CalSoc 2016

caledonian society for endocrinology and diabetes

Crieff Hydro

November 25th/26th

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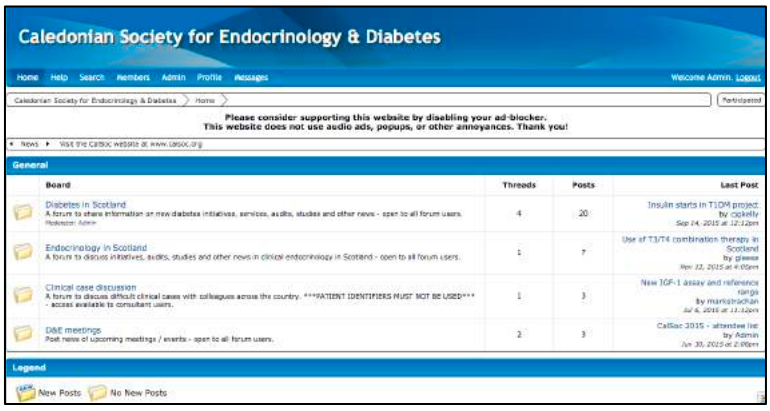


A reminder that the CalSoc online forum is open to all D&E healthcare professionals in Scotland.

It is the ideal place to share initiatives, audits, pose clinical questions and advertise local meetings.

To succeed, it will require a ‘critical mass’ of users and we’d encourage you to sign up.

calsoc.proboards.com

Contents

Programme of Events

Friday 25th November

13.00 – 14.30 Registration

13.15 – 14.00 **Meet the Professor – Trainee session – Diabetes Insipidus**
Prof. Chris Thompson

Session 1

Chair: Dr Paul Newey
Senior Lecturer / Honorary Consultant Endocrinologist
University of Dundee / Ninewells Hospital

14.30 – 15.15 **Update in the management of Primary Hyperparathyroidism**
Prof. Graham Leese
Professor of Endocrinology
University of Dundee / Ninewells Hospital

15.15 – 16.00 **CaHASEing control of androgens in congenital adrenal hyperplasia – challenges and novel strategies**
Dr. Roland Stimson
MRC Clinician Scientist / Honorary Consultant Endocrinologist
University of Edinburgh / Royal Infirmary of Edinburgh

16.00 – 16.15 Coffee

16.15 – 17.00 **Modern Management of SIAD**
Prof. Chris Thompson
Professor of Endocrinology / Consultant Endocrinologist
RCSI Medical School / Beaumont Hospital, Dublin

17.00 – 17.30 **Endocrine research in Scotland**

19.30 Dinner

Programme of Events

Saturday 26th November

08.45 – 09.00 CalSoc Annual General Meeting

Session 2

Chair: Dr. Debbie Wake
Consultant Endocrinologist / Senior Lecturer
Ninewells Hospital / University of Dundee

09.00– 09.45 **Update on Acromegaly**
Prof. Peter Trainer
Professor of Endocrinology / Consultant Endocrinologist
University of Manchester / Christie Hospital, Manchester

09.45 – 10.45 **Abstract Presentations**
Dr. Bala Muthukrishnan
Dr. Luke Boyle
Dr. Berit Inkster
Dr. Anna Anderson

10.45 – 11.00 Coffee

11.00 – 11.45 **Abstract Presentations**
Dr. Asha Hesarghatta
Dr. Laura Jack
Dr. Marcus Lyall

11.45 – 12.30 **Precision Medicine in Diabetes**
Prof. Ewan Pearson
Professor of Diabetic Medicine / Honorary Consultant Physician
University of Dundee / Ninewells Hospital

Welcome to CalSoc 2016

Welcome to Crieff for the 36th winter meeting of the Caledonian Society for Endocrinology. This is now the third year of the rejuvenated CalSoc programme and promises to be another great meeting, with a world-class range of guest speakers.

Some time has been allocated, on Friday afternoon, to discuss research opportunities within Scottish endocrinology. I firmly believe that CalSoc can provide a framework for taking forward national collaborative projects. One major advantage of belonging to a small nation is the strong relationships we are able to forge across the centres. When allied with data collection systems already available to us, a major opportunity exists to make an important contribution to evidence-based endocrinology, akin to the world-leading diabetes research facilitated by SCI-Diabetes. Hopefully this year's meeting can help build momentum towards this goal.

A final word of thanks to our sponsors: Ipsen, Lilly, MSD, Novo Nordisk and Sanofi. Due to their generous support, the meeting has been free of charge for the past 3 years. Their ongoing commitment to CalSoc is hugely appreciated.

Dr Fraser Gibb
On behalf of the CalSoc Committee

CalSoc Committee

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

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

'Caledonian Society for Endocrinology & Diabetes Annual Meeting' has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 6 category 1 (external) CPD credits. Code 109329

Attendees

Zeenat	Abdul-Wahid	Edinburgh	ST		Sharon	Mackin	Glasgow	ST
Prakash	Abraham	Aberdeen	Consultant		Iqbal	Malik	Dundee	Consultant
Anna	Anderson	Edinburgh	ST		Laura	McCreight	Glasgow	ST
Ganesh	Arungirinathan	Edinburgh	Consultant		Susan	McGeoch	Aberdeen	Consultant
Ei Thu	Aung	Edinburgh	ST		Martin	McIntyre	Paisley	Consultant
Luke	Boyle	Edinburgh	ST		Gerry	McKay	Glasgow	Consultant
Linda	Buchanan	Forth Valley	Consultant		Connor	McKeag	Glasgow	Clinical fellow
Raphael	Buttigieg	Edinburgh	CT		Frances	McManus	Glasgow	Consultant
Ross	Cairns	Wishaw	CT		Melissa	McNaughton	Edinburgh	Biochemist
David	Carty	Glasgow	Consultant		Muna	Mohamed	Dumfries	Spec Dr
Zhuo Min	Chong	Glasgow	ST		Azhar	Mohammed	Inverclyde	Consultant
Louise	Clark	Dumfries	Consultant		Kenneth	Muir	Inverness	Consultant
Alan	Connacher	Perth	Consultant		Bala	Muthukrishnan	Edinburgh	ST
Jenna	Cowan	Crosshouse	Consultant		Paul	Newey	Dundee	Consultant
Gemma	Currie	Glasgow	ST		Louise	Osborne	Greenock	Consultant
Marion	Devers	Monklands	Consultant		Alan	Patrick	Edinburgh	Consultant
Anna	Dover	Edinburgh	Consultant		Ewan	Pearson	Dundee	Consultant
Nazim	Ghouri	Glasgow	Consultant		Sam	Philip	Aberdeen	Consultant
Fraser	Gibb	Edinburgh	Consultant		Bhavya	Rajagopalan	Edinburgh	Student
Saket	Gupta	Fife	Consultant		Laura	Reid	Edinburgh	ST
Rachael	Harte	Glasgow	CT		Stuart	Ritchie	Edinburgh	Consultant
Asha	Hesarghatta	Aberdeen	ST		Tarek	Salem	Edinburgh	Visiting fellow
David	Hill	Wishaw	Consultant		Cathy	Shearing	Edinburgh	Biochemist
Isabel	Howat	Monklands	Consultant		Karen	Smith	Glasgow	Biochemist
Berit	Inkster	Edinburgh	ST		Roland	Stimson	Edinburgh	Consultant
Laura	Jack	Edinburgh	CT		Maria	Talla	Glasgow	ST
Pauline	Jones	Edinburgh	Consultant		Sandeep	Thekkepat	Monklands	Consultant
Chris	Jones	Greenock	Consultant		Chris	Thompson	Dublin	Consultant
Chris	Kelly	Forth Valley	Consultant		Craig	Thurtell	Dundee	ST
Graham	Leese	Dundee	Consultant		Peter	Trainer	Manchester	Consultant
Marcus	Lyall	Edinburgh	ST		Nyo Nyo	Tun	Edinburgh	ST
David	Macfarlane	Inverness	Consultant		Emma	Turtle	Fife	Consultant
Scott	Mackenzie	Edinburgh	Consultant		Deborah	Wake	Dundee	Consultant
Alison	Mackenzie	Forth Valley	Consultant		Rachel	Williamson	Borders	Consultant
Alasdair	Mackie	Dundee	Consultant		Rohana	Wright	Edinburgh	Consultant
Sharon	Mackin	Glasgow	ST		Nazia	Zahed	Edinburgh	Student
Iqbal	Malik	Dundee	Consultant		Nicola	Zammitt	Edinburgh	Consultant

Prof Graham Leese

Biography

Professor Graham Leese is Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School, Dundee. He was previous Lecturer at the University of Liverpool. He has undertaken research into the diabetic eye, diabetic foot and endocrine epidemiology, including the TEARS (thyroid), PEARS (parathyroid) and PROLEARS (prolactin) projects. TEARS has published on thyroid epidemiology and outcomes for patients on thyroid replacement and subclinical hyperthyroidism. PEARS has published on the epidemiology of parathyroid disease, the outcomes for those with "mild disease" and predictors of adverse outcomes. He is Associate Postgraduate Dean in the East region, Chairman of the SCE exam Board in Endocrinology and Diabetes, CMO advisor on Endocrinology and Diabetes and also clinical research lead for Endocrinology to the CSO in Scotland.

Abstract

AN UPDATE ON PRIMARY HYPERPARATHYROIDISM

Traditionally primary hyperparathyroidism (PHPT) was associated with symptoms of bony disease, renal stones, constipation, depression along with thirst and polyuria. Most patients had significant hypercalcaemia and studies showed a benefit of parathyroidectomy (PTX). The nature of PHPT has completely changed over the last 30 years as it has become easier to request serum calcium, such that most patients now are asymptomatic. This has also resulted in the prevalence of disease burgeoning, with a current prevalence of around 1%, but it is much more common in older people. The NIH have developed consensus guidelines as to who should go for PTX, and cinacalcet is available for the small group of patients with secondary HPT who are inoperable, or who have parathyroid carcinoma. However it has become apparent that many of the patients who do not fit the NIH criteria may have subtle symptoms such as muscle aches, nausea and neuro-psychiatric complaints. Whether such patients benefit from PTX is controversial. In addition, some of the asymptomatic patients appear to be at risk of cardiovascular disease and other conditions, including an increased mortality. There is however no evidence that PTX helps such patients, with the possible exception of improving bone density. However it seems possible that PTX could possibly help with other endpoints, and this is particularly intriguing as adverse outcomes are correlated with plasma PTH concentrations. More recently it has become apparent that some patients may have "normo-calcaemic" PHPT. There is a strict definition for this, and people with this condition may have adverse outcomes similar to those with standard PHPT. The role of treating the hyper-parathyroidism in such patients remains unclear, but some of these patients do progress to hypercalcaemic PHPT, especially those who are older or who have higher serum calcium concentrations at baseline.

References:

Fraser WD. Hyperparathyroidism. Lancet 2009 July 11;374(9684):145-58

Bollerslev J, Rosen T, Mollerup CL, Nordenstrom J, Baranowski M, Franco C et al. Effect of surgery on cardiovascular risk factors in mild primary hyperparathyroidism. J Clin Endocrinol Metab 2009 July;94(7):2255-61.

Rao DS, Phillips ER, Divine GW, Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 2004 November;89(11):5415-22

Yu N, Donnan PT, Leese GP. A record linkage study of outcomes in patients with mild primary hyperparathyroidism. The Parathyroid Epidemiology and Audit Research Study (PEARS) Clin Endo (2011) 75: 169-176

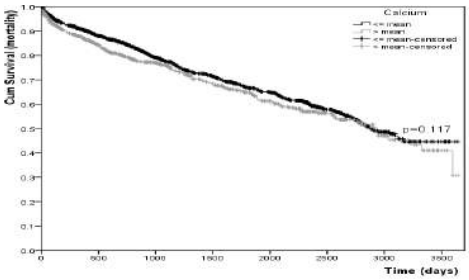
Yu N, Leese GP, Donnan PT. What predicts adverse outcomes in untreated primary hyperparathyroidism? The Parathyroid Epidemiology and Audit Research Study (PEARS). Clin Endocrinol (Oxf) 2013 July;79(1):27-34.

Lowe H, McMahon DJ, Rubin MR, Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype. J Clin Endocrinol Metab 2007 August;92(8):3001-5.

