Senior Clinical Lecturer
Royal Infirmary of Edinburgh / University of Edinburgh

'Caledonian Society for Endocrinology & Diabetes Annual Meeting' has been submitted to the Federation of the Royal Colleges of Physicians of the United Kingdom for 6 category 1 (external) CPD credits. Approval pending.

Attendees

First name	Second name	Site
Prakash	Abraham	Aberdeen
Ganesh	Arungirinathan	Edinburgh
James	Boyle	Glasgow
Luke	Boyle	Edinburgh
Ross	Cairns	Glasgow
David	Carty	Glasgow
Helen	Casey	Glasgow
Louise	Clark	Hairmyres
Alan	Connacher	Perth
Ruth	Cordiner	Glasgow
Marion	Devers	Monklands
Charlotte	Dewdney	Shetland
Russell	Drummond	Glasgow
Catriona	Farrell	Dundee
Evgenia	Foteinopoulou	Edinburgh
Amy	Frank	Glasgow
Marie	Freel	Glasgow
Natasha	Galloway	Edinburgh
Nives	Gattazzo	Edinburgh
Priya	George	Dundee
Rob	Gifford	Edinburgh
Alex	Graveling	Aberdeen
Sheila	Grecian	Edinburgh
Fiona	Green	Dumfries
Lesley	Hall	Glasgow
Kate	Hughes	Glasgow
Mohammad	Jeeyavudeen	Aberdeen
Emma	Johns	Edinburgh
Pauline	Jones	Edinburgh
Angus	Jones	Exeter
Chris	Jones	Inverclyde
Chris	Kelly	Forth Valley
Brian	Kennon	Glasgow
Jan	Klepacki	Aberdeen
Catriona	Kyle	Edinburgh

First name	Second name	Site
Graham	Leese	Dundee
Robbie	Lindsay	Glasgow
Kathryn	Linton	Edinburgh
David	Macfarlane	Inverness
Alison	Mackenzie	Forth Valley
Sharon	Mackin	Glasgow
Laura	McCreight	Dundee
Neil	McGowan	Paisley
Martin	McIntyre	Paisley
Laura	McLaren	Forth Valley
Adeeb	Naasan	Glasgow
John	Newell-Price	Sheffield
Paul	Newey	Dundee
Maroria	Oroko	Glasgow
Louise	Osborne	Inverclyde
Alan	Patrick	Edinburgh
Catherine	Patterson	Kirkcaldy
Colin	Perry	Glasgow
Sam	Philip	Aberdeen
Roby	Rajan	Aberdeen
Rebecca	Reynolds	Edinburgh
Stuart	Ritchie	Edinburgh
Anne	Sillars	Glasgow
Lee	Sit	Edinburgh
Karen	Smith	Glasgow
Chris	Smith	Paisley
Angus	Stirling	Glasgow
Mark	Strachan	Edinburgh
Peter	Taylor	Cardiff
Craig	Thurtell	Dundee
Nyo Nyo	Tun	Edinburgh
Victoria	Tyndall	Edinburgh
Rachel	Williamson	Borders
Kirsty	Wood	Inverness
Rohana	Wright	Livingston

Dr Fraser Gibb

Biography

Dr Gibb graduated from the University of Edinburgh Medical School in 2000. He undertook specialist training in Endocrinology & Diabetes in Edinburgh between 2005 and 2012. He was appointed to a Consultant post in Endocrinology & Diabetes in 2012 at the Royal Infirmary of Edinburgh. His clinical interests include the management of type 1 diabetes, general endocrinology and the management of differentiated thyroid cancer.

Dr Gibb was awarded a PhD, from the University of Edinburgh, for research examining the metabolic effects of sex steroid hormones and has a number of active clinical research projects. He is currently Secretary-Treasurer of the Caledonian Society for Endocrinology & Diabetes and Chair of the Type 1 Diabetes subgroup of the Scottish Diabetes Group.

Abstract

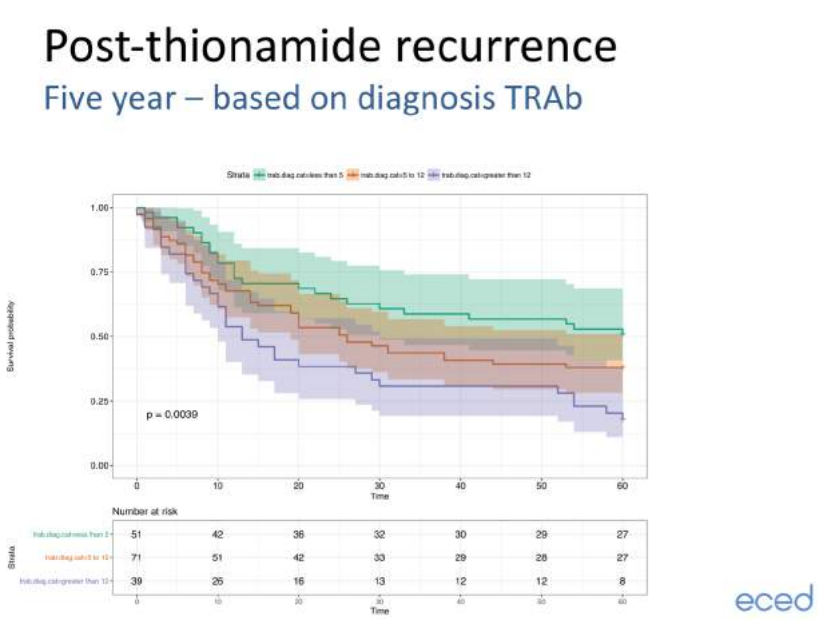
Graves' disease – optimising management

Thionamides

Recurrence after a course of thionamide occurs in 61.5% of individuals at 5 years. This risk is between 70 – 80% in those with high TRAbs at diagnosis (>12 U/L) or cessation of therapy (>1.5 U/L). Lower age but not gender or fT4 at diagnosis are associated with recurrence risk.

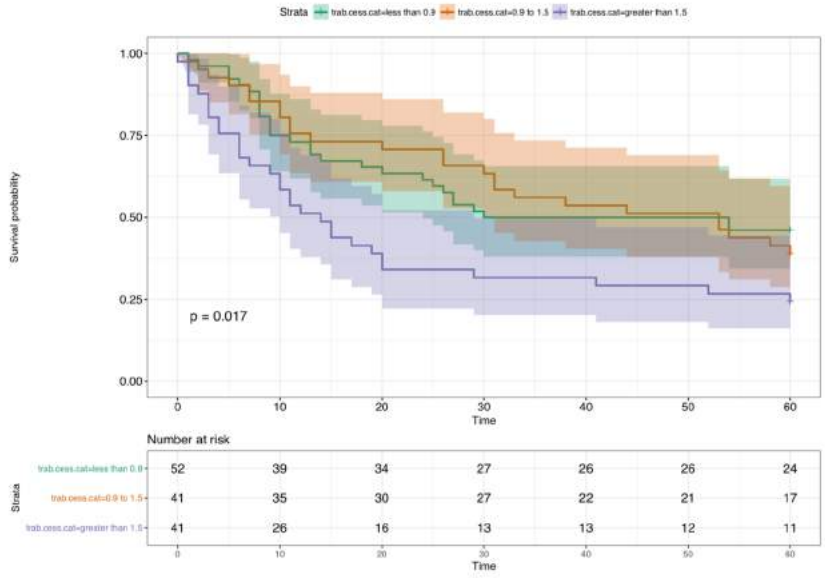
Radioiodine

Treatment failure is very common in people with high TRAb at diagnosis (40 – 50%).
Weight gain greater than 10% of baseline occurs in 31.1%.
Thyroid eye disease development is difficult to predict in a modern cohort of radioiodine patients.
Thyroid symptoms are common after RAI but treatment satisfaction is very high.
Higher dose (550MBq) may be associated with less treatment failure than lower dose (400MBq) RAI.



Post-thionamide recurrence

Five year – based on cessation TRAb



eced

Post-thionamide recurrence

Diagnosis TRAb

	Pre TRAb low	Pre TRAb mid	Pre TRAb high
	<5 U/L	5 - 12 U/L	>12U/L
Year 1	19/87 (21.8%)	35/125 (24.8%)	30/68 (44.1%)
Year 2	25/84 (29.8%)	49/120 (40.8%)	38/67 (56.7%)
Year 3	30/80 (37.5%)	56/114 (49.1%)	41/63 (65.1%)
Year 4	30/69 (43.5%)	55/98 (56.1%)	40/59 (67.8%)
Year 5	24/51 (47.1%)	44/71(62.0%)	31/39 (79.5%)
Year 6	15/34 (44.1%)	28/50 (56.0%)	21/25 (84.0%)
Year 7	13/27 (48.1%)	24/38 (63.2%)	19/22 (86.4%)

eced

Dr Fraser Gibb

Post-thionamide recurrence

Cessation TRAb

	End TRAb low	End TRAb mid	End TRAb high
	<0.9 U/L	0.9 - 1.5 U/L	>1.5 U/L
Year 1	21/97 (21.6%)	17/72 (23.6%)	28/61 (45.9%)
Year 2	31/94 (33.0%)	20/70 (28.6%)	36/61 (59.0%)
Year 3	38/88 (43.2%)	27/67 (40.3%)	37/60 (61.7%)
Year 4	35/74 (47.3%)	27/58 (46.6%)	37/54 (68.5%)
Year 5	28/52 (53.8%)	24/41 (58.5%)	30/41 (73.2%)
Year 6	22/41 (53.7%)	15/32 (46.9%)	22/28 (78.6%)
Year 7	22/35 (62.9%)	13/25 (52.0%)	17/21 (81.0%)

eced

RAI failure at first episode

Univariate analysis

	Treatment success (n = 478)	Treatment fail (n = 98)	P
Free T4 at diagnosis (pmol/L)	31 (24-41)	43 (30-57)	<0.0001
Free T4 prior to RAI (pmol/L)	22 (15-30)	24 (15-35)	0.157
TRAb at diagnosis (U/L)	7.5 (4.5-17.2)	13.3 (7.1-37.2)	<0.0001
TRAb prior to RAI (U/L)	6.3 (3.5-12.8)	11.0 (3.7-25.4)	0.002
Age at RAI (y)	52 (44-64)	50 (40-60)	0.110
Male	116/147 (78.9%)	31/147 (21.1%)	0.128
Female	362/429 (84.4%)	67/429 (15.6%)	
Pre-RAI thionamide	230/304 (75.7%)	74/304 (24.3%)	<0.0001
No pre-RAI thionamide	248/272 (91.2%)	24/272 (8.8%)	
Post-RAI thionamide	118/166 (71.1%)	48/166 (28.9%)	<0.0001
No post-RAI thionamide	360/410 (87.8%)	50/410 (12.2%)	
Current smoker at RAI	131/160 (81.9%)	29/160 (18.1%)	0.480
Non-smoker at RAI	234/277 (84.5%)	43/277 (15.5%)	
RAI within 6 mo	225/286 (89.2%)	31/286 (10.8%)	<0.001
RAI after 6 mo	223/290 (76.9%)	67/290 (23.1%)	

Continuous variables are compared by Mann-Whitney *U* test and categorical variables by chi-square.