DIFFERENCES BETWEEN MORBIDITY RATIOS AND INCIDENCE RATIOS in "mild PHPT"

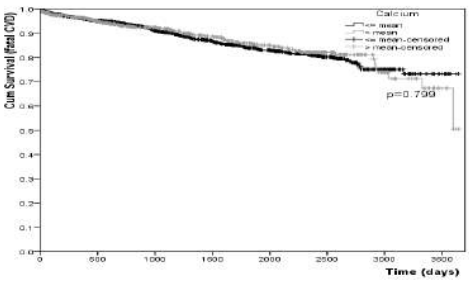
Observed morbidity endpoints	SMR	SIR
Cardiovascular disease	1.70	2.53
Cerebrovascular disease	1.61	3.10
Renal Failure	8.40	14.14
Renal Stones	2.77	4.85
Psychiatric disease	2.75	5.56
Hypertension	3.10	3.77
All fractures	1.34	1.96
Cancer	1.20	1.54
Diabetes	2.64	2.16

Yu et al 2010

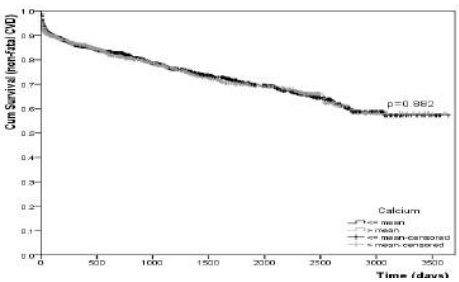


CALCIUM AS A PREDICTOR OF OUTCOME in "mild PHPT"

SURVIVAL



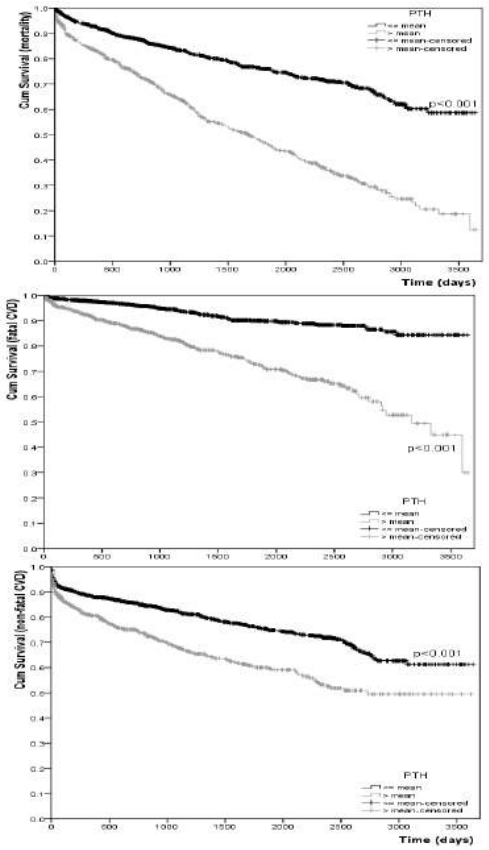
Fatal CVD



Any CVD

- Yu et al Clin Endo 2013

Prof Graham Leese



PTH AS A PREDICTOR OF OUTCOME in "mild PHPT"

SURVIVAL

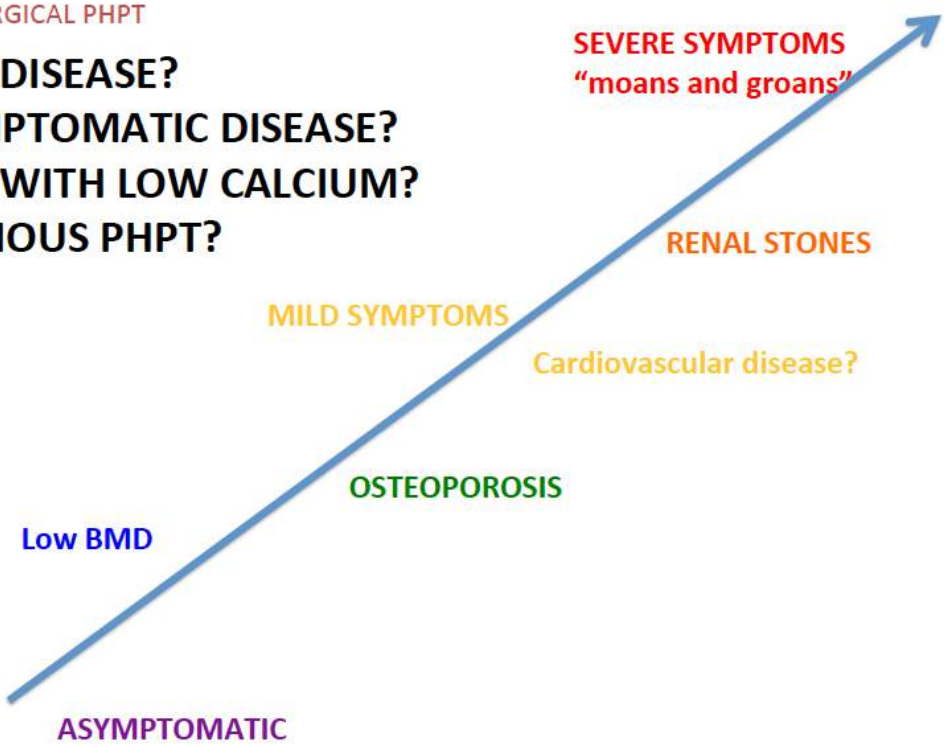
Fatal CVD

Any CVD

Yu et al Clin Endo 2013

NON-SURGICAL PHPT

MILD DISEASE?
ASYMPTOMATIC DISEASE?
PHPT WITH LOW CALCIUM?
INSIDIOUS PHPT?



CONCEPTS

"MILD DIABETES" ?!

- Relatively Low Blood Glucose
- Relatively asymptomatic
- Devastating long-term complications

"MILD PRIMARY HYPERPARATHYROIDISM" ???

- Need to establish risk
- Need to establish predictors of poor outcome
- Need to establish interventions

DIAGNOSTIC CRITERIA of Normocalcaemic PHPT

- Normal Serum corrected and ionized calcium
- Raised Serum PTH concentration in the absence of:
- Vitamin D deficiency / malabsorption
- Reduced eGFR: PTH rises when eGFR<60
- Medications of Thiazides, Lithium, bisphosphonates, denosumab

Dr Roland Stimson

Biography

Roland Stimson was born in Glasgow and undertook medical undergraduate training in Edinburgh. Following early clinical training in Fife he moved to Edinburgh to commence a PhD examining the role of glucocorticoid metabolism in obesity. He continued his clinical training in diabetes and endocrinology in Edinburgh as a clinical lecturer and currently holds a MRC Clinician Scientist fellowship at the University of Edinburgh. His research interests include the role of adipose tissue in energy metabolism, dysregulation of glucocorticoid action in metabolic disease and glucocorticoid replacement in the treatment of glucocorticoid deficiency. He works as an honorary consultant in the Royal Infirmary of Edinburgh with subspecialist interests in congenital adrenal hyperplasia and type 1 diabetes.

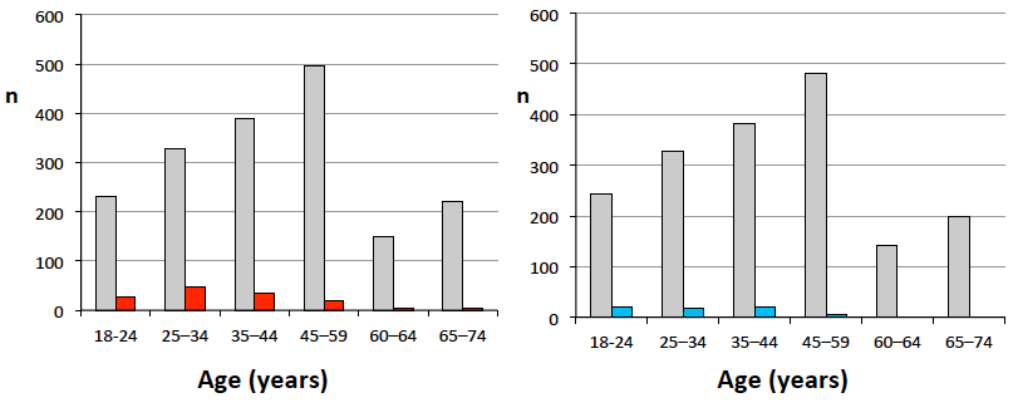
Abstract

CaHASEing control of androgens in congenital adrenal hyperplasia - challenges and novel strategies

Congenital adrenal hyperplasia (CAH) is the most common genetic endocrine disorder, with a prevalence of approximately 1 in 15,000 with the vast majority due to mutations in 21-hydroxylase. Traditional treatment relies on two principles: to replace insufficient production of adrenal glucocorticoids +/- mineralocorticoids, and to suppress production of adrenal androgens which are under ACTH control. However, the doses of glucocorticoids required to normalise androgen concentrations are often supraphysiological and cause substantial side effects. At present, only a small proportion of patients have androgen levels within the recommended range (1). In comparison with the general population, adults with CAH are shorter and have higher prevalence of obesity, diabetes, hypertension, osteoporosis, and infertility, and have a quality of life not dissimilar to patients with chronic heart failure (1,2). However, the majority of adults with this condition are not currently under specialist care. Guidelines have focused on management of CAH in children to promote normal growth (3) and evidence for the ideal glucocorticoid regimen in adults is lacking. Higher glucocorticoid dose is associated with adverse outcomes while patients receiving dexamethasone have a higher incidence of adverse metabolic features (4). Although patients on hydrocortisone monotherapy have improved quality of life many patients do not achieve adequate androgen suppression on hydrocortisone. New treatment options are being developed to better manage CAH, such as altering the pharmacokinetics of hydrocortisone replacement by using delayed release hydrocortisone or continuous subcutaneous hydrocortisone infusion. Alternative strategies such as a 'block and replace regime' using drugs to inhibit the HPA axis or block androgen production are being tested, as are the use of alternative glucocorticoids which should adequately suppress the HPA axis but hopefully cause fewer metabolic side effects (5). Success of one or more of these new strategies is urgently required to improve outcomes for patients with this condition.

Arlt W *et al*. JCEM 2010; 95(11): 5110-21. Health status of adults with congenital adrenal hyperplasia: a cohort of 203 patients.
Stewart PM *et al*. JCEM 2016 (in press); Exploring Inpatient Hospitalizations and Morbidity in Patients with Adrenal Insufficiency
Speiser PW *et al*. JCEM 2010; 95(9): 4133-60. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline.
Han TS *et al*. Clin Endo 2013; 78(2): 197-203. Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia.
Nixon M *et al*. Sci Trans Med 2016; 8(352): 352ra109. ABCC1 confers tissue-specific sensitivity to cortisol versus corticosterone: A rationale for safer glucocorticoid replacement therapy.

CaHASE – Female and Male Patients with CAH under treatment by Specialist Centres vs expected numbers



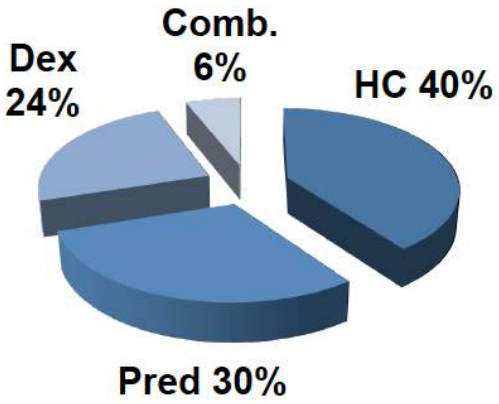
3% of men and 5% women with classic CAH under review by specialist centres

Arlt et al., JCEM 2010

Glucocorticoid Replacement

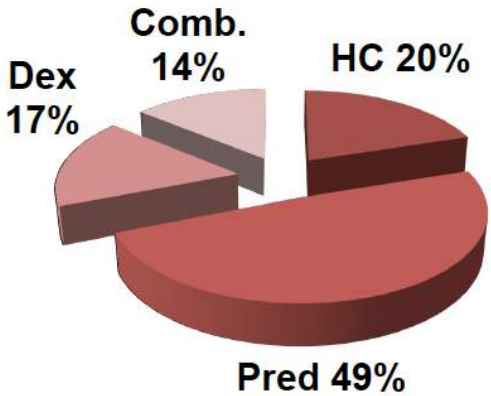
UK CaHASE Data

Classic CAH Men (n=62)



Reverse circadian: 34%

Classic CAH Women (n=103)



Reverse circadian: 50%

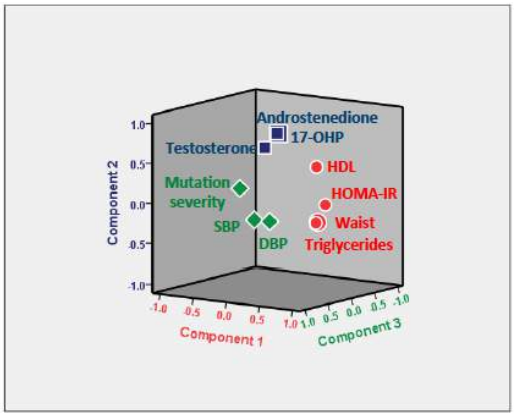
Reverse circadian administration not associated with improved control

Dr Roland Stimson

CaHASE: GC dose associates with adverse outcomes

Glucocorticoid	Prednisolone	Hydrocortisone	Dexamethasone
Equivalent dose (mg)	1	4	0.15

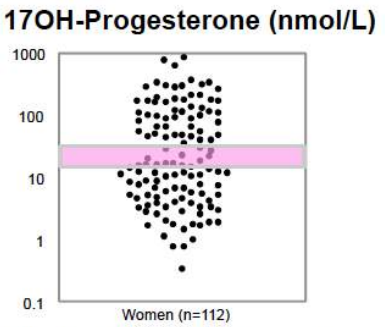
- PredEq:
  - Increased SBP and DBP
  - Worse disease control
  - More severe mutations
- Hydrocortisone monotherapy assoc with improved QoL (vitality and mental health)