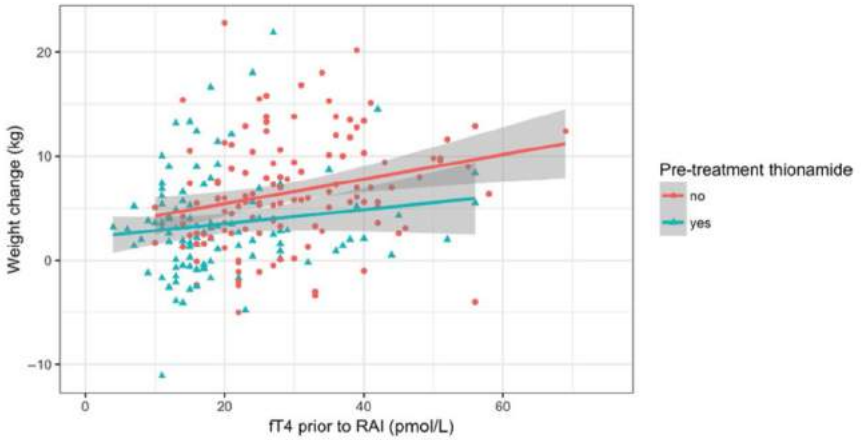
fT4, TRAb, post RAI thionamide all independently associated with failure

Clinical Endocrinology. 2019;90:192–199.

eced

Post-thionamide recurrence

Seven year



18.4% gained more than 10kg
31.1% gained more than 10% baseline weight

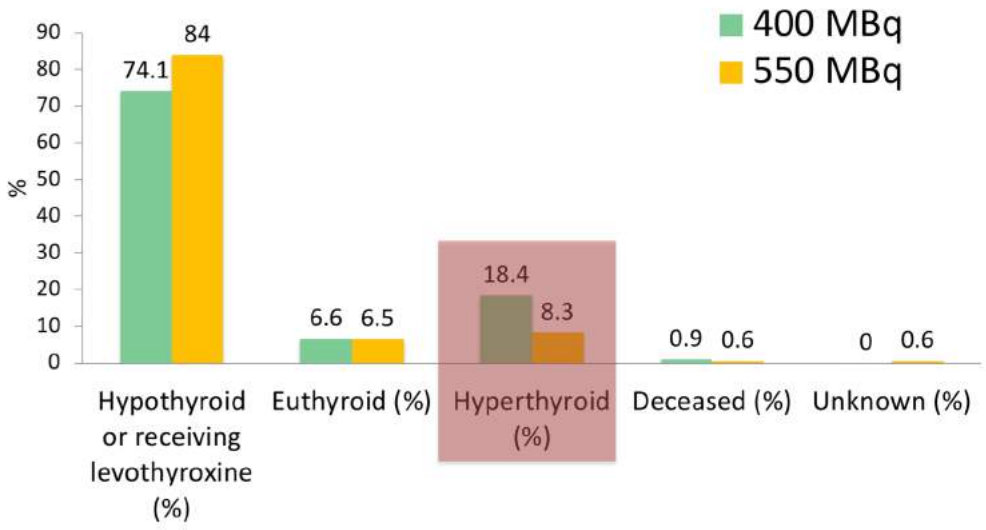
Median +3.2kg if normal/low fT4 at RAI
Median +5.8kg if high fT4 at RAI

Clinical Endocrinology. 2019;90:192–199.

eced

High versus low RAI

Edinburgh and Aberdeen outcomes compared



unpublished

eced

Prof John Newell-Price

Biography

John Newell-Price (MA PhD FRCP) is Professor of Endocrinology at the University of Sheffield. He qualified in medicine at the University of Cambridge, and undertook his clinical endocrine specialist training at St Bartholomew's Hospital in London, where he was also a Medical Research Council Training Fellow for his PhD.

Since 2000, he has been at the University of Sheffield, and a Consultant Endocrinologist at Sheffield Teaching Hospitals NHS Foundation Trust where he is the Clinical Lead for Endocrinology, Chairs the MDTs, and is Lead for the Sheffield ENETS European Centre of Excellence for Neuroendocrine Tumours. He has set up and co-runs the joint gamma knife radiosurgery service for pituitary tumours at the National Radiosurgery Centre in Sheffield.

His research interests include glucocorticoids, pituitary and neuroendocrine tumours, and has published widely in these areas.

He is Senior Editor of the journal 'Clinical Endocrinology' and has served on the Editorial Board of 'Journal of Clinical Endocrinology and Metabolism', and on task forces for clinical guidelines authored on Cushing's syndrome (2008 and 2015) for the American Endocrine Society and Adrenal Incidentaloma (2016) for the European Society for Endocrinology. He chaired The Royal College of Physicians, UK Joint Specialist Committee for Diabetes and Endocrinology (2012-2016) and is NIHR Research Lead for the Clinical Reference Group for Specialist Endocrinology NHS England, Chair (President) of the UK and Ireland Neuroendocrine Tumour Society, and serves on the Society for Endocrinology Clinical Committee. He was the Chair of the American Endocrine Society's 100th Annual Meeting, Chicago 2018.

Summary of talk

1. Peri-operative management and long-term outcomes from pituitary surgery for Cushing's disease

Whilst pituitary surgery remains the primary intervention for Cushing's disease, reported outcomes of biochemical remission vary widely. These outcomes depend not only on surgical expertise and experience, but also on the classifications used in the post-operative setting and on follow-up. Identification of relapse and when to intervene remains a challenge and requires a high level of experience and care, given the data that some patients may experience relapse up to 30 years later.

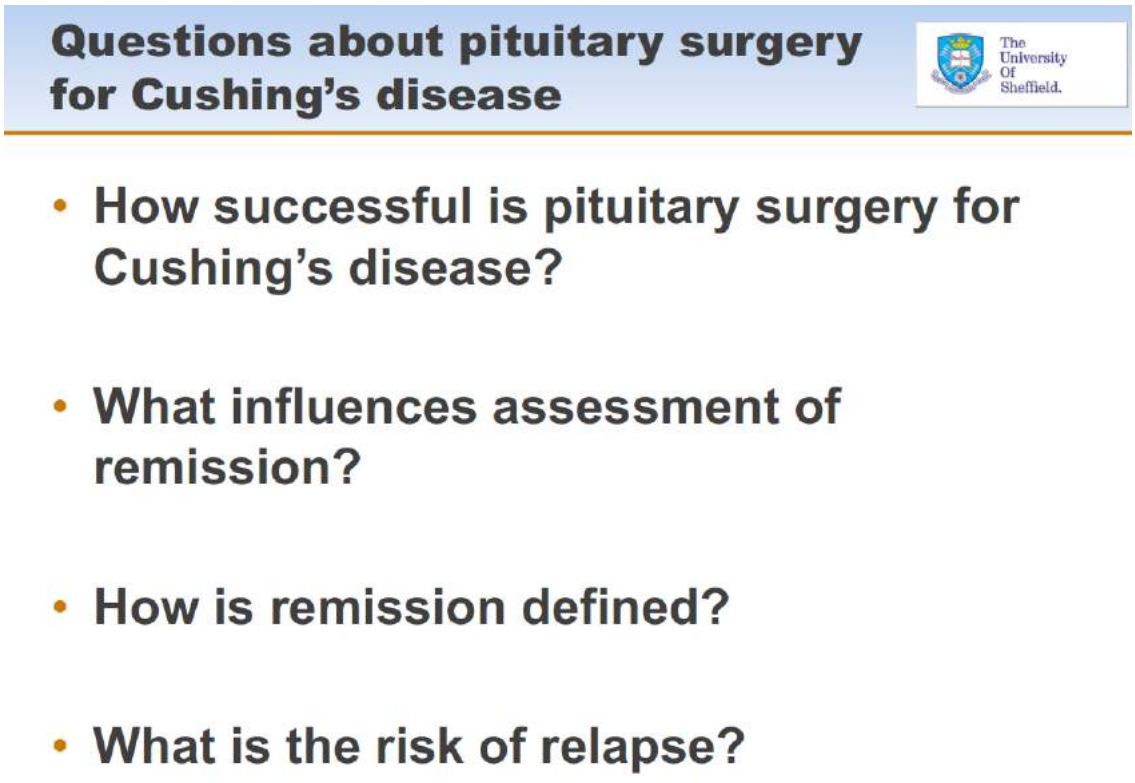
2. Clinical impact of mild cortisol excess in patients with adrenal incidentaloma

Many patients with adrenal incidentaloma have evidence of mild biochemical cortisol excess. This is usually demonstrated by dexamethasone suppression tests with measurement of serum cortisol. Since around 10% of the population have an adrenal incidentaloma, and as 30-50% of these demonstrate lack of suppression of serum cortisol post-dexamethasone (depending on differing series), 3-5% of the ageing population have biochemical evidence of excess cortisol. If this excess truly has important clinical impact it is a significant public health issue and may be contributing to the mal-effects to health seen in the ageing population.

There is an extensive literature reporting an increase in cardiovascular, metabolic and bone morbidities in patients with adrenal incidentaloma and mild cortisol excess, and a growing literature reporting an increased mortality. In addition, we, and others, have observed increases in visceral fat in these patients. We have recently re-analysed our originally reported data on mortality and confirmed that the findings are still the same, but from data with a further

five years of follow-up: the higher the post-dexamethasone cortisol the higher the risk of death on follow-up. What is not yet formally established is whether cortisol is simply a marker of mortality risk or whether it is a true driver. Excess death from cardiovascular and infectious diseases in these patients suggests a plausible causal relationship, but intervention studies are still needed to assess if this really is the case.

We have more recently assessed the effects of very short-term intervention to block steroidogenesis and 're-set' the abnormal cortisol circadian rhythm that we demonstrated in these patients, with a resultant immediate improvement in inflammatory cardiovascular markers. We have used this strategy in selected patients as interventional treatment and have observed improved metabolic control. A formal intervention study is still required to formally assess these observations.



Prof John Newell-Price

Factors influencing remission rates

The University Of Sheffield.

- Rates of initial remission and recurrence vary
- Surgical success is influenced by:
  - Experience of the surgeon
  - Size, location and invasiveness of the tumour
  - Age of the patient
- Lack of standardization in assessing patients post-operatively also leads to variation in remission rates
- Endocrine Society guidelines recommend assessment of:

Surgical success in the first week post-surgery	Identify those requiring early re-exploration

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. A*J Clin Endocrinol Metab* **2015**;Aug;100(8):2807-31

Assessing the risk of recurrence and long-term follow-up

The University Of Sheffield.

- Post-operative serum cortisol:
  - <50nmol/L - remission + low likelihood of disease recurrence
  - 50-138nmol/L - suggests remission, but patient should be observed, without treatment, for recurrence
  - >138 nmol/L indicate that the patient should be further evaluated and possibly given further treatment
- Patients should be followed-up long term and their cortisol levels (serum/saliva/urine) monitored regularly to assess whether they remain in remission
- Additional treatment should be given if disease recurs

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. A*J Clin Endocrinol Metab* **2015**;Aug;100(8):2807-31

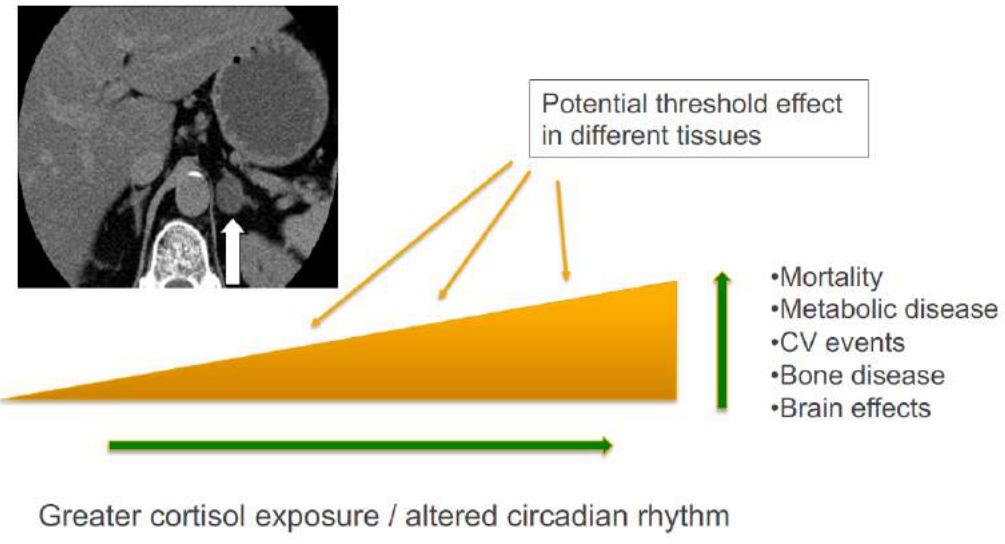
Conclusions

The University Of Sheffield.

- Remission and relapse rates are variable in patients undergoing transsphenoidal surgery for Cushing's disease
- Clear failure – consider re-exploration
- Some cases improve over days to weeks – clinical assessment and patience….
- Recurrence rates increase with time since surgery – overall upto 30%-40% of patients may relapse on long-term follow-up
- Recurrence of Cushing's disease appear to occur at any time after initial remission
- Follow-up should therefore be long-term with clinical assessment and monitoring of cortisol (serum/salivary/urinary) levels

Conclusions

The University Of Sheffield.



Prof Mark Strachan

Biography

Mark Strachan is a consultant in Diabetes, Endocrinology and Acute Medicine at the Western General Hospital, Edinburgh and Honorary Professor of the University of Edinburgh. His main clinical interests are in endocrine oncology and pituitary disease. He has published widely on the effects of Type 2 diabetes on cognitive function and was previously awarded the RD Lawrence Lectureship by Diabetes UK. He is Secretary of the Royal College of Physicians of Edinburgh and former president of the Scottish Society of Physicians. He is an editor of the international medical textbook 'Davidson's Principles and Practice of Medicine.'

Abstract

2018 – The Year in Diabetes and Endocrinology

I can genuinely say that 2018 was one of the most interesting and exciting times in my professional career.

We are in the midst of an explosion of active research into new technologies and therapeutics in diabetes. The rapid roll-out of flash glucose monitoring and the slower roll-out of CGMS has brought substantial benefits to people with Type 1 diabetes. In autumn 2018, formal clinical trials of bi-hormonal pumps commenced in the USA, with the promise of management algorithms for diabetes driven by technology and not by (usually erroneous) human interference.

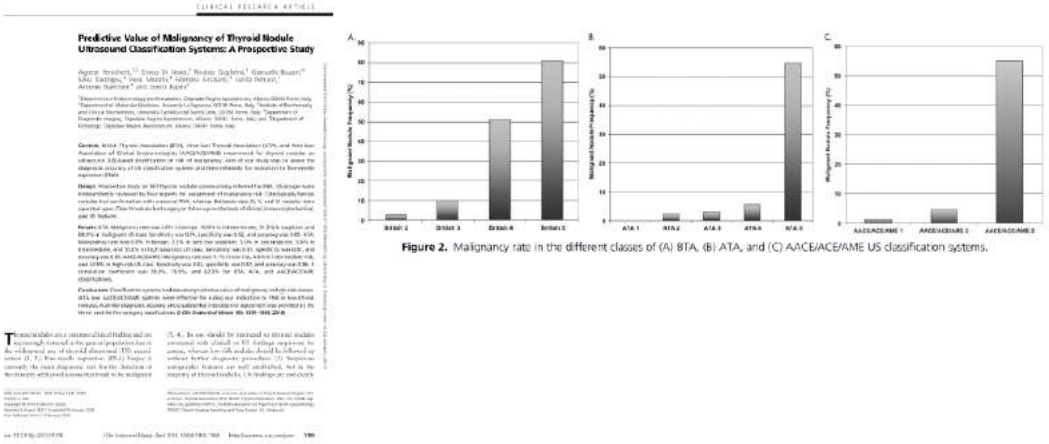
In Type 2 diabetes, it has become clearer that GLP-1 and SGLT2 agents bring substantial additional benefits beyond glycaemia, and should be the standard of care for most patients. Choice of agents within these classes looks increasingly important as data show that while there are class effects, these drugs may not all be the same.

The 'lumping' of patients into the 'Type 2 diabetes' diagnostic category is also changing and we are seeing exciting data on how we may better classify people with diabetes in a way that may really open the door to precision therapeutics. Overall, we are making progress in the development of better diagnostic algorithms for people with diabetes.

T3 has dominated the headlines in endocrinology and there is increasing pressure from patients…and now Parliament….to offer this treatment, despite the lack of robust evidence of efficacy and cost. Data were published in 2018 showing that altering T4 doses in people with a TSH in the normal range does not make them feel better. The evidence supporting widespread use of Vitamin D looks increasingly shaky and our current scoring algorithm for thyroid nodules looks as though it may perform less well than US counterparts. There was further evidence of the benefits and harms of testosterone replacement therapy in men, but we still lack crucial long-term trial data on cardiovascular safety.

Prof Mark Strachan

Thyroid Nodules – British may not be best ☹

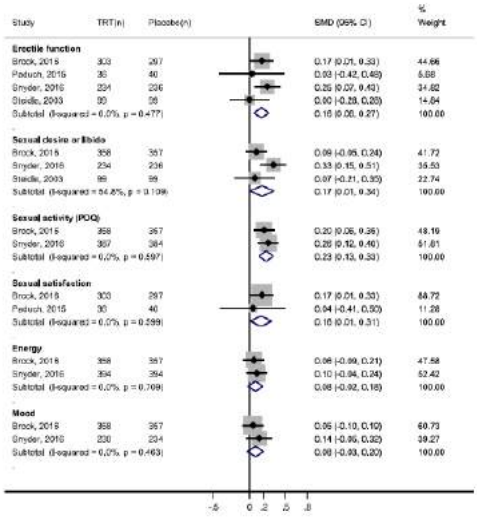


Predictive Value of Malignancy of Thyroid Nodule Ultrasound Classification Systems: A Prospective Study

Figure 2. Malignancy rate in the different classes of (A) BTA, (B) ATA, and (C) AACE/ACE/AME US classification systems.

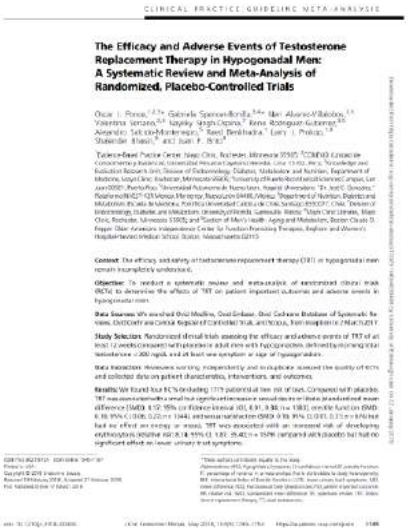
Testosterone Replacement Works...

The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials



Prof Mark Strachan

...but causes side effects!!



CLINICAL PRACTICE GUIDELINE META-ANALYSIS

The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

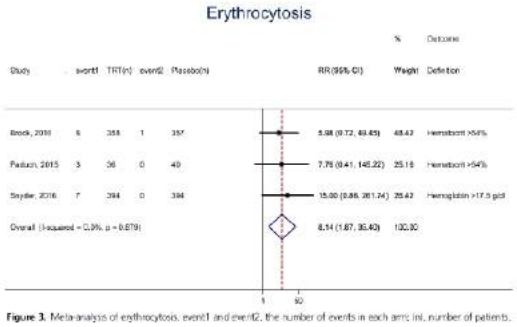


Figure 3. Meta-analysis of erythrocytosis. event1 and event2, the number of events in each arm; int, number of patients.

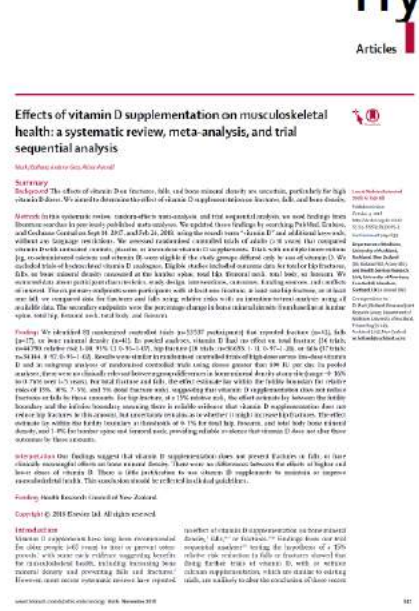
Tinkering Around with Levothyroxine Dose May Make You Feel Better...