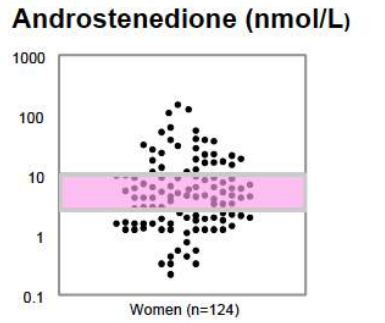


Han TS et al, Clin Endo 2013, EJE 2013

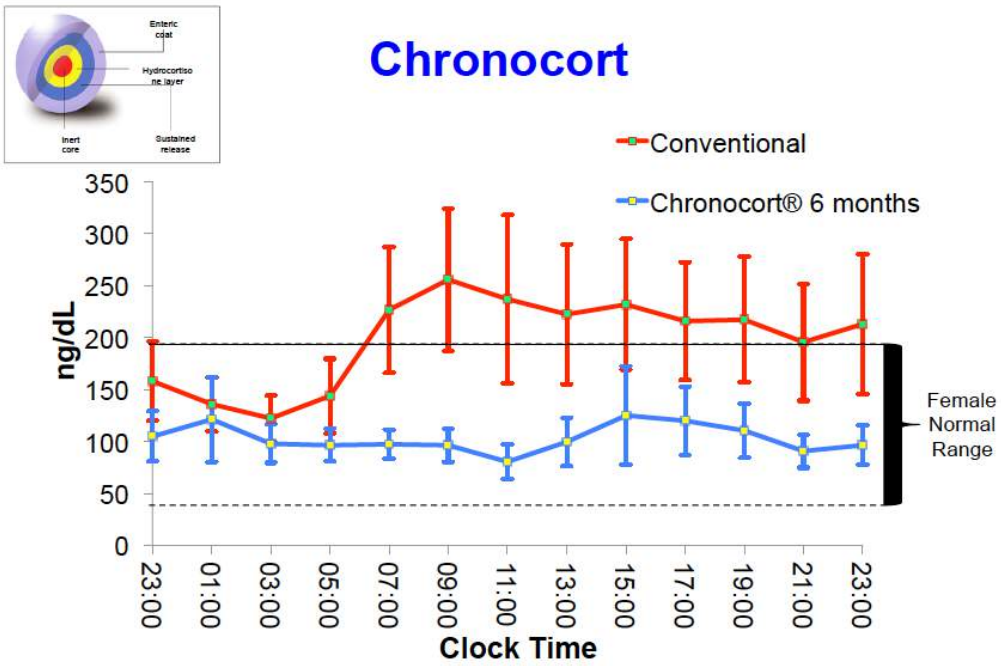
UK CaHASE: Biochemical Control

- ~45% of patients had 17-OHP levels <12nmol/L
- ~40% had 17-OHP levels > 36nmol/L
- ~40% had A_4 levels < 3nmol/L
- ~30% had A_4 levels >11nmol/L
- 16% of women had low and 30% high testosterone





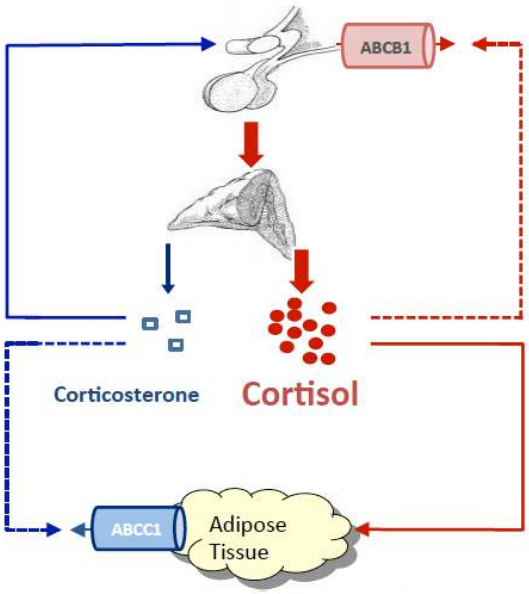
Arlt et al, JCEM 2010



Chronocort reduces androstenedione levels throughout the day

Mallappa *et al*, JCEM 2015

Corticosterone – a novel treatment for CAH



Corticosterone but not cortisol is exported from adipose tissue but not the brain

Nixon *et al*, Sci Trans Med 2016

Prof Chris Thompson

Biography

Professor Thompson qualified in Medicine from Dundee University in 1981. He worked subsequently in Newcastle upon Tyne, where he completed an MD thesis on osmoregulation in type 1 diabetes, funded with a MRC Training fellowship. He worked as lecturer in Medicine in Edinburgh University and was awarded an MRC Travelling Fellowship to UCSF, California, where he worked as Associate Professor in Physiology. He was appointed Senior Lecturer in Medicine at the University of Glasgow in 1996 and took up post in Beaumont Hospital in 1997, as Consultant Endocrinologist and Professor of Endocrinology at the RCSI Medical School. He has over 200 publications in the field of endocrinology, with strong interests in pituitary disease, hyponatraemia and posterior pituitary function. He has served as Chairman of Diabetes Ireland, Secretary/Treasurer of the Irish Endocrine Society and Chairman of the European Hyponatraemia Network. He is currently Chairman of the4 Irish speciality Interest Group in Endocrinology. He won the bid to bring the European Congress of Endocrinology to Dublin in 2015, where he was local organiser. He has served on the medical and scientific committee of the Gaelic Athletic Association and is team doctor to the Dublin Senior Hurling team.

Abstract

MODERN MANAGEMENT OF SIADH

SIADH is the commonest cause of hyponatraemia in hospital practice, accounting for 43% of hyponatraemic presentations[1]. SIADH must be distinguished, on the basis of clinical and biochemical criteria from hypovolaemic and hypervolaemic hyponatraemia; mortality is lower in SIADH than in these two variants of hyponatreamia, and treatment is different[2]. Once a diagnosis of euvolaemic hyponatraemia is established, the main differential is between SIADH and glucocorticoid deficiency; 4% of all patients presenting to hospital with euvolaemic hyponatraemia haVe steroid insufficiency[1] .
Not all cases of SIADH require active management. Mild hyponatraemia which accompanies reversible conditions such as lobar pneumonia, often need no treatment other than treatment of the underlying condition. However, as evidence accumulates that hyponatraemia is associated with increased morbidity and mortality, interest has grown in active management.

Chronic hyponatraemia. The evidence base for the success of active management is sparse. Most clinical guidelines recommend fluid restriction (FR) as first line therapy, though the evidence base for success of therapy is limited[3]. Demeclocycline is unreliable, unlicensed, has no evidence base, and had significant side effects. Urea has a limited, poor quality evidence base, and there is no available compound for clinical use. Vasopressin receptor antagonists have the backing of well-designed prospective studies, and undoubted clinical efficacy[4], though they are expensive.

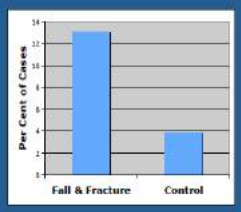
Acute hyponatraemia. Acute symptomatic hyponatraemia is a medical emergency associated with high mortality which can be reduced substantially by active management. New guidelines have been altered to recommend an initial rise in plasma sodium of 4-6 mmol/l over the initial 4-6 hours, as opposed to a steady rise in plasma sodium; the use of bolus hypertonic saline compared with continuous infusion to achieve this goal will be discussed.

1. Cuesta et al. The contribution of undiagnosed adrenal insufficiency to euvolaemic hyponatraemia; results of a large prospective, single-centre study. Clin Endocrinol 6; 2016
2.Cuesta M & Thompson CJ The syndrome of inappropriate antidiuresis Best Pract Res Clin Endocrinol Metab;30: 175-187 2016
3. Verbalis JG et al. Diagnosis evaluation and treatment of hyponatraemia: expert panel recommendations Am J Med 126; S1-42; 2013
4.Schrier RW et al Tolvaptan, a selective oral vasopressinV2 receptor antagonist for hyponatraemia N Eng J Med 355; 2099-2112 2006

Prof Chris Thompson

Hyponatraemia; morbidity and mortality

Renneboog. *Am J Med.* 2006



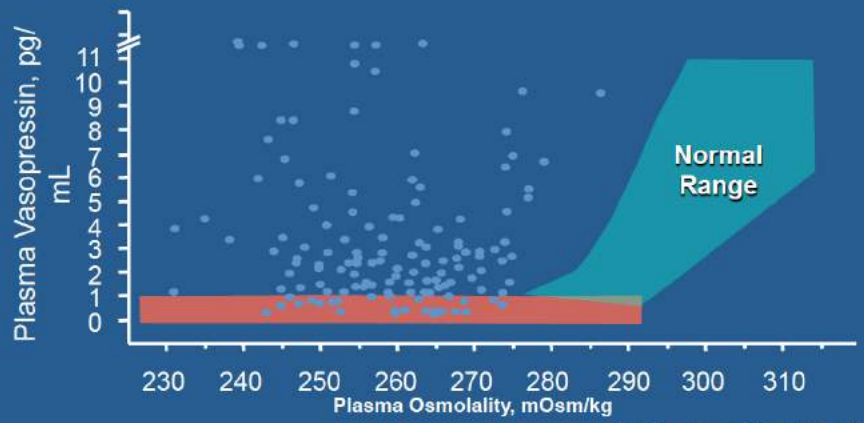
Kinsella *Clin J Am Soc Neph* 2010

Verbalis JG *JBMR* 2009

- Mortality increased in almost every published study of hyponatraemia
- Patients not specifically treated for hyponatraemia have higher mortality than those who are (37% vs 13%)

(Hoorn EJ et al, Nephrol Dial Transplant, 2006)

Plasma AVP levels are inappropriately elevated in almost all patients with SIAD



Robertson GL, *Am J Med.* 1982

Hyponatremia treatment algorithm based on neurological symptoms

LEVEL 3 – SEVERE SYMPTOMS:
coma, obtundation, seizures, respiratory distress, vomiting

→ ***ALL:*** hypertonic NaCl, followed by fluid restriction ± vaptan

LEVEL 2 – MODERATE SYMPTOMS:
altered mental status, disorientation, confusion, unexplained nausea, gait instability

→ ***EUVOLEMIC***: vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction

LEVEL 1 – NO OR MINIMAL SYMPTOMS:
difficulty concentrating, irritability, altered mood, depression, unexplained headache

→ ***ALL***: fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
- *inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)*

Prof Chris Thompson

Alternative options for SIADH

	COST	EFFICACY	RELIABILITY	EVIDENCE	SE
Fluid restriction	-	+	+	_	_
Demeclocycline	+	++	+	_	++++
Urea	++	+++	++++	++	+
Frusemide + oral NaCl	+	+++	+++	_	+
Vaptans	+++++	+++++	+++++	++++	+

Management of Severe Hyponatraemia

Verbalis, Greenberg, Stern, Thompson , Am J Med (2013)

1. Initial elevation of pNa 4-6 mmol/l over 2-4 hours by bolus IV injection of 100 mls 3%saline, repeated x2 if needed
2. Thereafter, slow IV infusion of 3% saline
3. Measurement pNa 2-4 hourly

	Target rise in pNa/ 24h	Maximum rise of pNa in 24h
Standard patient	8	12
Alcoholic or Malnourished	6	8

Key Learning Points

1. Accurate data necessary for diagnosis of SIAD
2. Be alert for underlying glucocorticoid deficiency
3. Fluid restriction is often unsuccessful, with subsequent need for second line therapy
4. Bolus therapy for severe symptomatic hyponatraemia may be more effective than traditional hypertonic saline infusion

Prof Peter Trainer

Biography

Professor Peter Trainer qualified in Edinburgh and continued his higher training in St. Bartholomew's Hospital London, Aberdeen, Utrecht (Netherlands) and Portland (Oregon, USA). He was a senior lecturer at Bart's in London before becoming a consultant endocrinologist at the Christie Hospital (Manchester) in 1998 which he combines with being the Clinical Director of the Manchester Academic Health Science Centre (www.MAHSC.ac.uk) and chairman of Bioscientifica (www.bioscientifica.com).

Professor Trainer is an active leader in the international endocrine community. He has served on the senior executive committees of the Society for Endocrinology (UK), the Endocrine Society and the European Society of Endocrinology (ESE). He chaired the programme organising committee for ECE2011 and the clinical programme of ENDO2007. In 2014 ESE presented him with a 'special recognition award' for his contribution to the Society and in particular education. His prime areas of research are diseases of the pituitary and adrenal glands, particularly Cushing's syndrome and acromegaly, which have resulted in over 150 peer-reviewed publications.

Abstract

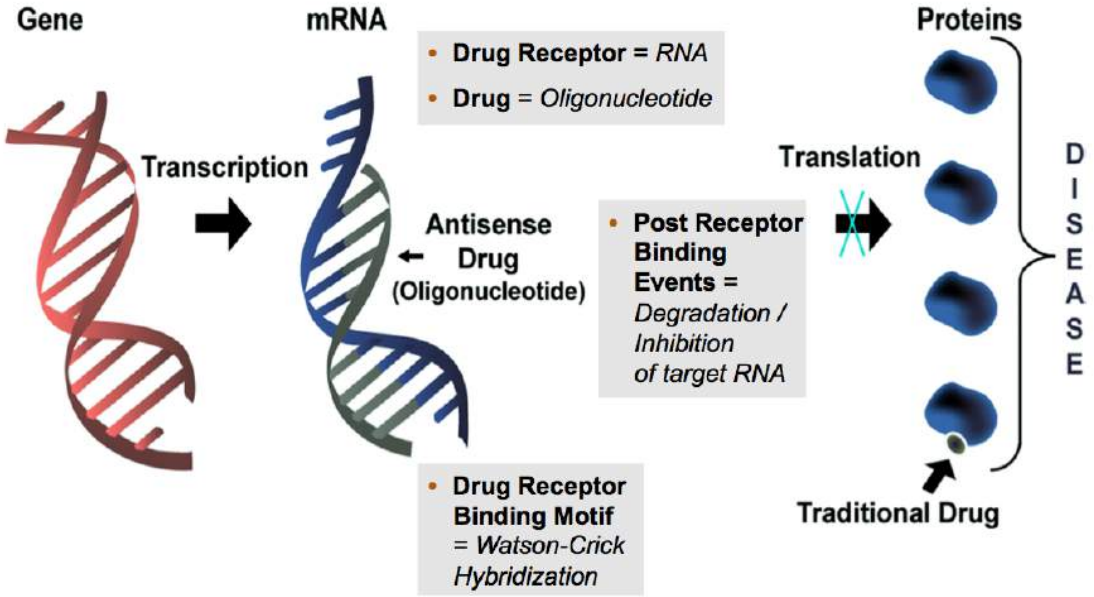
Antisense Oligonucleotide therapy for Acromegaly

Conventional therapy is directed at the pituitary and attempts to reduce GH secretion by means of surgery, radiotherapy or medical therapy in the form somatostatin analogues and dopamine agonists. An alternative therapeutic approach is to lower IGF-I levels by blocking GH action; the GH receptor (GHR) antagonist pegvisomant has been reported to normalise IGF-I in over 90% of patients. Antisense oligonucleotides (ASOs) are single-stranded synthetic oligonucleotides that have been developed as therapeutic agents that block protein synthesis by binding the target mRNA through sequence-specific Watson–Crick base-pair interactions to inhibit gene expression. ATL1103 is a second generation, antisense oligomer targeted at the human GHR. It comprises 20 nucleotides with a phosphorothioate backbone and 2'-O-methoxyethyl modifications of the terminal five nucleotides at each end which in combination increase its plasma half-life and affinity for the mRNA. Post-hybridization RNaseH degradation results in inhibition of GHR translation. In pre-clinical primate studies, ATL1103 has been shown to reduce GHR mRNA levels in the liver and serum IGF-I. Phase 1 studies in healthy male volunteers demonstrated a fall in serum IGF-I.