CLINICAL RESEARCH ARTICLE

Effects of Altering Levothyroxine (L-T4) Doses on Quality of Life, Mood, and Cognition in L-T4 Treated Subjects

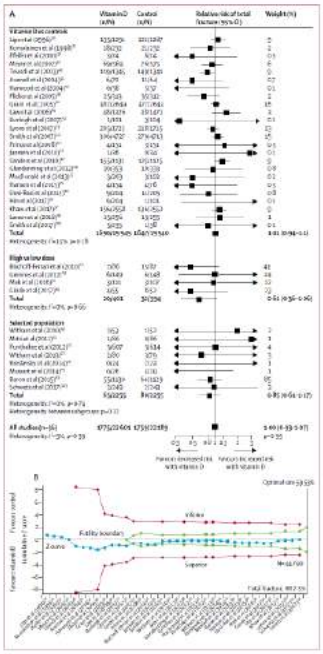
Prof Mark Strachan

Vitamin D – what's all the hype?



Articles

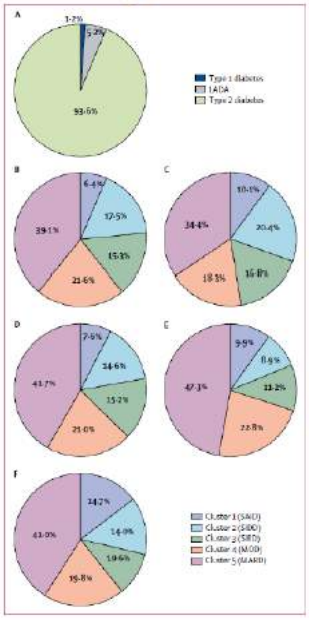
Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis



Diabetes Subtypes – the Gateway to Precision Prescribing

Articles

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables



Dr Angus Jones

Biography

Angus is a Clinical Senior Lecturer at the University of Exeter and an Honorary Consultant Physician in the Royal Devon and Exeter Hospital. He trained in medicine in London and worked as a clinician in London, Southampton, Malawi and Southwest England before undertaking an NIHR Doctoral Research Fellowship with Professor Andrew Hattersley in Exeter from 2011 to 2014. His research focuses on clinical questions directly relevant to the management of diabetes. Interests include developing a stratified (or personalised) approach to the management of Type 2 diabetes, diabetes classification and the assessment of endogenous insulin secretion (C-peptide) in the clinical management of diabetes. He received an NIHR Clinician Scientist Fellowship in 2016 to investigate and integrate biomarkers and clinical features for diabetes classification in adults, research that is using a combination of existing datasets, electronic healthcare records and prospective studies to develop fully validated prediction models for diabetes classification at diagnosis. He was awarded the Diabetes UK Type 2 Diabetes Research Prize in both 2014 and 2015 and a European Foundation for the Study of Diabetes Rising Star Award in 2016.

Abstract

The clinical utility of C-peptide measurement in the care of patients with diabetes.

This talk will review when C-peptide measurement is helpful in clinical practice, how to measure C-peptide and how to interpret the result. C-peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion in patients with diabetes. Advances in assays have made C-peptide measurement both more reliable and inexpensive. Recent work has demonstrated that C-peptide is more stable in blood than previously suggested and for clinical purposes can be reliably measured using simple blood or urine tests. The key current clinical role of C-peptide is to assist classification and management of insulin-treated patients. Utility is greatest after 3-5 years from diagnosis when persistence of substantial insulin secretion suggests Type 2 or monogenic diabetes. Patients with low C-peptide have high glycaemic variability, high hypoglycaemia risk, absolute insulin requirement and lack of response to most non-insulin co-therapies. They require Type 1 diabetes treatment and education regardless of apparent aetiology.

References:

Angus G Jones, Andrew T Hattersley. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabetic Medicine 2013 Jul;30(7):803-17.

Berger B, Stenstrom G, Sundkvist G. Random C-peptide in the classification of diabetes. Scand J Clin Lab Invest. 2000;60:687–693

Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the Diabetes Control and Complications Trial. Diabetes Care. 2003;26:832–836.

Ludvigsson J, Carlsson A, Forsander G, Ivarsson S, Kockum I, Lernmark A, et al. C-peptide in the classification of diabetes in children and adolescents. Pediatr Diabetes. 2012;13:45–50

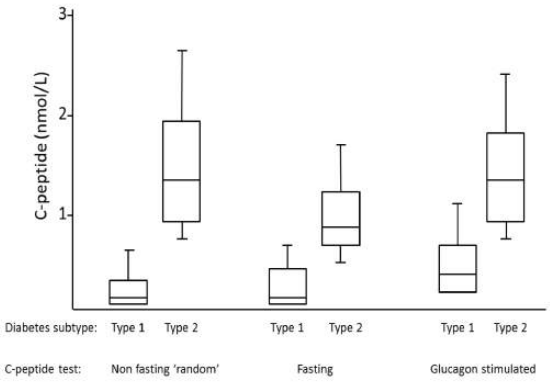
Angus G Jones, Timothy J McDonald, Beverley M Shields, Anita V Hill , Christopher J Hyde, Bridget A Knight, Andrew T Hattersley for the PRIBA Study Group. Markers of beta cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. Diabetes Care 2016 Feb;39(2):250-7

SV Hope, BA Knight, BM Shields, AT Hattersley, TJ McDonald & AG Jones., Random non-fasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. Diabetic Medicine. Diabetic Medicine 2016 Nov;33(11):1554-1558

Suzy V Hope, Bridget A Knight, Beverley M Shields, Anita V Hill, Pratik Choudhary, W. David Strain, Timothy J McDonald & Angus G Jones. Random non-fasting C-peptide testing can identify patients with insulin treated Type 2 diabetes at high risk of hypoglycaemia. Diabetologia. 2018 Jan;61(1):66-74

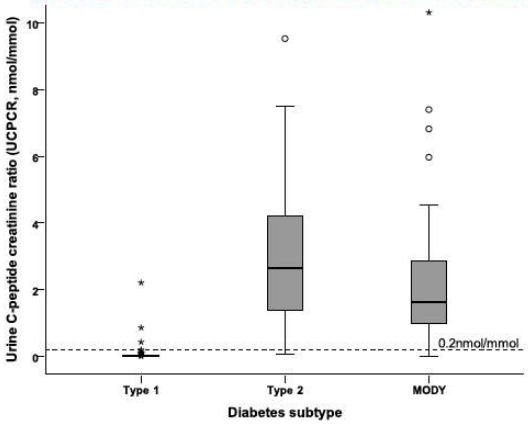
Simple C-peptide measures can differentiate Type 1 diabetes from Type 2 diabetes and MODY

Type 1 vs Type 2 diabetes
(blood C-peptide)



Berger et al 2000 Scan J Clin Med

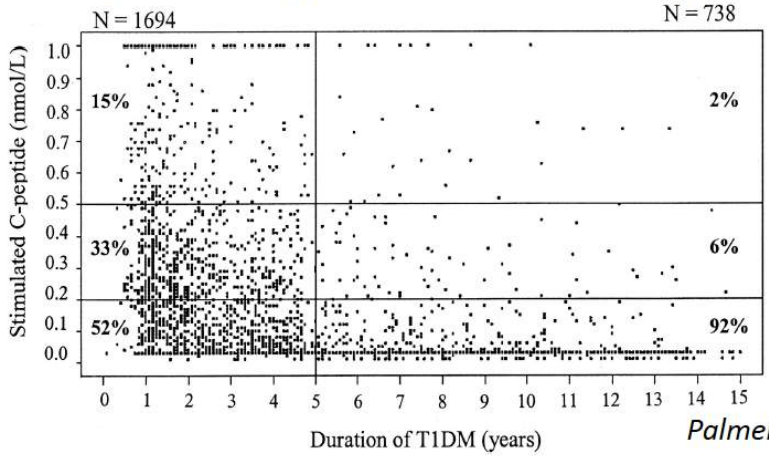
Type 1 vs Type 2 vs MODY
(home meal urine c-peptide creatinine ratio)



Besser et al 2011 Diabetes Care

Rapid decline in C-peptide in Type 1 Diabetes

Adult (age 18-39) onset Type 1 diabetes at DCCT screening (n=2432)



Palmer 2004 Diabetes

- Low C-peptide at any time confirms Type 1 diabetes
- High C-peptide at diagnoses increases chances of T2D/MODY but should be interpreted with caution, particularly in the obese

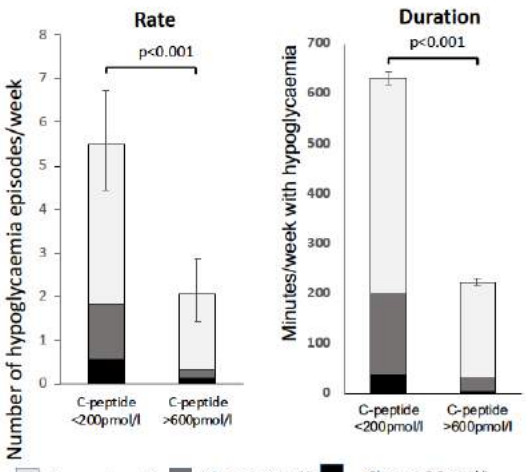
(*Ludvigson et al Paediatric diabetes 2011, Thunander et al 2012, Redondo et al 2012)*

- Decline is log linear for 7 years, T1/2 1.1 years *(Shields et al Diabetes Care 2018)*

Dr Angus Jones

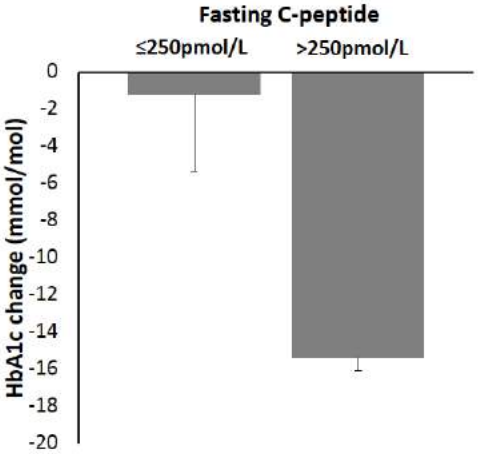
Endogenous insulin secretion, not clinical diagnosis determines glucose variability, hypoglycaemia risk and treatment response

CGM Assessed Hypoglycaemia



Hope et al Diabetologia 2017

HbA1c reduction post GLP-1RA



Jones et al Diabetes Care 2016

When is C-peptide measurement useful?