A phase 2, randomised, open-label, parallel group study of the safety, tolerability, and efficacy of subcutaneous administered ATL1103 in adult patients with acromegaly demonstrated it to be well tolerated with mild to moderate injection site reactions being the most common drug-related AE. Four SAEs were reported, of which three occurred in a single patient, but none were felt to be study drug related. There was a significant fall in serum IGF-I of 26% by week 14 with 200 mg twice weekly (577 ± 198 v 411 ± 174 ng/ml (mean ± SD), P <0.0001). Once weekly dosing did not result in a significant fall in IGF-I. The fall in IGF-I with twice weekly dosing was associated with a mean reduction in ring size of 0.92 (P=0.02), a fall in serum GHBP -453.0 (range -2219 to 237 (P=0.0046)) and -309.3 (-2392 – 443, P=0.0186) pmol/l, and an increase in GH (AUC during an OGTT, P=0.001).
The study provided proof-of-concept that ATL1103 is able to significantly lower IGF-I in patients with acromegaly and offers a novel therapeutic approach.

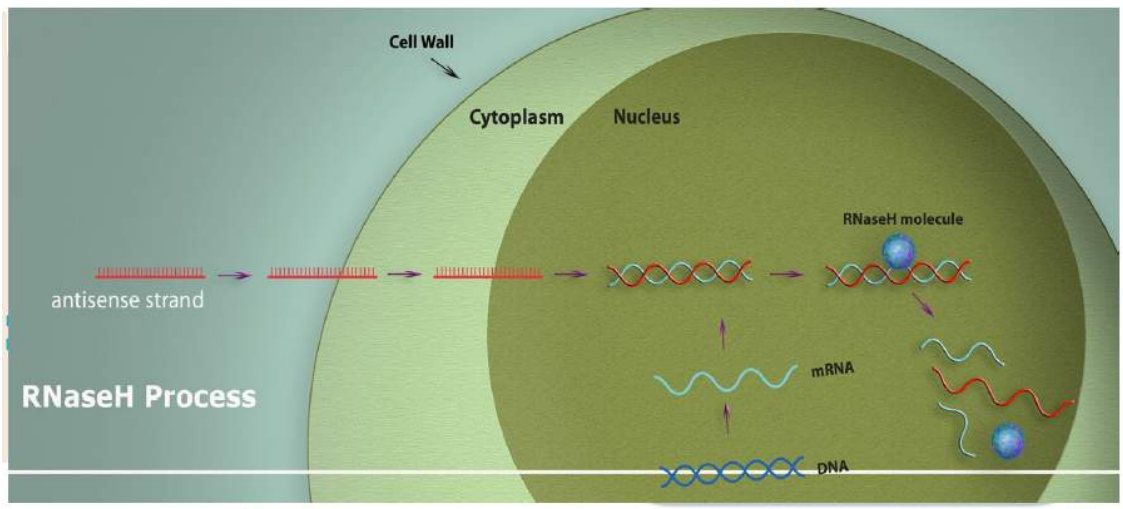
Prof Peter Trainer

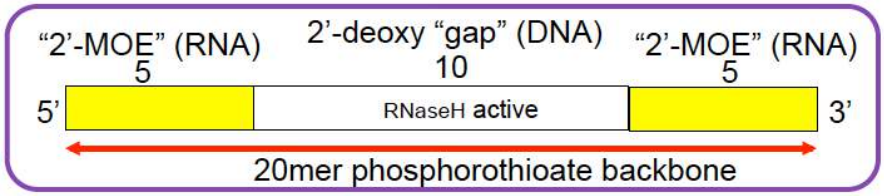
Antisense drugs: RNA-targeting mechanism of action



Ionis Pharmaceuticals Inc.

ATL1103 antisense 20mer oligonucleotide directed at GH receptor





Manchester Academic Health Science Centre

Phase 2, randomised, open-label, parallel group study (EudraCT 201200314730)

Ethical approval obtained in each jurisdiction

Powered for 24 patients

Inclusion criteria included:

- active acromegaly (IGF-I >130% ULN)
- washout from medical therapy (Long acting SMS analogues 4 months, DA 6 - 8 weeks)

Exclusion criteria included:

- tumour within 3 mm of optic chiasm
- pituitary surgery within 3 months
- radiotherapy within 1 year

Manchester Academic Health Science Centre

Protocol

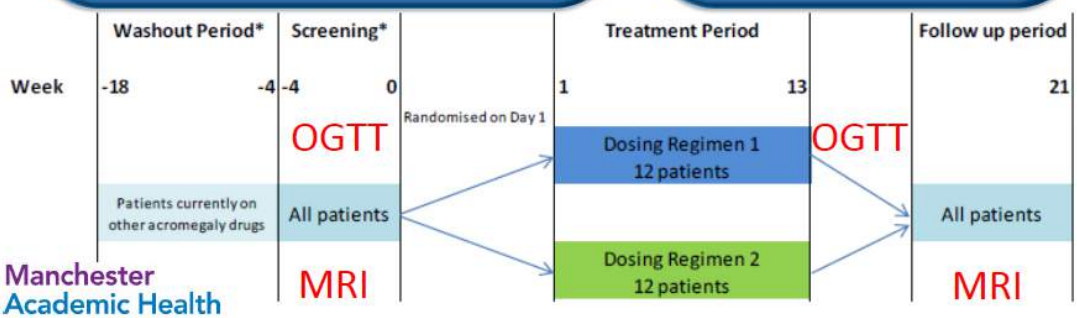
ATL1103 subcutaneously for 13 weeks (3 doses in first week)

Randomised to:
200 mg once weekly
or
200 mg twice weekly

IGF-I & GH assay

IDS iSYS

Bidlingmaier
JCEM 2014 99 1712



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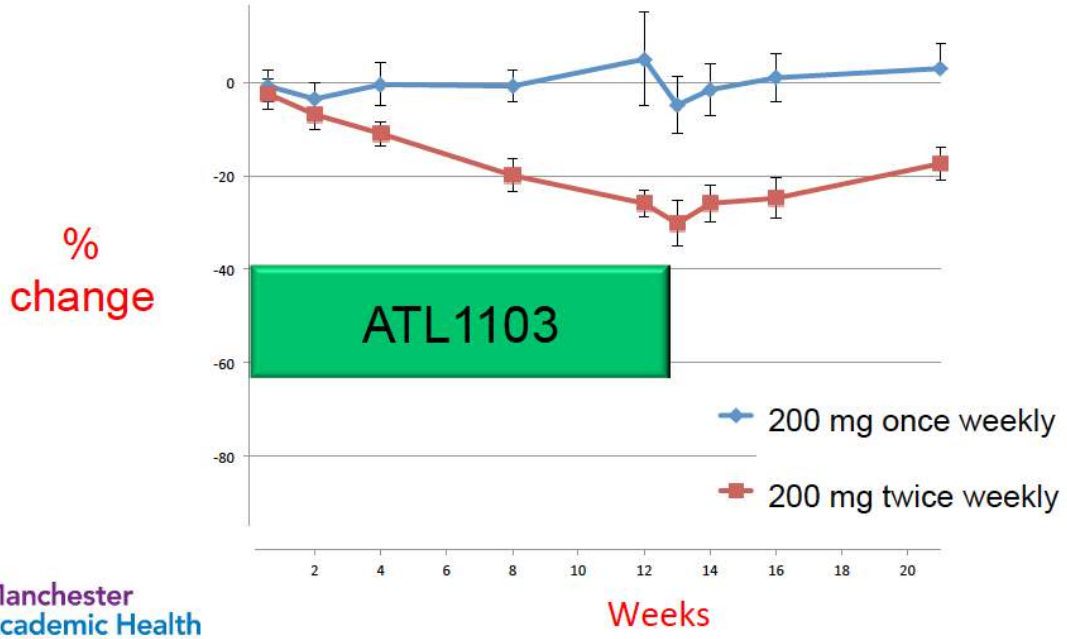
Prof Peter Trainer

Change in IGF-I with 13 weeks of ATL1103



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Summary

No patient withdrawals or SAEs related to ATL1103

Injections site reactions most reported adverse event

Liver enzymes elevations in two patients

Transient platelet reductions in one patient

2 x 200 mg/week ATL1103

26% mean reduction of IGF-I one week after 13 weeks

IGF-I had not reached nadir by week 13

Dose-response relationship with ATL1103 (mg/kg/week) *vs* change in IGF-I

Manchester Academic Health Science Centre

Prof Ewan Pearson

Biography

Ewan Pearson is a Professor in Diabetic Medicine at the University of Dundee, UK, and is Honorary Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School in Dundee. Professor Pearson obtained his medical degree from the University of Cambridge School of Clinical Medicine, UK. He undertook a Wellcome Trust Clinical Training fellowship with Prof Andrew Hattersley at the University of Exeter Medical School, UK and completed his PhD in the physiology and treatment of monogenic diabetes. His research interests are the phenotypic and genotypic determinants of drug response and drug side effects, the aetiology of young-onset diabetes and the mechanisms driving progression of diabetes. He is the academic lead on the €46M IMI-DIRECT project on stratification in Type 2 diabetes and is Strand 2 lead on the £6M MRC funded MASTERMIND project. Professor Pearson's New Investigator Award funding by the Wellcome Trust aims to gain deeper phenotypic, physiological and molecular insights into the mechanism of action of metformin and other diabetes drugs and how patients respond differently and experience different side effects to these agents.

Abstract

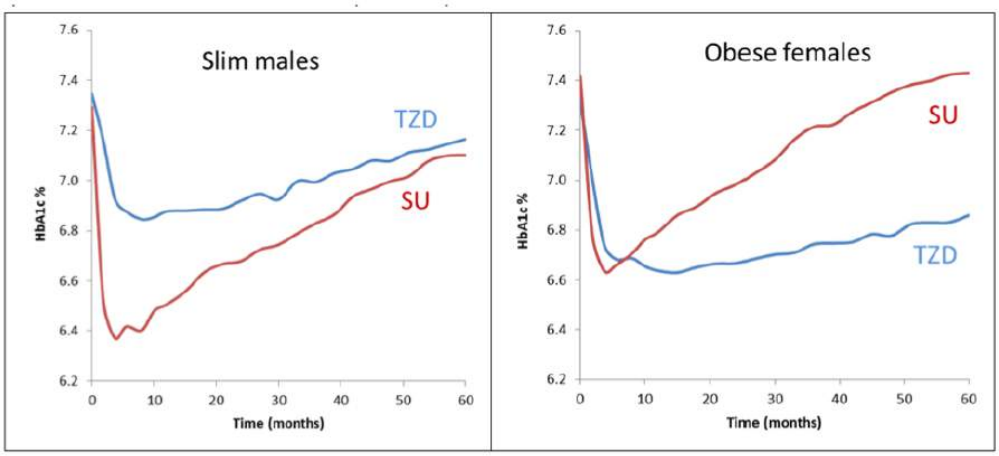
Stratification in diabetes – the role of phenotype and genotype in clinical decision-making

There are a number of approaches to the therapy of patients with Type 2 diabetes. One common sense approach is to trial a drug and, as recommended by SIGN, to stop therapy if a drug is ineffective. However, this trial-and-error approach is poorly practiced, with over 60% of individuals in Tayside who show poor response to a drug continuing it when a new drug is started rather than stopping it.

An alternative approach is the stratified approach, or even the individualized approach to therapy, as advocated by the joint ADA/EASD guidelines. Yet these guidelines offer no evidence base for how drugs should be individualized. In the MRC-ABPI Mastermind study we show that thiazolidinediones work best in obese patients, yet metformin, another 'insulin sensitizer' works best in slimmer patients who are more insulin sensitive with preserved beta-cell function. Thus BMI, diabetes duration and insulin sensitivity can be used to begin to stratify therapy.

In addition genetic variation may alter response to or side effects of therapy. Metformin response is variable and heritable suggesting an individual's genetics will influence response. We have shown that variants at the ATM locus alter response to metformin, but the clinical effect is small. However for metformin intolerance, OCT1 genotype, and use of OCT1 interacting drugs have a large clinically important impact on risk of intolerance to metformin.
In summary, we are making steps towards tailored prescribing, but to move forward we need trials specifically to assess within person response to different diabetes drugs.

Stratification in ADOPT



Unpublished. Perry et al. for the Mastermind Consortium

How can you identify MODY in your clinic?