- In insulin treated patients > 3 years duration where there is uncertainty around diagnosis
  - Adult onset diabetes treated with insulin within 3 years of diagnosis
  - Overlapping features for T1D/T2D
  - Discordant current clinical picture e.g. stable glucose in longstanding 'type 1'
- Prior to a treatment decision with major implications if misdiagnosed
- When considering a diagnosis of MODY

What test should you use in clinic?

- 'Random' non fasting blood in clinic
  - Check concurrent glucose, and if carbohydrate containing meal within 5 hours
  - If result low and concurrent hypoglycaemia, or inadequate intake, repeat the test
  - A concurrent glucose >8mmol/mol can be considered 'stimulated'
  - Collect in EDTA (stable >24 hours at room temperature)
- Fasting
  - Check concurrent glucose, use lower thresholds
- Urine C-peptide Creatinine Ratio (UCPCR)
  - Post home meal or send spot clinic sample if non fasting
  - Collect in boric acid (stable 72 hours at room temperature)

What does the test result mean? Clinical thresholds

Stimulated C-peptide level (Post meal blood, post MMTT)	Interpretation
<200pmol/L	Severe/'absolute' insulin deficiency, treat as T1D regardless of aetiology, MODY unlikely.
>600pmol/L	Substantial endogenous insulin secretion: If duration >3 years confirms T2D or MODY. May achieve glycaemic control without insulin.
200-600pmol/L	Some insulin secretion. Interpret with caution. Likely T1D/insulin requirement. Consider MODY if longstanding 'T1D' & antibody negative.

For fasting blood samples divide above by 2.5
(600pmol/L = 250pmol/L 200pmol/L = 80pmol/L)

Caution around thresholds:
- Biological & assay variation

1 nmol/l = 1000 pmol/l = 3 ng/ml

Jones Hattersley Diabetic Medicine 2013

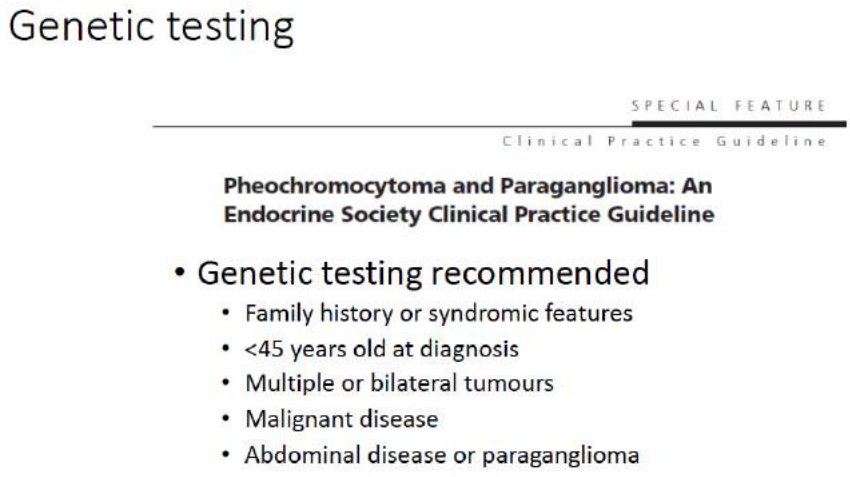
Dr Colin Perry

Biography

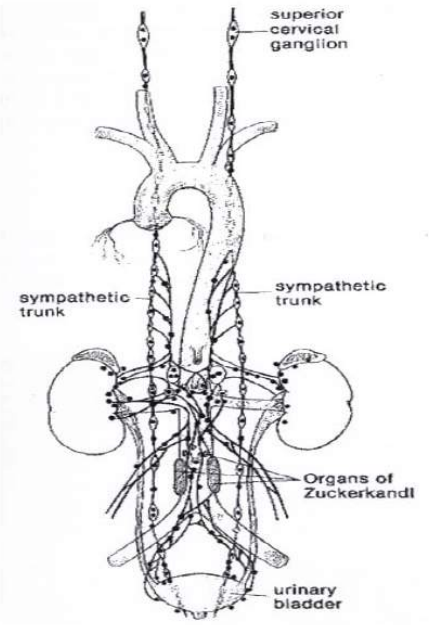
I am a Consultant Endocrinologist at the Queen Elizabeth University Hospital in Glasgow, where I am also Clinical Director. I have interests in endocrinology in transition, endocrine oncology and endocrine genetics.
I undertook a Welcome funded PhD in insulin sensitivity and the renin angiotensin system in 2000, and was a visiting fellow in the Mayo Clinic, Rochester in 2004. I am a member of the American Endocrine Society and the Society for Endocrinology and I write questions in endocrinology for the MRCP part III. I also have a commitment to undergraduate teaching and I am an Honorary Associate Clinical Professor in the University of Glasgow

Abstract

Phaeochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumours of the adrenal medulla, sympathetic and parasympathetic nervous system. Most adrenal and sympathetic chain tumours present with symptoms associated with secretion of noradrenaline and adrenaline, causing headache, cold sweats and palpitations, and may be associated with high blood pressure, though some tumours are identified as an incidental finding. Biochemical investigation is now centred upon measurement of urinary or plasma normetanephrine or metanephrine, the metabolites of noradrenaline and adrenaline, though there is interest in the value of measurement of 3 methoxytyramine, the catechol – O – methyl transferase metabolite of dopamine, especially in head and neck paraganglioma that may otherwise appear to be non-secretory. Increasing availability of more novel imaging modalities, and in particular 68Ga-DOTATATE and 18F-FDG PET/CT, have allowed improved detection of these tumours and early identification of metastatic disease. The most marked recent development in our understanding of these tumours has been in the appreciation that, rather than the traditional teaching of 10% of these tumours having a genetic basis, it is now apparent that 30-40% have an underlying genetic cause. The identification of mutations in the genes encoding the subunits of the succinate dehydrogenase enzyme complex has led to characterisation of the previously named hereditary paraganglioma syndromes, with increasing quantification of the risk associated with these mutations influencing screening protocols for otherwise well individuals who carry disease causing mutations. With there being now more than 20 genetic mutations identified as being associated with PPGL, there is now far greater understanding of the molecular mechanisms underlying the development of disease, and with this it seems likely that there will be therapies targeted directly at tumorigenesis, resulting in improved control of progressive and disseminated disease.



Phaeochromocytoma/paraganglioma



Phaeochromocytoma

arise from catecholamine producing chromaffin cells in adrenal medulla

Paraganglioma

extra-adrenal sympathetic and parasympathetic (usually HNPGL) tumours

- 1.5 - 8 cases per million
- rule of 10% now inaccurate

Clinical features

- Secretors
  - ***Headache***
  - ***Sweats***
  - ***Palpitations***
  - Chest pain
  - Panic attacks / spells / pallor
  - Hypertension (sustained / paroxysmal)
- Non-secretors
  - Mass effect

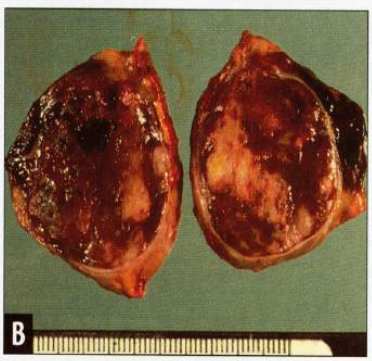


Figure 4-36B, Page 4.17

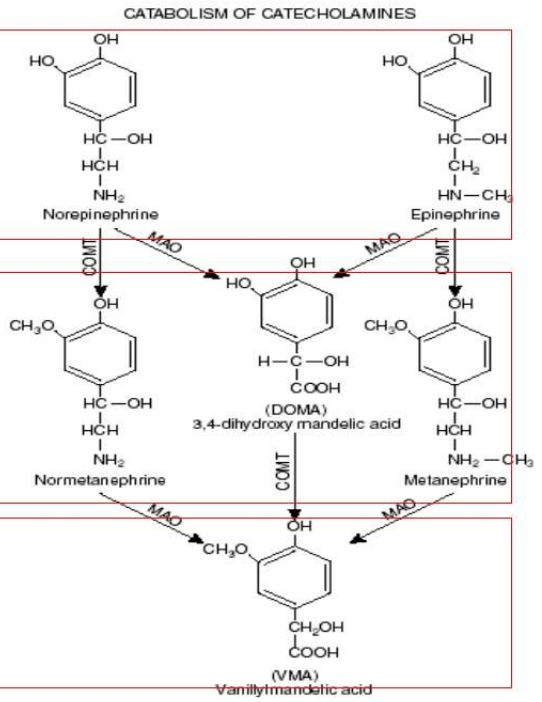
Dr Colin Perry

Biochemical investigations

- Plasma *catecholamines*
- Urinary *catecholamines*

- Plasma *metanephrines*
- Urinary *metanephrines*
  - Conjugated
  - Free

- Urinary *metabolites*
  - HMMA / VMA



Risk stratification by secretory status

Catecholamine Types	Number of Patients	Number of Metastasis	Ratio of Metastasis (%)
Epinephrine	78	11	14.1
Norepinephrine	79	29	36.7
(Adrenal)	(49)	(13)	(26.5)
(Extra-adrenal)	(30)	(15)	(50.0)
Non-functioning (Extra-adrenal)	6	1	16.7
Total Number	163	41	25.1

High levels of methoxytyramine also associated with malignancy, as is the SDHB mutation

SDH and phaeo / PGL

syndrome	PGL4	PGL1	PGL3
inheritance	AD	AD	AD
gene name	SDHB	SDHD	SDHC
location	1p36	11q23	1q21
age at diagnosis	34	27	46
multifocal	11%	55%	9%
adrenal	43%	86%	0%
Extra adrenal abdo	62%	59%	0%
Head/neck	8%	41%	100%
malignant	32%	rare	0%
associations	RCC, GIST	PTC, GIST	GIST

Summary

- Phaeochromocytomas are rare tumours
- Biochemical investigation should be done in the context of the clinical scenario
- There are an increasing number of cases with an identifiable genetic basis
- Understanding of mechanisms underlying disease may lead to therapeutic options

Dr Sharon Mackin

Biography

I graduated from the University of Dundee in 2009 and thereafter moved to Glasgow for my clinical training, progressing through the traditional foundation and core training routes. I took up my specialty post in Diabetes and Endocrinology back in 2013 and am now ST6. More recently, I have been awarded a personal fellowship from the Glasgow Children's Hospital Charity to research the role of glucose-lowering on maternal and placental vascular function in gestational diabetes. My research is being conducted at the University of Glasgow's Institute of Cardiovascular and Medical Sciences under the supervision of Dr Robert Lindsay and Professor Christian Delles, and I have been in post since August 2017.