- Young onset (usually before age 25)
- Non insulin requiring (but may be treated with insulin)
- Usually a strong family history
  - Caution – can occur de novo;
  - Caution – GCK
- Do they have 'atypical' diabetes?
  - Slim
  - Absence of insulin resisitance
- hsCRP
  - Low in HNF1A
- Renal cystic kidney disease/Genital tract malformation
  - HNF1B
- Macrosomia and neonatal hyperinsulinemia
  - HNF4A

OCT1 transport

Genetic variation

R61C
C88R
G401S
M420del
G465R

8% of us carry two loss of function variants

OCT1 Interacting Drugs

TCA
PPI
VERAPAMIL
DILTIAZEM
DISOPYRAMIDE
QUINIDINE
PRAZOSIN
DOXAZOSIN
SPIRONOLACTONE
TRIMETHOPRIM
ROSIGLITAZONE
REPAGLINIDE

Side effects

Tanja Dujic,[1] Kaixin Zhou,[2] Louise A. Donnelly,[2] Roger Tavendale,[2] Colin N.A. Palmer,[2] and Ewan R. Pearson[2]

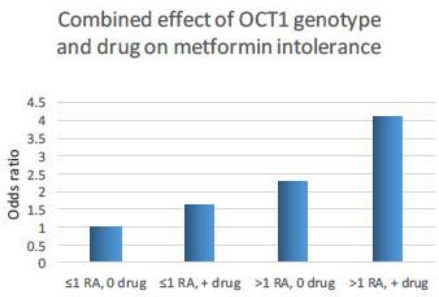
Association of Organic Cation Transporter 1 With Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study

Diabetes 2015;64:1786–1793 | DOI: 10.2337/db14-1388

Table 2—Logistic regression model of metformin intolerance

	OR (95% CI)	*P*
Age	1.10 (1.08–1.12)	<0.001
Sex (females vs. males)	1.85 (1.33–2.57)	<0.001
Weight	0.99 (0.98–1.00)	0.064
Use of OCT1-inhibiting drugs	1.64 (1.20–2.25)	0.002
Two reduced-function OCT1 alleles	2.41 (1.48–3.93)	<0.001

Logistic regression analysis included 205 intolerant and 1,650 tolerant patients.



Prof Ewan Pearson

Which Drug is Best for you?

Metformin

Best in slim people
Better with reduced GLUT2 transport

Side effects in those with reduced OCT1 transport

TZDs

Best in obese women

Response and weight gain with Rosiglitazone altered by CYP2C8 and SLCO1B1 activity

Sulphonylureas

Best in slim men
3.44 times better in those who metabolise SU slowly (CYP2C9)
Better with KCNJ11/ABCC8 mutation
Worse in those with TCF7L2 risk variants
EXCELLENT in those with HNF1A/4A/ABCC8

DPP-4i

Best in asians?

Response altered by CTRB1 variants

Dr Bala Muthukrishnan

Abstract

Extensive Clinical Experience in the Investigation and Management of Primary Hyperparathyroidism

Laura J Reid, Balakumar Muthukrishnan, Andrew Ditchfield, Andrew Brodie & Fraser W Gibb

Introduction

Primary hyperparathyroidism is an increasingly common condition, caused by a single benign parathyroid adenoma in 85% of cases. Surgery provides a definitive cure with parathyroidectomy. Conservative management to observe calcium levels or treat with medications such as bisphosphonates or cinacalcet can provide a suitable alternative to surgery, particularly in older patients with relatively modest hypercalcemia.

Objectives

(1) To characterise the diagnostic features and management of patients referred for evaluation of primary hyperparathyroidism. (2) To assess effects of vitamin D replacement on follow up calcium levels in medically treated primary hyperparathyroid patients deficient in vitamin D. (3) To compare longer-term outcomes and calcium levels for patients receiving medical versus surgical management. (4) To assess association between mortality and degree of hypercalcaemia, levels of PTH, vitamin D and serum creatinine.

Methods

Retrospective review of all patients with a new diagnosis of primary hyperparathyroidism referred to a large university teaching hospital in Edinburgh, Scotland. In total, around 450 patients diagnosed between 2009 and 2013 were included. Clinical information was obtained via electronic patient records. Information on signs, symptoms and risk factors was characterised from clinic letters. Results of investigations were obtained from the laboratory and radiology record systems.

Results –

1. Median PTH at presentation was 12.4 pM (9.45-19.4 pM). Median calcium at presentaion was 2.76 mM (2.67-2.89), and was >0.25mM above the upper limit of normal (2.85mM) in 30.8%. In total, 140/333 (42.6%) proceeded to surgery. Surgical patients were younger (64.4 [53.75-74.25] vs. 67.7 years [61-79], p <0.01). There was no significant difference in calcium (2.81 [2.7-2.81] vs. 2.74 mM [2.65-2.83], p = 0.4). A higher proportion of patients managed surgically had renal stones ($p < 0.01$) and osteoporosis ($p < 0.01$). Abdominal imaging identified nephrolithiasis in 29/151 (19.2%). Genetic testing was done in 32/333 patients (9.6%): 2 patients were confirmed to have MEN1, 2 to have Hyperparathyroid-jaw tumour syndrome and 1 to have Familial Hypocalciuric Hypercalcaemia.

2. Vitamin D deficiency (<25nmol/l) was present in 56/154 (36.4%) and was associated with higher PTH (15.5 [12.03-22.95] vs. 11.5nM [8.4-16.53], than replete individuals. There was no significant rise in calcium in patients given vitamin D replacement at Year 1 ($p = 0.71$) or Year 2 ($p = 0.99$).

3. Surgical cure was achieved in 92.5%. At least one imaging modality was positive in patients with persistent disease post-surgery. Where surgery was not performed, median calcium was typically maintained below the threshold for surgical intervention. Bisphosphonates were used in 62/190 (32.6%), and cinacalcet in 18/190 medical patients (9.4%).

4. Higher mortality rate was noted in patients with higher PTH levels. Mortality in those with PTH above the median was 21.7% compared to 13.8 % below the median ($p < 0.05$). There was a non-significant trend towards higher mortality with lower vitamin D (19.5 % vs. 9.6%, $p = 0.09$). Plasma calcium levels were not associated with subsequent mortality.

Dr Bala Muthukrishnan

Abstract (continued)

Conclusions

Conservative management (including vitamin D replacement) is not associated with worsening hypercalcaemia over a 3-year observation period. This is in keeping with previous studies suggesting stable disease for up to a decade[1]. This may be falsely reassuring as high PTH at diagnosis has been associated with higher mortality[2] which has been recapitulated in our analysis. Large prospective databases present an opportunity to optimize care in this common condition.

References

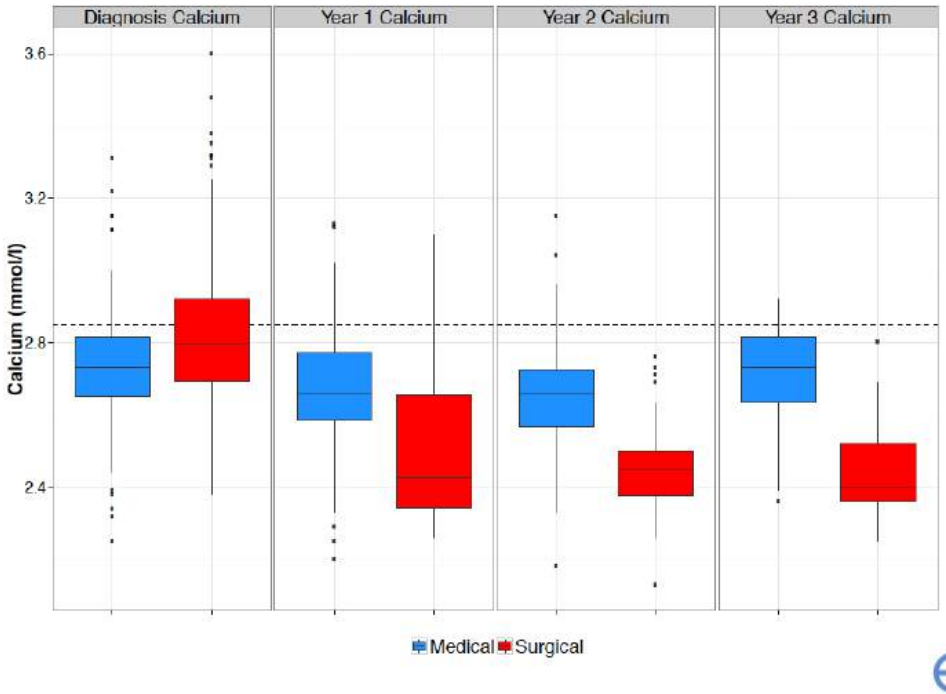
The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. Rubin MR et al., J Clin Endocrinol Metab. 2008 Sep;93(9):3462-70.

What predicts adverse outcomes in untreated primary hyperparathyroidism? The Parathyroid Epidemiology and Audit Research Study (PEARS). Yu N1, Leese GP, Donnan PT. Clin Endocrinol (Oxf). 2013 Jul;79(1):27-34

Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. Cipriani C et al. J Clin Endocrinol Metab. 2015 Apr;100(4):1309-15.

Calcium at presentation

And over the following 3 years



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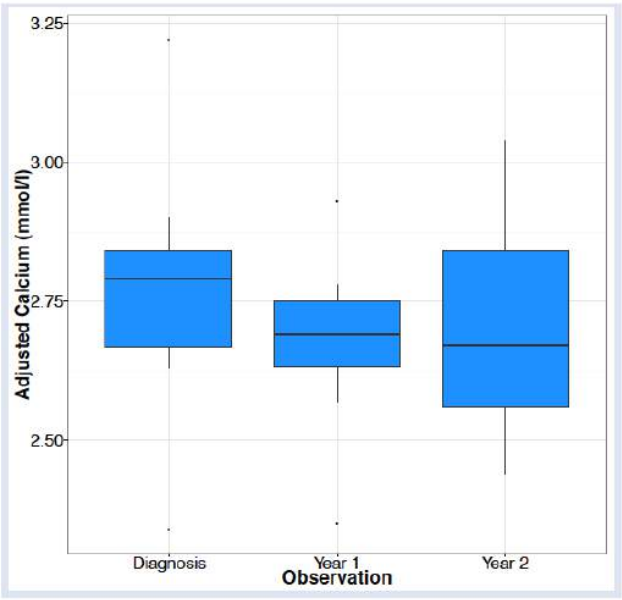
Treatment of vitamin D deficiency

No change observed in calcium over 2 years



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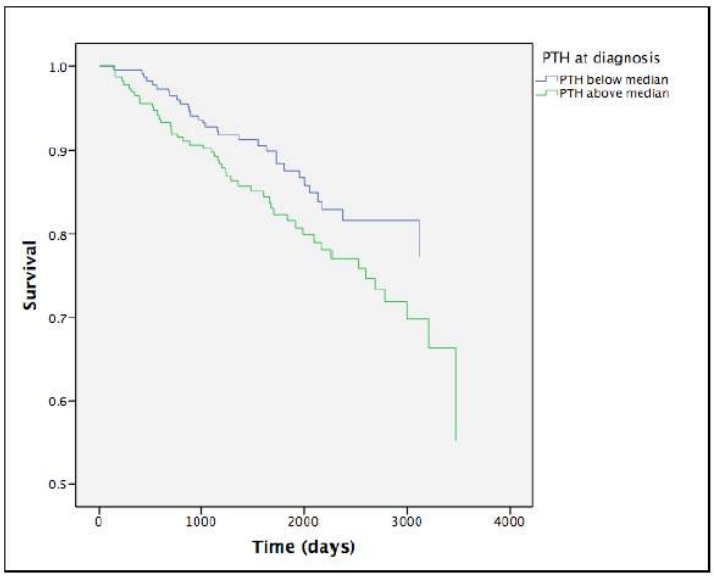
PTH levels at diagnosis

Associated with subsequent mortality



Log Rank (Mantel-Cox)
p = 0.046

N = 450

13.8% Mortality in lower PTH
21.7% Mortality in higher PTH

Median follow-up:
(4.8 years [IQR 3.4 – 6.9])

No correlation between
age and PTH

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Dr Luke Boyle

Biography

Luke Boyle studied medicine at Queen's University Belfast, graduating in 2012 with an intercalated MSc in Public Health. He then undertook academic foundation training at Aintree University Hospital in Liverpool, and investigated the effect of circulating vitamin D on adipose tissue inflammation under the supervision of John Wilding. He later moved to Edinburgh in 2014 for core medical training in SE Scotland. Luke has been a clinical research fellow at the BHF/University of Edinburgh Centre for Cardiovascular Sciences since August of this year, studying for his PhD under the supervision of Brian Walker, Roland Stimson and Mark Nixon. He intends to start his specialist training in Diabetes & Endocrinology in 2019.

Abstract

Identification and Validation of Criteria for the use of Random Serum Cortisol as a Screening Test for Adrenal Insufficiency

Scott D Mackenzie, Luke D Boyle, Robert M Gifford, Fraser W Gibb

Background: In the investigation of suspected adrenal insufficiency (AI), a single measurement of unstimulated ('basal') serum cortisol offers convenience and cost advantages compared to the widely used short Synacthen test (SST). Cut-offs for basal serum cortisol which predict intact adrenal function have been defined, but with variable accuracy, and have not been validated. Our aim was to assess the utility of random serum cortisol as a screening tool in the investigation of suspected adrenal insufficiency, using validated criteria, in both an in- and out-patient setting.

Methods: We undertook retrospective review of all SSTs performed in the outpatient departments and acute medical units at two teaching hospitals in Edinburgh between 2011 and 2014. Serum cortisol was measured by immunoassay before and 30 mins after intravenous synthetic $ACTH_{1-24}$ (Synacthen®) 250μg. AI was defined according to local reference ranges by a stimulated serum cortisol of <430 nM. Tests performed in the outpatient department at one hospital were used as a derivation cohort (n=1628) to identify cut-offs for morning and afternoon basal serum cortisol which detected AI with sensitivity 99%. The criteria were tested in two validation cohorts, one comprising outpatients from the second hospital (n = 875) and one comprising individuals admitted to the acute medical units of both hospitals (n=797).

Results: In the derivation cohort, to detect AI with sensitivity >99%, cut-offs for basal serum cortisol of 307nM (am) and 324nM (pm) were required. A basal cortisol of <50nM was strongly (95%) predictive of a subnormal response. Of those patients with random serum cortisol <50nM, subnormal adrenal response was seen in 24/25 (97.8%) in morning samples and 14/15 (92.9%) in afternoon samples. In the outpatient validation cohort, morning basal cortisol >307nM remained highly sensitive (98.6%), with a NPV of 99.2%. Of 23 patients with basal serum cortisol <50nM, 22 (95.6%) had a subnormal adrenal response. Assuming patients lying between these cut-offs would require a Synacthen test, application of the criteria would result in a 43% reduction in the number of Synacthen tests required. A random morning cortisol >307nM was 100% sensitive for the detection of AI in inpatients. Of 7 patients with basal serum cortisol <50nM, 6 (85.7%) had a subnormal adrenal response. Assuming patients lying between these cut-offs would require a Synacthen test, application of the criteria would result in a 68% reduction in the number of Synacthen tests required.

Conclusion: A random morning serum cortisol result of >307nM makes AI highly unlikely. Random cortisol offers promise in in-patients, although given the low incidence of AI and heterogeneity of the patient group, criteria ideally require validation in a larger cohort. Due to poorer specificity, afternoon serum cortisol is a less useful measure. Use of basal serum cortisol as a screening test minimizes the need for the SST and offers a convenient and accessible means of identifying those patients who require further assessment.

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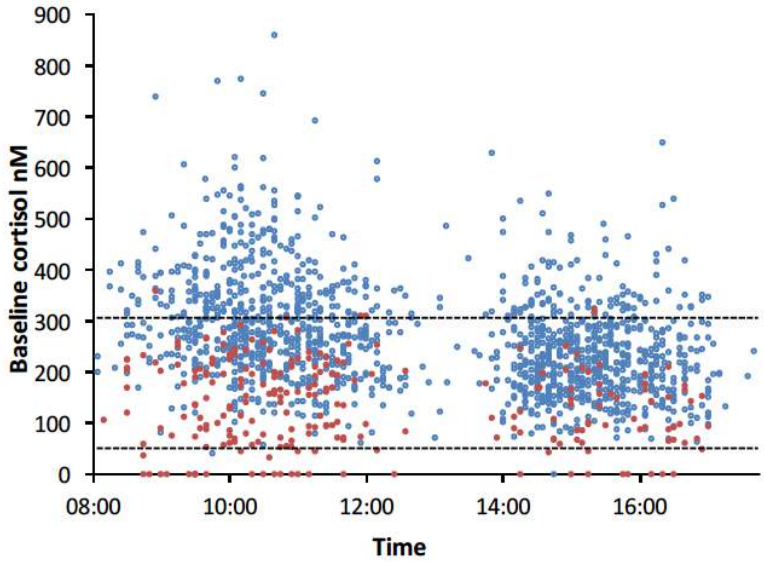
Baseline Cortisol vs Time (Derivation Cohort)

NHS Lothian



○ = normal adrenal response (stimulated cortisol ≥430 nM) ○ = individuals diagnosed with adrenal insufficiency

Dashed line indicates proposed cut-offs to predict response to Synacthen (for am samples)

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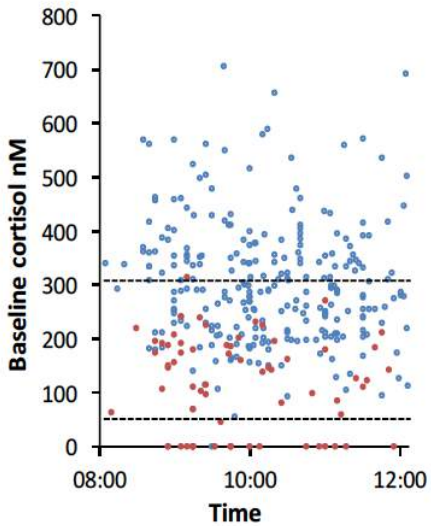
Baseline Cortisol vs Time (Outpatient Validation Cohort)

NHS Lothian



○ = normal adrenal response. ○ = adrenal insufficiency. ()=95% confidence intervals

Sensitivity	98.6% (92.3-100)
NPV	99.2% (95.4-100)
Specificity	45.6% (39.4-51.8)
PPV	32.9% (26.5-39.7)

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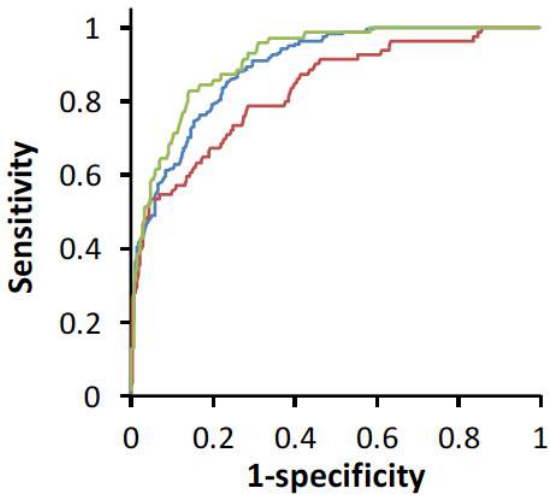
ROC for Baseline Cortisol in the Diagnosis of AI in Outpatients

NHS Lothian



ROC AUC (outpatients)	
Derivation cohort (am)	0.89
Derivation cohort (pm)	0.83
Validation cohort (am)	0.91

Blue = derivation cohort (morning); red = derivation cohort (afternoon); green = validation cohort (morning samples). AUC = Area under curve

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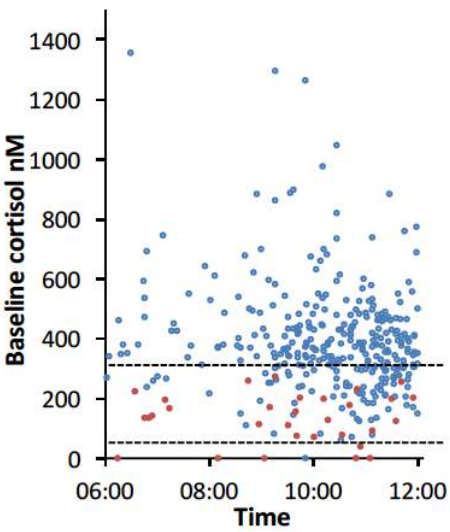
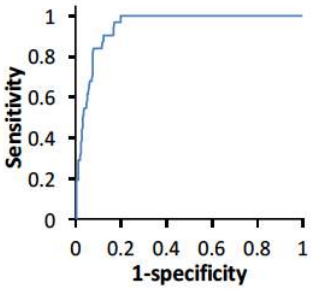
Baseline Cortisol vs Time (Inpatient Validation Cohort)

NHS Lothian





Sensitivity	100% (N/A)
NPV	100% (N/A)
Specificity	72.2% (67.0-77.0)
PPV	25.6% (18.1-34.4)

○ = normal adrenal response.
○ = adrenal insufficiency.
()=95% confidence intervals

Dr Berit Inkster

Biography

- Graduated Aberdeen 2005
- Started endocrine training in Edinburgh 2011
- Currently working in SJH as ST7/acting consultant

Abstract

Case presentation of hyperparathyroidism in pregnancy treated with parathyroidectomy in second trimester

A case of primary hyperparathyroidism (pHPT) presenting with severe hypercalcamia at 24 weeks gestation is discussed. pHPT in pregnancy is rare and under-recognised. Diagnosis is made with elevated calcium (ionised or corrected for albumin) and high or normal PTH. Neck ultrasonography is the imaging investigation of choice. Case reports suggested a high risk of maternal and obstetric complications including hyperemesis, nephrolithiasis, pancreatitis, depression, fracture, abortion. More recent retrospective case control studies suggest that most cases of pHPT in pregnancy are mild and do not hold an increased risk of adverse pregnancy outcomes. If hypercalcaemia is mild it can be managed conservatively, however in more severe cases parathyroidectomy in the second trimester is the treatment of choice.

Dr Berit Inkster

Primary HPT in Pregnancy - overview

- Rare - <1% of pregnancies, but probably under recognised (approx 200 reported cases)
  - Symptoms non-specific and often related to pregnancy – fatigue, anorexia, nausea, vomiting, constipation, depression
- Diagnosis if raised serum (corrected) Ca or ionised Ca and raised or inappropriately normal PTH
- Radio-labelled scans contra-indicated therefore neck USS is imaging of choice
- 85% solitary adenoma
  - otherwise hyperplasia (10%), multiple adenoma (2%) carcinoma (1%)

Treatment options

- Conservative medical treatment with iv or oral rehydration +- forced diuresis
- Calcitonin – does not cross placenta and appears safe in case reports, but insufficient data and poor effectiveness limit use
- Bisphosphonates cross placenta and accumulate in foetuses in rats
- Cinacalcit – used in few cases with good results. Cross the placenta – more safety evidence required

Parathyroidectomy

- Surgery in second trimester appears safe (in experienced hands)
  - 95% success rate
  - 1-3% complications (RLN palsy, post op hypocalcaemia)
- If diagnosis in 3rd trimester discussion regarding risks & benefits of surgery.
- Concurrent CS and parathyroidectomy seems safe

Summary

- Primary hyperparathyroidism in pregnancy is uncommon and under-recognised
- Most cases are mild, and can be managed conservatively
- In more severe cases surgery in second trimester is treatment of choice

Dr Anna Anderson

Biography

I graduated from the University of Edinburgh in 2005 before undertaking my foundation years and core medical training between Edinburgh and Glasgow. I returned to Edinburgh in 2010 but shortly afterwards took time out of programme to undertake a PhD looking into the cellular regulation of cortisol *in vivo* by 11-beta hydroxysteroid dehydrogenase type 1 under the supervision of Prof Brian Walker and Ruth Andrew. I returned to my clinical training in 2014 and am currently in the penultimate year of my training at the Western General Hospital.

Abstract

Tissue-specific regulation of recycling between cortisol and cortisone by insulin and obesity

Anna J Anderson, Ruth Andrew, Natalie Z M Homer, Kate A Hughes, Fredrik Karpe, Roland H Stimson, Brian R Walker

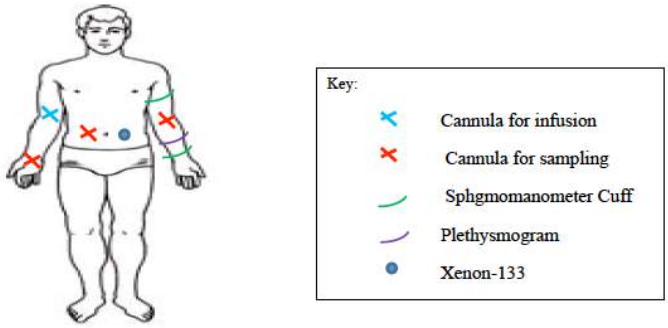
Intracellular cortisol is regulated by 11βHSD1. Although the field has focused on regeneration of cortisol from inert cortisone by 11β-reductase activity of 11βHSD1, we have used stable isotope tracers and arteriovenous sampling to quantify simultaneous dehydrogenase (cortisone generation) and reductase (cortisol regeneration) in human adipose and skeletal muscle. In vitro studies suggest insulin regulates this balance of reductase versus dehydrogenase activity. In obesity, 11βHSD1 expression is increased in adipose. We hypothesised that the directionality of 11βHSD1 in metabolic tissues is regulated by insulin and that in obesity there is accelerated recycling between cortisol and cortisone.

Ten lean (BMI 23.8±0.4 kg/m^2) and ten obese (32.9±0.9 kg/m^2) otherwise healthy men participated in a two-phase crossover single-blinded study comparing saline infusion with a hyperinsulinaemic euglycaemic clamp. 9,11,12,12-[^{2}H]$_4$-cortisol (D4-cortisol, measuring reductase) and 1,2-[^{2}H]$_2$-cortisone (D2-cortisone, measuring dehydrogenase) were infused, samples obtained of arterialised blood and from veins draining forearm skeletal muscle and abdominal subcutaneous adipose, and blood flow measured by occlusion plethysmography and Xenon washout, respectively. Data are lean vs obese, mean±SEM.

Before insulin/saline infusion, whole body 11β-reductase (Rate of appearance (Ra) D3-cortisol 22.66±2.17 vs 26.17±2.15 nmol/min; p=0.64) and 11β-dehydrogenase (Ra cortisone 15.34±3.91 vs 15.82±2.67 nmol/min; p= 0.52) did not differ between lean and obese. However, reductase and dehydrogenase activities were only detectable across adipose tissue in obese individuals and across skeletal muscle in lean. Acute hyperinsulinaemia upregulated cortisol regeneration across adipose tissue in obese (insulin vs placebo p=0.006) and tended to upregulate cortisone generation across skeletal muscle in lean (insulin vs placebo p=0.06).

In conclusion, insulin has tissue-specific effects to increase net cortisol regeneration in adipose tissue but not skeletal muscle, potentially amplifying post-prandial lipid storage. Up-regulation of 11βHSD1 in adipose in obesity accelerates recycling between cortisol and cortisone, enhancing the dynamic response to insulin but not necessarily increasing basal intracellular cortisol.