Abstract

Diabetes and stillbirth: risk factor prevalence and timing of delivery in Scotland

ST Mackin, SM Nelson, SH Wild, HM Colhoun, R Wood, RS Lindsay

Aims: Recent national data has shown stillbirth rates 4-5-fold higher in mothers with pregestational diabetes compared with mothers without diabetes. Fear of stillbirth has major influence on obstetric decision-making in these women, particularly around timing of delivery. We analysed national data to describe timing of stillbirths in women with diabetes and their prevalent risk factors.

Methods: National databases (SMR-02 and SCI-Diabetes) were linked and data collected on singleton deliveries to 3778 T1DM mothers and 1614 T2DM mothers from 1998-2016. Data on maternal and fetal demographics, maternal glycaemia and Characteristics of mother and baby were compared between stillborn and liveborn groups using $\chi 2$ or t-test. Logistic regression analysis was used to estimate effect of risk factors on stillbirth risk.

Results: Stillbirth rates were 16.1 (per 1000 births) in T1DM and 22.9 (per 1000 births) T2DM. Mothers with T1DM who suffered stillbirth had a shorter duration of diabetes (mean 11.4+9.2 vs 14.1+8.4 years $p<0.05$) but were of similar age at delivery, socioeconomic score and smoking history. Mothers with T2DM who suffered stillbirth showed no significant difference in these factors.

Mean pre-conceptual HbA1c was 79±22 mmol/mol in the stillbirth group versus 68±19 mmol/mol in the livebirth group (n= 12 stillborn and 1625 liveborn: $p<0.0001$) and remained higher at all stages of pregnancy ($p<0.001$), whereas in T2DM only preconceptual HbA1c was different (71+25 versus 59+20 mmol/mol).

Stillborn infants were delivered much earlier than liveborn infants: T1DM (33.8±4.1 weeks vs 36.6 ± 2.2 weeks; $P<0.0001$) and T2DM (33.7± 4.7 weeks vs 37.2 ± 2.3 weeks; $P<0.0001$). One third of stillbirths occurred at term with highest rates in the 38th week in T1DM (7.0: 95% CI 3.7-12.9 per 1000 ongoing pregnancies) and 39th week in T2DM (9.3: 95% CI 2.4-29.2 per 1000 ongoing pregnancies).

In type 1 diabetes, higher HbA1c before ($\beta=0.024$, $p=0.0003$) and in later pregnancy ($\beta=0.058$, $p<0.0001$) were associated with stillbirth, whilst in type 2 diabetes higher maternal BMI ($\beta=0.069$, $p=0.02$) and pre-pregnancy HbA1c ($\beta=0.023$, $p=0.02$) were. Risk was highest in infants with birth weights <10th centile (6-fold type 1 diabetes, 3-fold type 2 diabetes) and >95th centile (2-fold type 2 diabetes) versus 10-90th centile.

Conclusion: Maternal glycaemia and BMI are the main modifiable risk factors for stillbirth in diabetes but with significant overlap between live and stillborn pregnancies. Babies at extremes of weight centiles are at most risk. Stillbirth risk is highest at term in women with diabetes and more accurate prediction of this risk is needed to guide care.

Dr Sharon Mackin

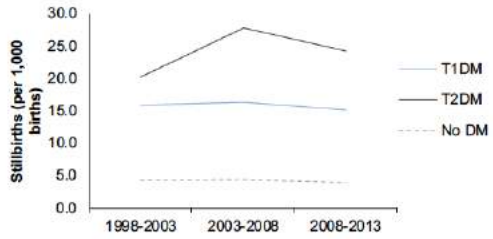
Introduction

Diabetologia (2018) 61:1081–1088
https://doi.org/10.1007/s00125-017-4529-3

ARTICLE

Diabetes and pregnancy: national trends over a 15 year period

Sharon T. Mackin[1] · Scott M. Nelson[2] · Joannes J. Kerssens[3] · Rachael Wood[4] · Sarah Wild[4] · Helen M. Colhoun[5] · Graham P. Leese[6] · Sam Philip[7] · Robert S. Lindsay[1,8] · on behalf of the SDRN Epidemiology Group



- Increasing earlier gestational age at delivery and larger birthweight babies
- Demographic differences in diabetes versus non-diabetes population

Aim

To describe timing of stillbirth in women with diabetes and prevalent risk factors

Dr Sharon Mackin

Methods

- SMR02 and SCI-Diabetes
  - All inpatient singleton deliveries ≥ 24 weeks gestation
  - 1st April 1998 – 30th June 2016
  - Type 1 and type 2 diabetes only

- Comparison of stillbirth vs livebirth groups:
  - Maternal and infant demographics
  - Timing of delivery
  - HbA1c data

- Risk factor estimation
  - Logistic regression – univariate and multivariate

Dr Maroria Oroko

Biography

Dr Maroria Oroko is an ST3 in Diabetes and Endocrinology in the West of Scotland, currently based at Inverclyde Royal Hospital.

Abstract

There is a Role for 1-hour OGTT Sample in Diagnosis of Gestational Diabetes
Dr Maroria Oroko, Dr Mohammed Azharuddin

Abstract

Aim
The diagnosis of gestational diabetes mellitus (GDM) has long been a controversial area, largely because of the incremental rise in perinatal risk that occurs with it and the difficulty therefore to determine diagnostic thresholds. As a result, international consensus was reached in 2010 and adopted by SIGN, which recommends performing 0-, 1-, and 2-hour samples in 75g oral glucose tolerance test (OGTT). These guidelines are estimated to diagnose 18% of pregnancies with GDM and, as a result, many stretched Scottish centres do not measure OGTT results at 1 hour. We estimate the impact this policy may have on perinatal outcomes.

Method
Retrospective analysis of 397 cases over 12 years of practice at Inverclyde Royal Hospital. Our centre performs full 3-sample OGTT. Method of diagnosis analysed using Clinical Portal online records system. Ultimate reatment requirements determined using SCI Diabetes system - diet vs metformin vs insulin. 123 excluded for: inadequate data (97), alternative/unclear diagnostic technique (26). 274 included. SIGN guidelines for GDM management used.

Results
53 (19%) were diagnosed purely on derangement of 1 hour OGTT. 23 of these (43%) required medication, 15 with insulin (28% of total). These proportions are comparable to the average across the sample (53% of the 274 patients required medication, 31% with insulin). Also comparable to those diagnosed on fasting (43% required treatment, 25% wtih insulin).

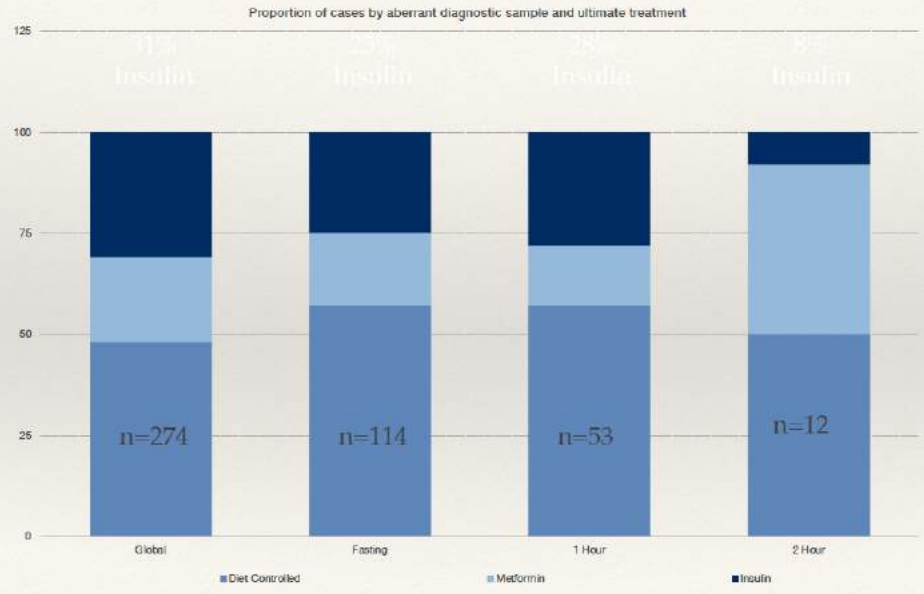
Conclusion
Scottish centres adopting the use of 1-hour readings of OGTT in addition to 0-, and 2-hour readings may expect a 24% increase in numbers. It should logically be adopted by these centres as rates of progression to requiring treatment are significant and non-inferior to other readings. Should economic factors be a concern, may there be a role of raising diagnostic thresholds to match perinatal adverse outcomes odds ratio of 2 rather than the present 1.75?

Dr Maroria Oroko

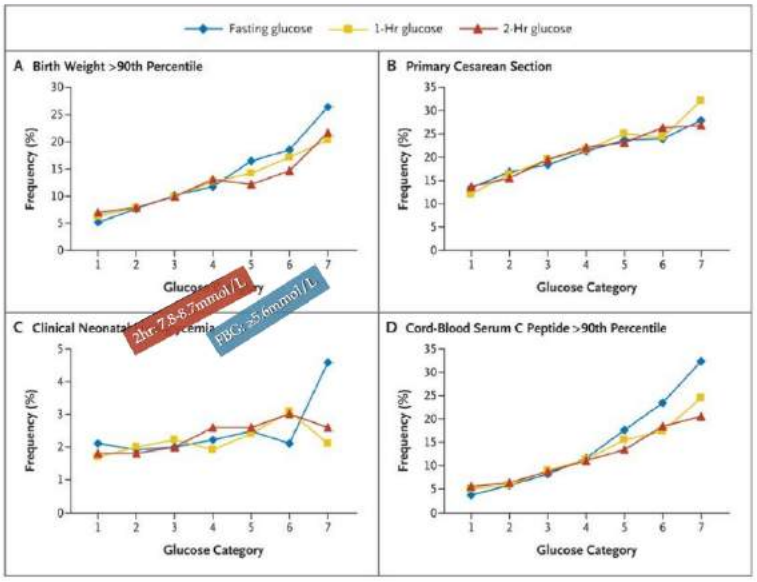
Context- Economic Modelling

- NICE reject IADPSG 2010. Expectation of 18% GDM prevalence
- Many Scottish centres follow SIGN 2010 partially - fasting and 2-hr samples only
- Inverclyde Royal Hospital has performed full 75g 2hr OGTT - fasting, 1- and 2-hr samples since as early as 2009
- Aim: to assess what difference 1 hour sampling makes:
  - to maternal hyperglycaemia
  - to perinatal outcomes

Results



Perinatal Outcomes



Taken from D

Conclusions

- In terms of maternal hyperglycaemia, patients diagnosed purely on 1 hour criteria have non-inferior rates requiring medication to fasting and 2 hour
- 1hr may even be superior predictor of adverse perinatal outcomes (HAPO)
- Doesn't make sense to miss out 1hr. Including may increase GDM clinic numbers by ~25%
- Consider increase to OR 2 if staffing/financial concerns?