Protocol



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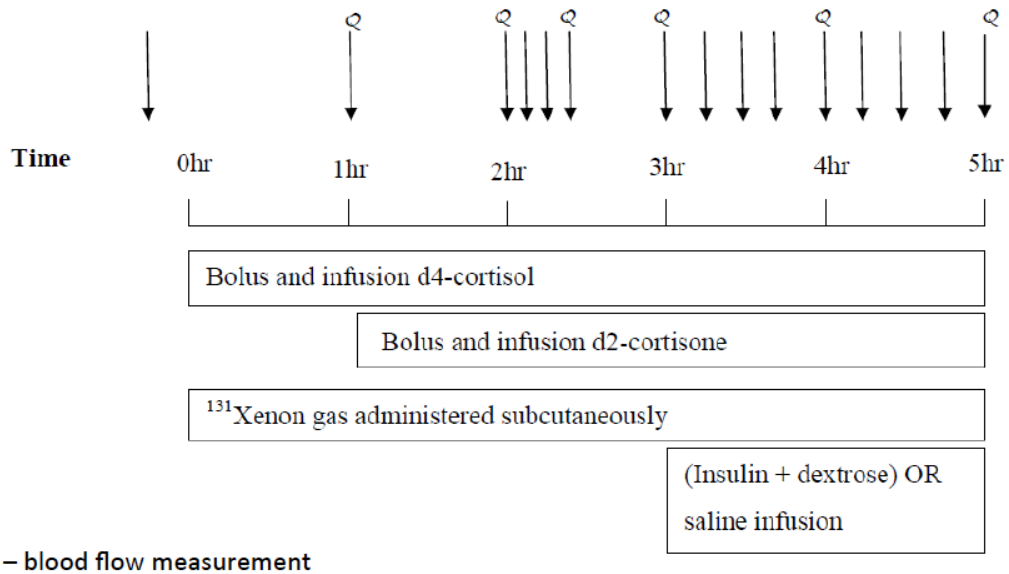

Q – blood flow measurement
Insulin – 35 mU/m^2/hr

Dr Anna Anderson

AV rates of appearance across adipose tissue and skeletal muscle

		Ra cortisol (nmol/100g tissue/min)	Ra D3-cortisol (nmol/100g tissue/min) REDUCTASE	Ra cortisone (nmol/100g tissue/ min) DEHYDROGENASE	Ratio reductase: dehydrogenase
Skeletal muscle	Lean	19.6 ± 9.19*	1.11 ± 3.91	5.84 ± 1.33	0.20
	Obese	-3.38 ± 4.60	7.26 ± 3.81	5.14 ± 3.11	1.41
Adipose tissue	Lean	38.79 ± 19.04	2.13 ± 2.03	8.30 ± 5.37	0.26
	Obese	27.03 ± 7.50	9.91 ± 3.22†	3.04± 2.94	3.26

* $P < 0.05$
† $P < 0.1$

Dr Asha Hesarghatta

Biography

Dr. Asha Hesarghatta completed her training in Internal Medicine and Endocrinology in India and worked as a faculty in Endocrinology and Diabetes at Christian Medical College, Vellore, India. She has recently moved to the UK, and is working as a Medical training fellow in Diabetes and Endocrinology at Aberdeen Royal Infirmary. Her areas of special interest include- pituitary and adrenal disorders, multiple endocrine neoplasias and diabetes in young people. She was involved in research on the genetics of MEN-1 in India, and clinical trials on new therapeutic agents for Cushing's disease.

Abstract

Adrenal Crisis: an audit of patient education

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Department of Diabetes & Endocrinology, Aberdeen Royal Infirmary, Aberdeen, UK

Adrenal crisis (AC) is a life-threatening endocrine emergency with an incidence of 6-10 adrenal crises per 100 patient years. The aim of our audit was to assess the prevalence of adrenal crisis in our clinic population and the preventative measures in use.

Method: Adrenal crisis was defined as worsening of general condition with signs and symptoms of glucocorticoid and mineralocorticoid deficiency with at least two of the following conditions ¬ hypotension, nausea/vomiting, severe fatigue, hyponatremia/hyperkalaemia/hypoglycaemia, followed by parenteral glucocorticoid administration. Data were obtained from electronic and paper records of patients with adrenal insufficiency.

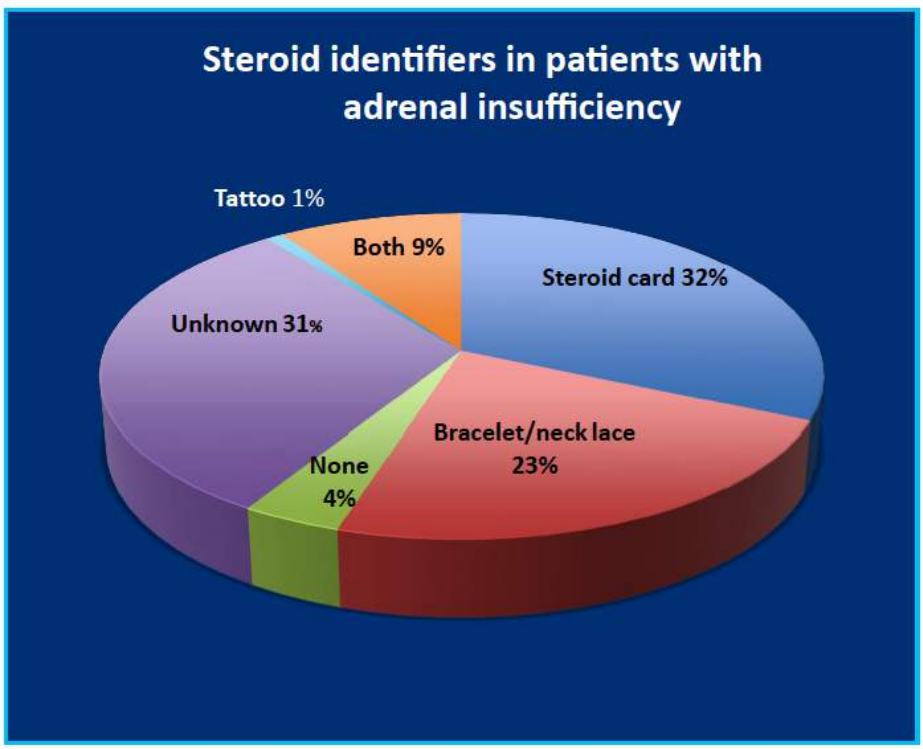
Results: 230 patients were identified between January 2015 and May 2016. These included 36% (n=83) presumed autoimmune primary adrenal insufficiency (PAI), 10% (n=23) non-autoimmune PAI and 54% (n=124) secondary adrenal insufficiency (SAI). There were 42 admissions with AC since 2010, which included 10.96, 0.9 and 0.4 per 100patient years with presumed autoimmune PAI, non-autoimmune PAI and SAI respectively. The common causes of adrenal crises were gastroenteritis, respiratory tract infection and acute kidney injury. Nine patients had recurrent episodes of AC.
Sixty-five percent had steroid identifiers in the form of a steroid card, bracelet or tattoo. Formal steroid education was delivered to 36% of presumed autoimmune PAI, 13% of non-autoimmune PAI and 21% in SAI. Ninety eight percent of patients with PAI received informal teaching.

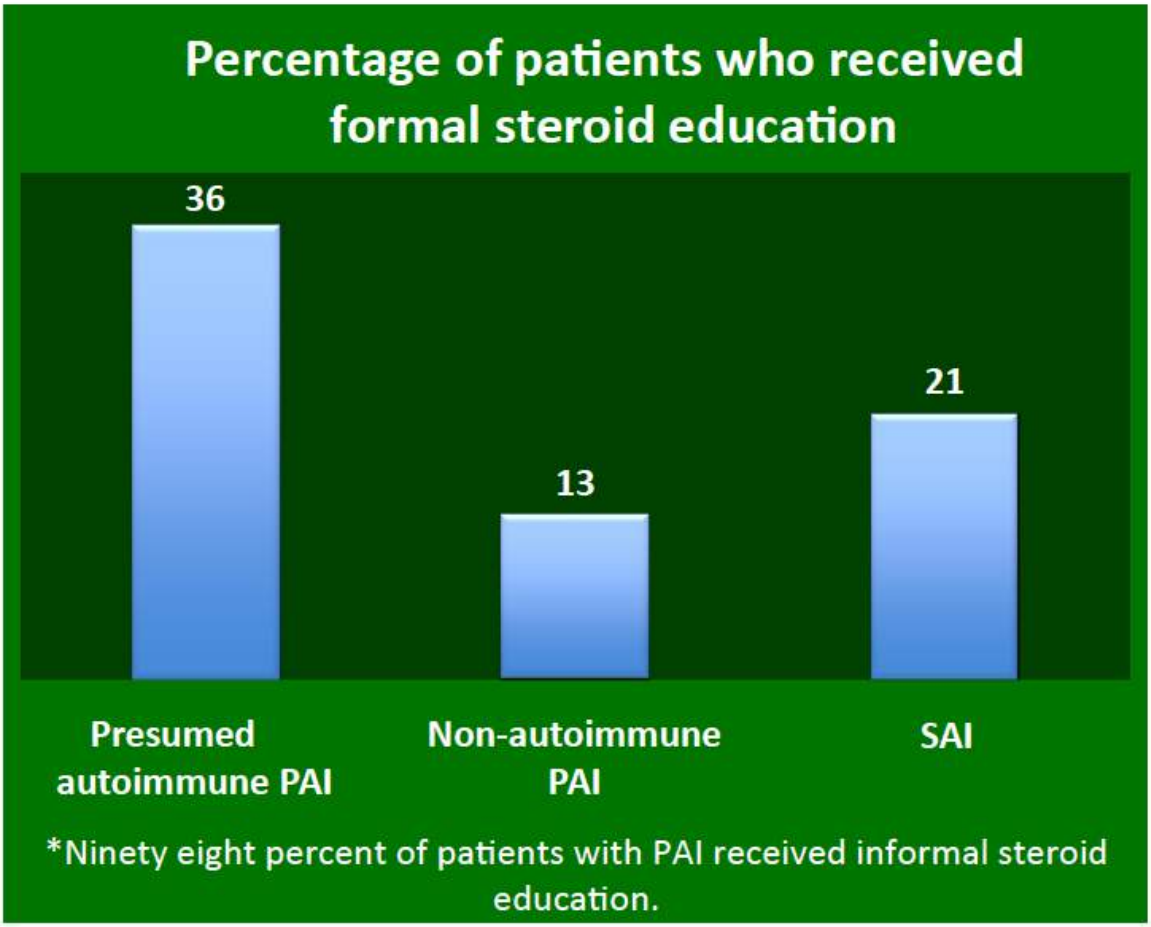
Conclusions: Patients with presumed autoimmune PAI experienced more frequent AC compared to the other groups and also received more steroid education. Structured steroid education could potentially avoid AC and reduce recurrence.

Dr Asha Hesarghatta

Prevalence of adrenal crises [AC]

Presumed autoimmune Primary adrenal insufficiency [PAI] n=83	•39 adrenal crises • 10.96 AC/100PYS
Non- autoimmune Primary adrenal insufficiency n=23	•1 adrenal crises • 0.9 AC/100PYS
Secondary adrenal insufficiency [SAI] n=124	•2 adrenal crises • 0.40 AC/100PYS




Percentage of patients who received formal steroid education
36
13
21
Presumed autoimmune PAI
Non-autoimmune PAI
SAI
*Ninety eight percent of patients with PAI received informal steroid education.

Dr Laura Jack

Biography

Laura Jack graduated from the University of Edinburgh in 2012, also completing an intercalated BMedSci in Reproductive Biology. She undertook foundation training in West of Scotland, including a particularily enjoyable rotation in Clinical Biochemistry. She is currently in her third year of Acute Care Common Stem (Acute Medicine) training in South East Scotland.

Abstract

The Use of Insulin & C-peptide Assay for Investigation of Adult Spontaneous Hypoglycaemia in NHS Lothian

Dr Laura Jack (CT3 Acute Medicine), Dr Catriona Clarke (Clinical Biochemist)
Department of Biochemistry, Western General Hospital, Edinburgh.

Background: Spontaneous hypoglycaemia presents in a nonspecific manner and is due to diverse pathology. Initial investigation relies on confirmation of symptoms during periods of low plasma glucose with symptomatic relief on correction to normoglycaemia (Whipple's Triad). There was suspicion that initial biochemical investigations were not optimally performed.

Aims: To establish the number of patients investigated for spontaneous hypoglycaemia in NHS Lothian and whether insulin and C-peptide samples were taken during hypoglycaemia.

Methods: All adult insulin and C-peptide samples taken within NHS Lothian between 2013- 2015 were considered (n=877). Electronic patient records were used to identify patients with suspected spontaneous hypoglycaemia and ascertain, where possible, the clinical presentation and diagnoses. The presence of contemporaneous plasma glucose measurement was recorded, with initial investigation deemed appropriate if plasma glucose < 2.5mmol/l.

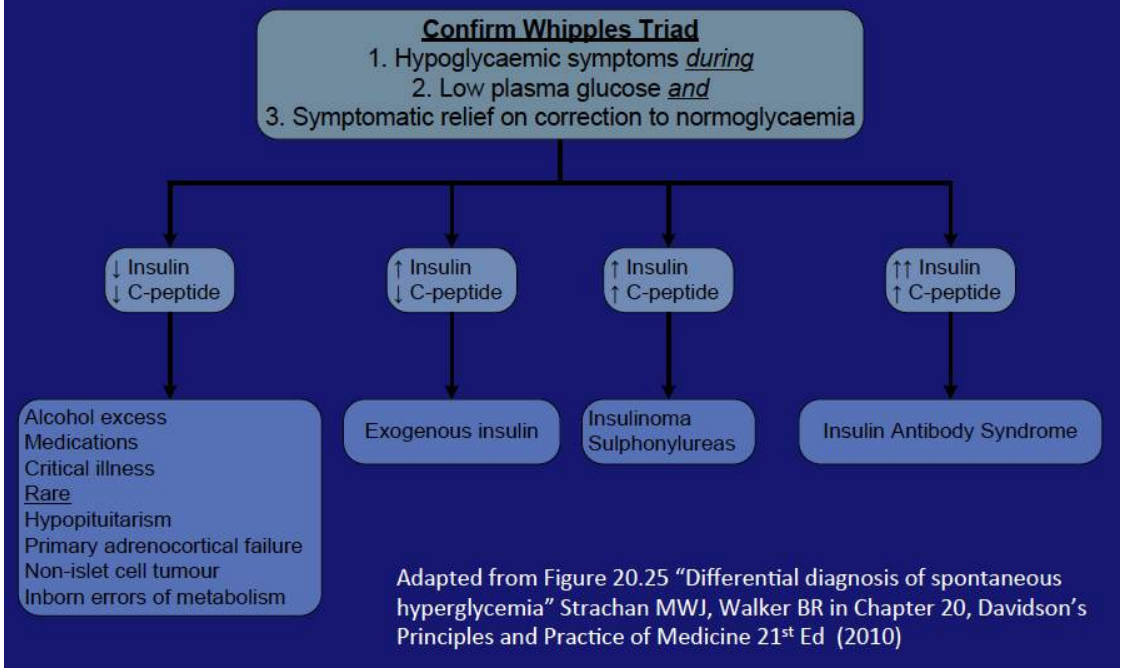
Results: 91 insulin and C-peptide samples were taken to investigate 61 patients for spontaneous hypoglycaemia over three years. Of the 91 samples, 65% (n=59/91) had contemporaneous glucose sent, with laboratories adding glucose to a further 12% (n=11/91). The patient had unknown glycaemic state in 23% of samples. Of the 70 samples with contemporaneous plasma glucose levels, only 29% (n=20/70) were taken when plasma glucose <2.5mmol/l. The most common diagnoses in hypoglycaemic patients were critical illness and exogenous insulin use, with two patients having insulinomas (one previously diagnosed).

Conclusion: In NHS Lothian, insulin and C-peptide samples investigating spontaneous hypoglycaemia did not have contemporaneous plasma glucose sent on 35% of occasions. Of samples with known contemporaneous plasma glucose, 71% were not taken during hypoglycaemia, defined as glucose <2.5mmol/l. Variable hypoglycaemia definitions, local guidance and availability of bedside glucose monitoring may contribute to requesting patterns. Further work may include prompting during insulin and C-peptide requesting to encourage contemporaneous venous glucose measurement during specified hypoglycaemia. Subsequently, assessment for improvements in use and interpretation of initial biochemical investigations for patients with suspected spontaneous hypoglycaemia could be performed.

Reference:

[1] Gama R, Teale JD, Marks V. "Clinical and laboratory investigation of adult spontaneous hypoglycaemia" *J Clin Pathol* 2003;**56**:641-646

Investigation of Spontaneous Hypoglycaemia



Adapted from Figure 20.25 "Differential diagnosis of spontaneous hyperglycemia" Strachan MWJ, Walker BR in Chapter 20, Davidson's Principles and Practice of Medicine 21st Ed (2010)

Identified Clinical Indications for C-peptide & Insulin Assays

Indication	Total Number (%)	2013 Number (%)	2014 Number (%)	2015 Number (%)
Diabetes	**614 (70)**	**154 (62.3)**	**127 (62.6)**	**333 (78)**
Fertility	32 (3.6)	7 (2.83)	15 (7.4)	10 (2.3)
Pancreatic/Hepatic Disease	10 (1.1)	4 (1.6)	2 (1)	4 (0.9)
VHL	87 (19)	29 (11.7)	28 (13.8)	30 (7)
MEN1	32 (3.6)	14 (5.7)	9 (4.4)	9 (2.1)
Requesting error	5 (0.6)	3 (1.2)	0	2 (0.5)
Endocrine without hypo symptoms	4 (0.5)	3 (1.2)	0	1 (0.2)
Spontaneous hypoglycaemia	**91 (10.3)**	**33 (13.4)**	**20 (9.9)**	**38 (8.9)**
Total	**877**	**247**	**203**	**427**

Dr Laura Jack

Diagnoses in Patients with Contemporary Glucose <2.5mmol/l (n=16)

Diagnosis	Number of patients	%
Critical Illness	3	18.8
Exogenous Insulin	3	18.8
Inconclusive	3	18.8
Insulinoma	2	12.5
SSRI Overdose	1	6.3
Malnutrition	1	6.3
Reactive Hypoglycaemia	1	6.3
Alcohol Excess	1	6.3
Insulin Antibody Syndrome	1	6.3
Total	**16**	

Dr Marcus Lyall

Biography

Marcus Lyall is Clinical Lecturer at the BHF Centre for Cardiovascular Science and MRC Institute of Genetics and Molecular Medicine at the University of Edinburgh. Having graduated in biochemistry and then subsequently medicine from the University of Dundee, he took up a specialty training post in diabetes and endocrinology in Lothian in 2011 before obtaining a position on the Edinburgh Clinical Academic Training (ECAT) Scheme in 2012. His PhD research under the supervision of Dr Mandy Drake and Professor Richard Meehan, is focused on the interaction between glucose metabolism and the epigenome in metabolic liver disease.

Abstract

Steroid Induced Hyperglycaemia during Treatment for Gynaecological Cancer.

Marcus J Lyall, Ishwinder Thethy, Lesley Steven, Fiona Nussey, Maria Sakala, Tzyvia Rye, Mark WJ Strachan, Melanie MacKean, Anna R Dover.

Introduction
Glucocorticoids are highly effective anti-inflammatory and immune modulating agents which may be used as an adjunct to chemotherapy. Glucocorticoid-induced hyperglycaemia occurs in up to 50% of patients, is associated with negative health outcomes and may reduce the efficacy of chemotherapeutic agents. However, little is known about the severity, diurnal rhythm, need for monitoring and optimal intervention of this common complication in the context of cancer therapy. We used continuous glucose monitoring to characterise the glycaemic profile of patients before and after treatment with dexamethasone in combination with carboplatin and taxol chemotherapy for gynaecological cancer.

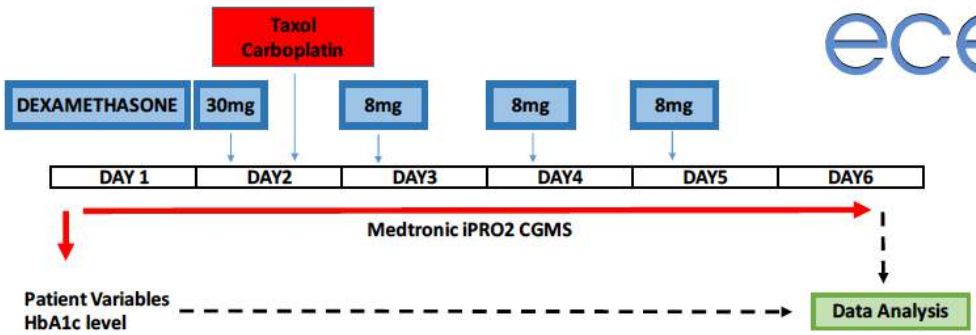
Methods
Using the Medtronic iPro2 system, blinded interstitial glucose measurements were recorded at 5 minute intervals 24 hours prior to, during and 24 hours after a four-day course of twice daily dexamethasone in fifteen patients. Patient age, height, weight and BMI were recorded and HbA1c measured. Data analysis and graphical output were performed using R version 3.3.1 (https://www.r-project.org/) and ggplot2 package (https://www.ggplot2.org) with bespoke scripts.

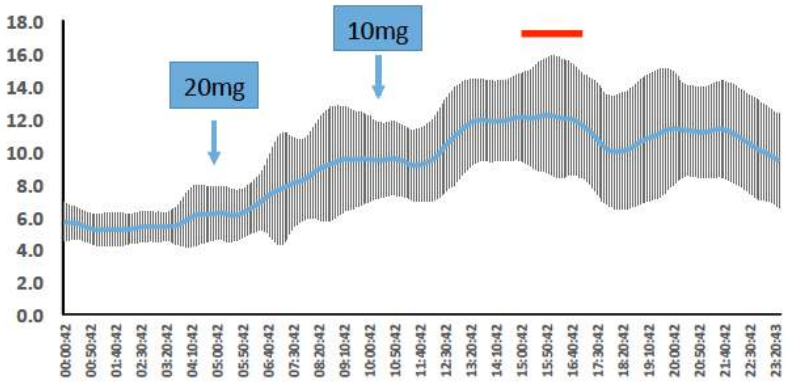
Results
14 (93%) patients had an HbA1c within the normal range (<42mmol/mol). All but one patient exhibited hyperglycaemia (>11.1mmol/l) during some stage of the continuous glucose monitoring. Mean peak glucose levels for all patients was 14.86mmol/l (range = 10.9–22.2) which occurred on the day of steroid initiation in 12 of 15 patients and the subsequent day in 3 patients. The mean time of day of peak glucose was 16:31hrs (range 12:55 – 22:12). Baseline HbA1c was significantly correlated with peak glucose level ($r^2 = 0.5314$, $p = 2.79x10^{-6,}$). Mean time spent in the hyperglycaemic range was 3.63 (+/-2.98), 1.85 (+/- 3.92), 1.10 (+/- 2.81) and 1.30 (+/- 3.61) hours (+/- SD) for each consecutive day of dexamethasone treatment. Only one patient (with an elevated HbA1c of 44mmol/l) remained persistently hyperglycaemic following cessation of glucocorticoid therapy.

Conclusion:
Patients receiving chemotherapy for gynaecological malignancy develop significant transient hyperglycaemia regardless of baseline glycaemic state. However, HbA1c is a strong predictor of severity of hyperglycaemia. Our data indicate that the optimal time for screening to detect peak glucose level is before the evening meal. This study contributes to current understand of the effects of high dose glucocorticoids on glucose metabolism in the context of cancer therapy. Future research is required to determine the impact of these glucose excursions on the efficacy of chemotherapeutic treatment and the incidence of chemotherapy toxicity and hyperglycaemic symptoms.

Dr Marcus Lyall

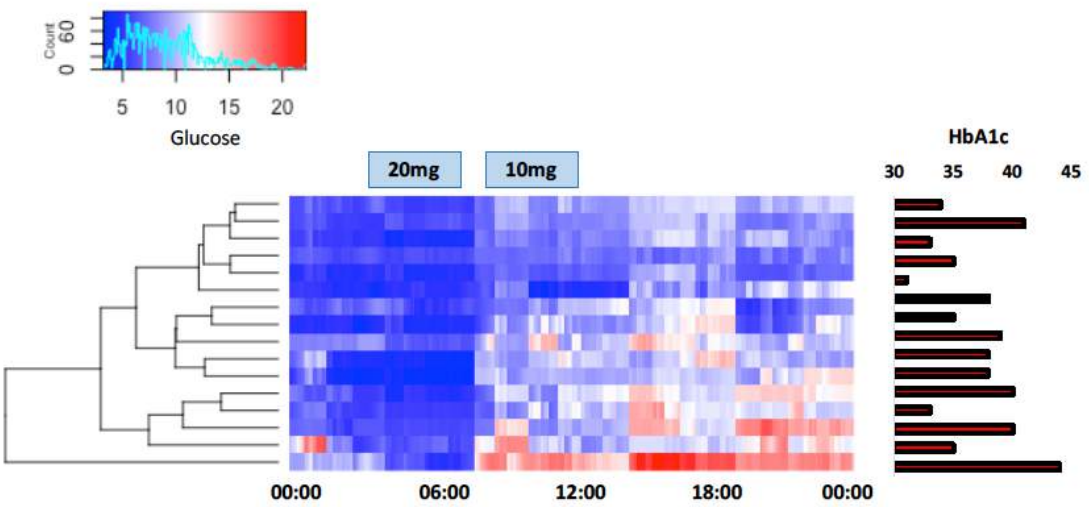
What is the impact of dexamethasone on glucose homeostatis in cancer therapy?





Mean interstitial glucose level (mmol/l) error bars +/- SD

Clustering CGMS trace by patient



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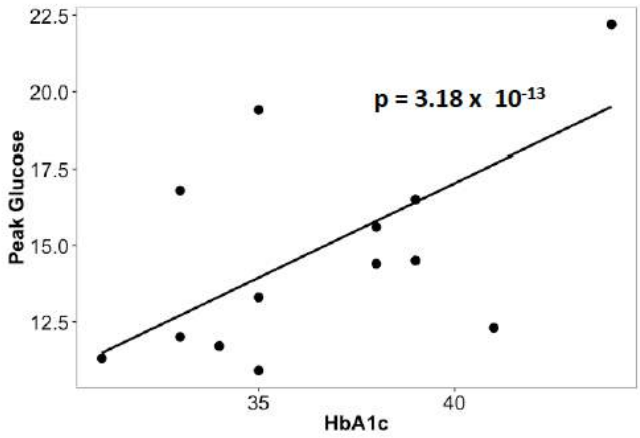
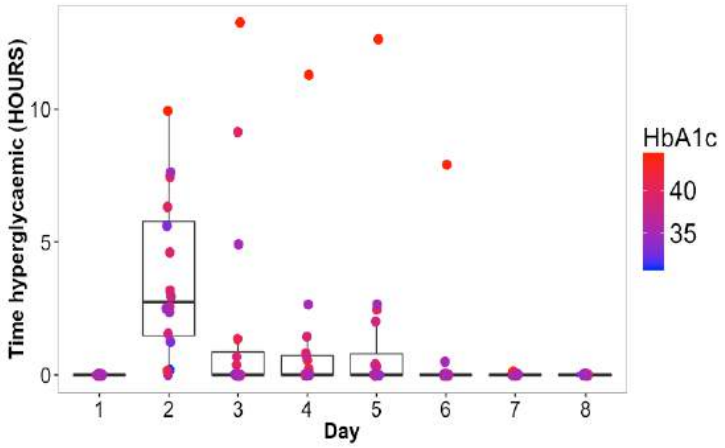
HbA1c predicts peak glucose level



Hours spent in hyperglycaemic range (>11.1mmol/l) per day



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