Dr Anne Sillars

Biography

Anne Sillars graduated from the University of Glasgow medical school in 2010. She undertook foundation training in Glasgow and then moved to Tasmania, Australia to work in general medicine and intensive care for two years. She returned to the West of Scotland to commence Core Medical training, which she completed in 2016. Since August 2016 she has been undertaking a Diabetes UK-funded PhD at the University of Glasgow, investigating the alternative pathways of triglyceride synthesis in skeletal muscle and its effects on insulin resistance, under the supervision of Prof Jason Gill, Dr Dilys Freeman and Prof Naveed Sattar.

Abstract

The Role of Intramuscular Triglyceride Synthesis in Insulin Resistance

Dr. A. Sillars, Prof N. Sattar, Prof J. Gill and Dr. D. Freeman
Institute of Cardiovascular and Medical Sciences, University of Glasgow

Introduction
The progression towards Type 2 Diabetes Mellitus (T2DM) is associated by impaired insulin-stimulated glucose uptake by peripheral tissues, particularly skeletal muscle, leading to insulin resistance. Ectopic deposition of triglyceride in skeletal muscle (IMTG) occurs in insulin resistant states. An increased use of skeletal muscle through exercise is prescribed as a first line treatment for patients with T2DM, to encourage glucose uptake. However, the 'Athletes paradox' describes increased skeletal muscle IMTG in highly trained athletes, despite increased insulin sensitivity. We examined alternative pathways of triglyceride (TG) synthesis, focusing on two enzymes involved in the final step of TG synthesis, DGAT1 and DGAT2, to better understand this paradox in human skeletal muscle.
Methods
We recruited 20 highly trained athletic men, 19 lean men and 17 men at risk of, or diagnosed with T2DM who were treatment naive. We assessed their fitness using a bicycle ergometer, measured body mass and body fat percentage, measured plasma glucose levels during a 2-hour OGTT and obtained skeletal muscle biopsies. Human satellite cells from the muscle biopsy were grown into myotubes and cultured in varying glucose and insulin quantities, and then challenged with DGAT 1 and 2 inhibition. We assessed the effects of these conditions in the three phenotypical groups, using protein electrophoresis to examine total to phosphorylated AKT expression as a measure of insulin signalling.
Results
Baseline characteristics of the three groups showed significant differences in BMI (kg.m2) ($p < 0.001$), body fat percentage (%) ($p < 0.001$), Hba1c (mmol/mol) ($p < 0.001$) and fitness levels (Vo2 Max ml.kg.min) ($p < 0.001$). Cellular extracts were obtained from the myotubes in the athletic (n=5) and control (n=7) cohorts and analysis demonstrated that hyperglycaemic conditions blunted insulin sensitivity, but that this was restored by DGAT2 inhibition. Conversely, it was not restored by DGAT 1 inhibition. DGAT1 inhibition blunted insulin sensitivity in normoglycemia, however. DGAT2 inhibition had no effect on insulin sensitivity in these groups.
Conclusion
We have confirmed significant differences in insulin sensitivity between highly trained athletes, lean controls and men at risk of T2DM at the whole body level. We have demonstrated that inhibition of DGAT1 and DGAT2 results in altered insulin sensitivity within an athletic and control cohort. Work is underway assessing DGAT1 and DGAT2 inhibition on the diabetic cohort.

Dr Anne Sillars

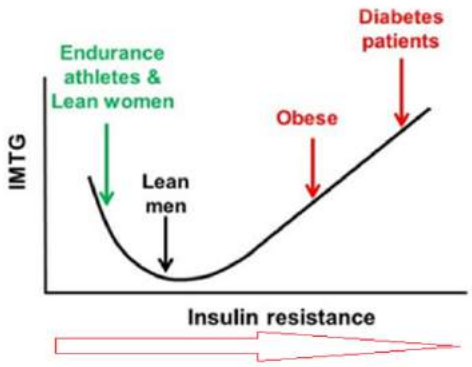
University of Glasgow

The M-FAT Study

University of Glasgow
College of Medical, Veterinary & Life Sciences

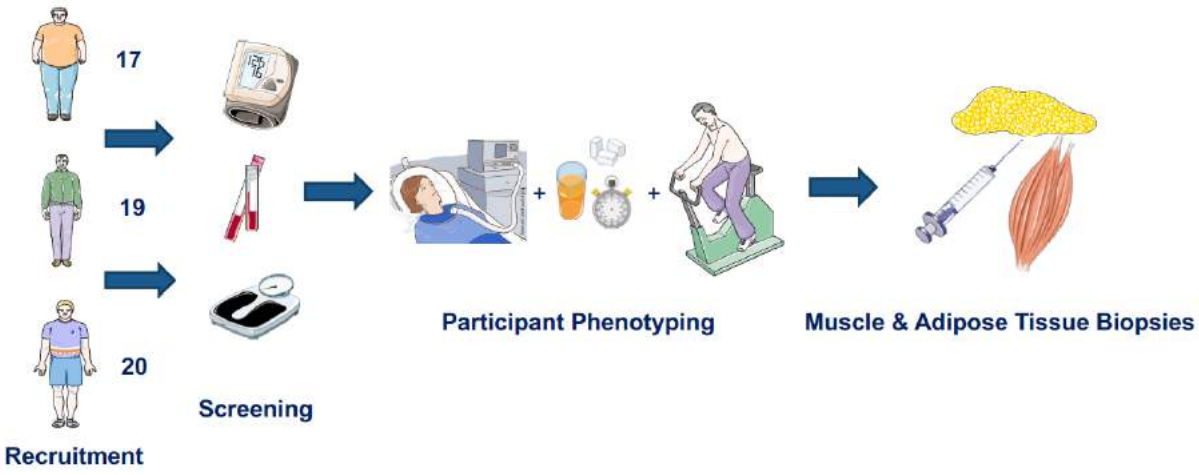
The Athlete's Paradox

THE UNIVERSITY OF WARWICK



University of Glasgow

The M-FAT Study



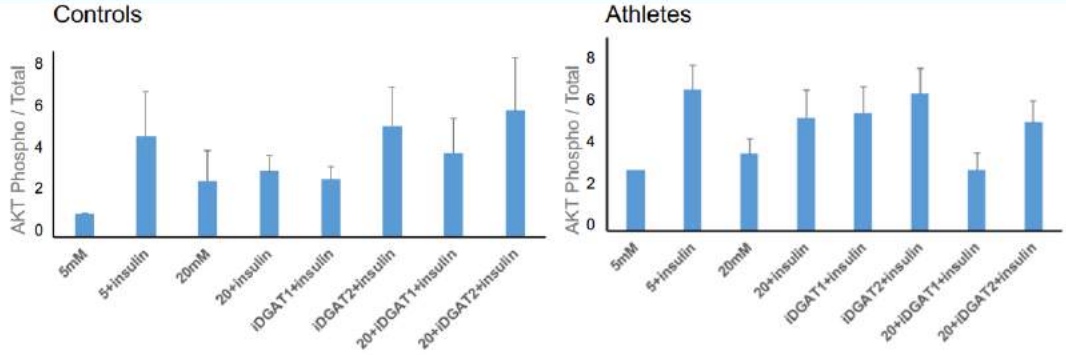
Dr Anne Sillars

Participant Demographics

	Athletes (n=20)	Controls (n=19)	Type 2 Diabetics (n=17)
Age (Years)	42.1 ± 1.59	44.9 ± 2.24	53.3 ± 4.0
Weight (Kg)	74.3 ± 1.66	77.1 ± 1.52	96.6 ± 4.0
BMI (kg.m^{-2})	23.4 ± 0.35	24.2 ± 0.43	30.7 ± 0.75
Waist Circumference (cm)	81.6 ± 1.04	87.2 ± 1.15	107.5 ± 2.2
Body Fat (%) (BodPod)	13.0 ± 1.49	19.7 ± 1.22	32.2 ± 4.2
Body Fat (%) (Skinfolds)	18.0 ± 1.01	24.8 ± 1.01	31.2 ± 3.3

	Athletes (n=20)	Controls (n=19)	Type 2 Diabetics (n=17)
Systolic BP (mmHg)	136.4 ± 2.40	132.1 ± 2.98	143.2 ± 4.5
Diastolic BP (mmHg)	79.8 ± 1.84	81.1 ± 1.46	90.2 ± 5.5
HbA1c (mmol/mol)	34.1 ± 0.49	33.0 ± 0.65	52.9 ± 2.0
FPG (mmol/L)	4.9 ± 0.10	5.3 ± 0.10	8.2 ± 0.12
RMR (kcal/kg/day)	22.3 ± 0.42	20.7 ± 0.53	20.2 ± 0.14
VO_2 Max (ml/kg/min)	54.7 ± 1.30	35.9 ± 1.27	32.7 ± 1.0

Results



Preliminary Data *Suggests:*

- Hyperglycemia (20mM) almost abolishes an insulin response
- This is restored by DGAT2 inhibition, but not by DGAT 1 inhibition
- DGAT1 inhibition blunts insulin sensitivity in normoglycemia; iDGAT2 has no effect

- **Little difference between Controls and Athletes**

Dr Rob Gifford

Biography

Squadron Leader Robert Gifford qualified from Glasgow in 2008 and is currently a PhD student at the University of Edinburgh. His project, entitled the Female Endocrinology in Arduous Training (FEAT) Programme, aims to explore endocrine changes associated with exercise, stress and energy deficit in military women (http://edin.ac/2zrn0kO). Before commencing a PhD in Aug 16, Rob worked as a registrar (ST4) in endocrinology and general medicine in South East Scotland. As a RAF medical officer, he is part of a team delivering aeromedical evacuation and has previously worked in the Role 3 Hospital in Camp Bastion, Afghanistan. His other research interests include the gender associations of heat illness and the metabolic effects of nerve agent poisoning.

Abstract

Preserved reproductive, adrenal and bone function in the first all-female Antarctic traverse: implications for mitigating the impact of military training on women.

Gifford RM,1,2 Reynolds RM,2 Woods DR1,3,4
1 Research and Clinical Innovation, Royal Centre for Defence Medicine, UK
2 Centre for Cardiovascular Science, University of Edinburgh, UK
3 Carnegie Institute for Sports and Exercise Science, Leeds Beckett University, UK
4 Newcastle University, UK

Background. High rates of reproductive dysfunction, stress fracture and adverse psychological outcomes have been reported among military women. Such conditions are closely linked with hormonal changes during stress and exercise.

Hypothesis. In women, an Antarctic traverse is associated with suppression of reproductive, adrenal and bone function.

Methods. Six women (aged 28-36, BMI 24.2 ±0.97 kgm-2) hauled 80kg sledges 1700km in 61 days. The following were assessed before and after: body composition (by DXA, skinfold and bioimpedance), bone health by high resolution quantitative CT (HRpQCT) and serum bone turnover markers (BTMs), and heartrate variability (HRV). Basal metabolic and endocrine blood markers and dynamic tests of pituitary-adrenal-gonadal function by combined low-dose dexamethasone suppression/ low-dose Gonadorelin and Synacthen tests were also performed before and after the expedition. Cortisol was assayed in hair (average monthly concentration) and saliva (diurnal variability).

Results. Participants lost 9.37 ±2.31 kg ($p<0.0001$), comprising fat mass only; lean mass was maintained. Basal sex steroids, corticosteroids, metabolic markers and BTMs were largely unaffected except leptin, which decreased during the expedition and recovered after 15 days. HRV parasympathetic activity and IGF-1 increased after 15 days. HRpQCT was unaffected. Luteinising hormone responsiveness was suppressed before and during the expedition, but recovered after 15 days. Follicle-stimulating hormone and cortisol responsiveness did not change during or after the expedition. Hair cortisol was elevated during the expedition.

DISCUSSION: Endocrine function, bone and lean mass were preserved, with evidence of latent physiological benefit, not harm. Possible mitigating factors which may be relevant to military training include comprehensive nutrition planning, psychological preparation, self-directed selection and expedition strategy.

Dr Rob Gifford

Study Question

What are the biological effects of an extreme training exposure on women?

Hypothesis

The first all-female Antarctic traverse would be associated with energy deficit, suppressed HPG and HPA axes and impaired bone health

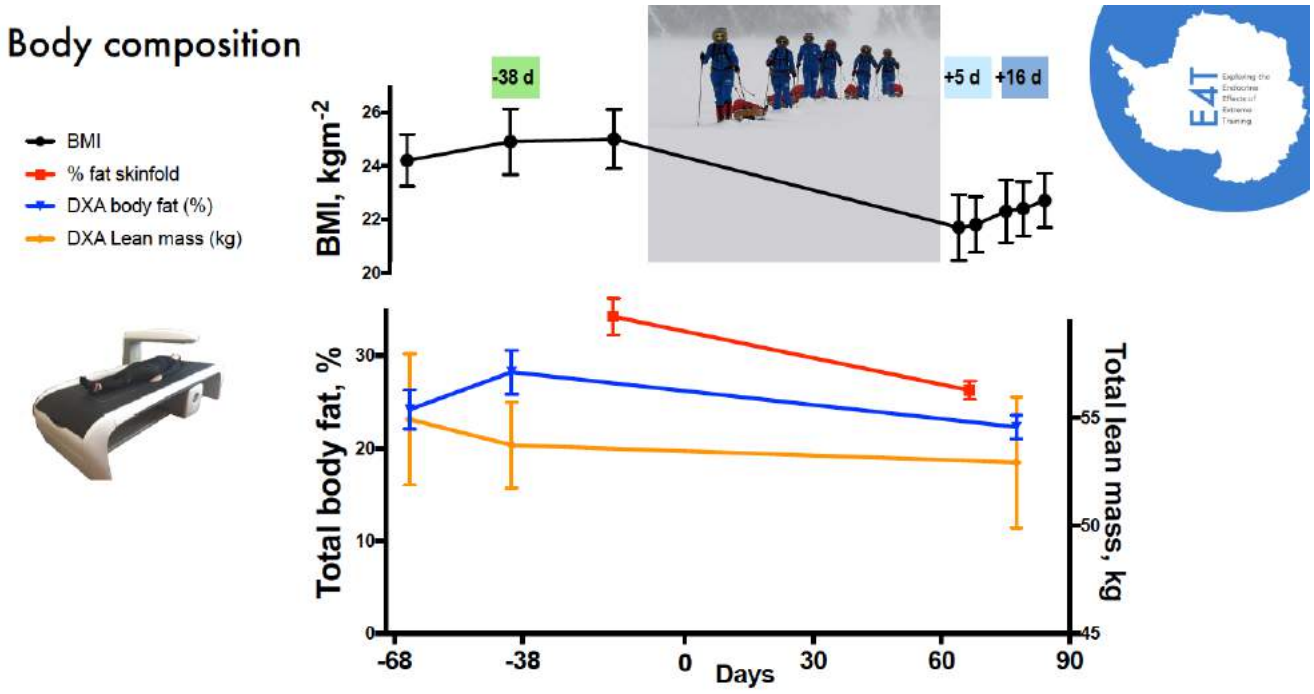
Methods

38 days before, 5 days after, 16 days after:

- **Energy balance**: DXA, basal metabolic markers
- **HPG axis**: Dynamic low dose GnRH test
- **HPA axis:** 0.25mg dexamethasone and 1µg SynACTHen test, hair and saliva samples
- **Autonomic function**: Heartrate variability
- **Bone:** High resolution peripheral quantitative CT (HRpQCT) scans distal tibia, turnover markers

Dr Rob Gifford

Body composition



Gifford et al Med Sci Sports Exerc 2018

Key findings

- Significant energy deficit but ***lean mass preserved***
- **LH/ FSH responses preserved** - trend towards recovery in LH by 15days
- **Cortisol response preserved** despite elevated free cortisol. Diurnal pattern maintained.
- **Bone strength, mineral content** and **tibial microarchitecture preserved** despite modest uncoupling of turnover

- Overall beneficial not detrimental effects?

Adeeb Naasan

Biography

I am an FY2 who studied in Dundee University and is now working in Glasgow Royal Infirmary.

Recurrent Hypoglycaemia with illicit drug use in Glasgow

Naasan AP, Connelly P, Carty D (Glasgow Royal Infirmary)

Introduction

Hypoglycaemia is an unusual presentation in a patient without diabetes mellitus. Here we report the case of a 53-year-old man who remained severely hypoglycaemic requiring continuous intravenous infusion of dextrose for more than 24 hours after using street Diazepam. Serum insulin and C-peptide levels confirmed marked endogenous hyperinsulinaemia as the cause of his severe hypoglycaemia.

Case Presentation

A 53-year-old ex-IVDU was brought in by ambulance having been found collapsed in a pool of his own vomit. Initial assessment revealed GCS 12/15 with a blood glucose level of 1.2 mmol/l. He was given an intramuscular Glucagon injection by the ambulance crew, and an intravenous bolus of 100ml of 20% Dextrose (D_{20}).

On arrival in the Emergency Department, he was again hypoglycaemic with a blood glucose of 2.6 mmol/l. He received a further 100ml intravenous bolus of D_{20}. Half an hour later, the patient's conscious level dropped and he was found to again be hypoglycaemic. He was given a D_{20} bolus and commenced on a continuous 10% Dextrose (D_{10}) infusion at 100 mL/hour. Despite this, the patient was found to be hypoglycaemic for a fourth time. He was given a further D_{20} bolus and the D_{10} IV infusion rate increased to 125 mL/hour. He was admitted to our Medical High Dependency Unit where he had a further hypoglycaemic episode and was commenced on a continuous D_{20} infusion at 100 mL/hour.

He admitted to use of Street Diazepam, known as "roaches", and investigations including FBC, U&Es, LFTs, Short Synacthen Test and Thyroid Function Tests were unremarkable. Insulin [81.4 mU/L, range: <13] and C-peptide [5.43 nmol/L, range: 0.36-1.12] levels were raised on a fasting sample [blood glucose level 2.3 mmol/L] confirming endogenous hyperinsulin production, rather than exogenous self-administration. Imaging including Abdominal USS, CT Abdomen and Pelvis, and MRCP revealed a dilated CBD (felt to be secondary to Methadone use) but nil else. Urine Sulphonylurea screen was sent 30 hours post-admission, and was negative.

Management & Outcome

After 24-36 hours, the patient's hypoglycaemia began to resolve, and he was slowly weaned off his continuous dextrose infusion. Repeat serum Insulin and C-peptide levels at this time had returned to normal, at 0.85 and 4.7 respectively. No further episodes of spontaneous hypoglycaemia were reported. The patient made a full recovery with no neurological deficits and was safely discharged.

Discussion

In addition to benzodiazepines, our patient tested positive for methadone, 3 tetrahydrocannabinol (THC) and amphetamines. In our review of the literature, methadone, amphetamines and THC have not been associated with endogenous hyperinsulinaemia. Interestingly, THC has been shown to suppress growth hormone and cortisol responses to hypoglycaemia, and this may have potentially prolonged the duration of hypoglycemia in our patient [1].

Since this case, a number of patients have presented similarly following ingestion of street Diazepam in Glasgow. Patients required continuous intravenous infusion of high-dose dextrose solutions for more than 24 hours, with raised serum Insulin and C-peptide levels. To date, we have been unable to isolate the causative agent in their presentation. A similar outbreak was reported in a Welsh town of Merthyr Tydfil in 2012, again following ingestion of street Diazepam [2].

This is an important case report of a growing area of concern for patients presenting following street Diazepam use. Early data suggests there has been a 43% rise in the number of people who have died of drug overdoses from January to October last year, compared to 2017. This has been attributed to the proliferation of street Diazepam use [3]. Repeat blood glucose monitoring should be maintained as an integral part of their inpatient management.

References

1. Muniyappa, R., Sable, S., Ouwerkerk, R., Mari, A., Gharib, A.M., Walter, M., Courville, A., Hall, G., Chen, K.Y., Volkow, N.D. and Kunos, G., 2013. Metabolic effects of chronic cannabis smoking. Diabetes care, p.DC_122303.
2. Pura, N.A.K., Williams, N., Agarwal, N. and Okosieme, O., 2012, March. Hypoglycaemia outbreak: a new danger on the streets?. In Society for Endocrinology BES 2012 (Vol. 28). BioScientifica.
3. BBC News Glasgow. (2019). Street valium blamed for spike in deaths. [online] BBC News. Available at: https://www.bbc.co.uk/news/uk-scotland-glasgow-west-47034644 [Accessed 29 Jan. 2019].

Notes

Notes

caledonian society for endocrinology and diabetes

CalSoc 2019 registration, meals and accommodation were covered by our sponsors:

MSD

SANOFI

NAPP

IPSEN
Innovation for patient care

novo nordisk®