CalSoc 2017

caledonian society for endocrinology and diabetes

Crieff Hydro

November 24th/25th

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Contents

Programme of Events

Friday 24th November

13.00 – 14.30 Registration

13.15 – 14.00 **Meet the Expert– Trainee session – Thyroid**
Dr Petros Perros / Prof Simon Pearce

Session 1

Chair: Dr Anna Dover
Consultant Physician / Honorary Senior Lecturer
Royal Infirmary of Edinburgh / University of Edinburgh

14.30 – 15.15 **Obesity & Diabetes in Pregnancy: Highlights in 2017**
Professor Rebecca Reynolds
Professor of Metabolic Medicine
University of Edinburgh

15.15 – 16.00 **Addison's Disease Update**
Professor Simon Pearce
Professor of Endocrinology
Newcastle University

16.00 – 16.15 Coffee

16.15 – 17.00 **Hypothyroidism goes to the Scottish Parliament**
Dr Petros Perros
Consultant Endocrinologist / Honorary Senior Lecturer
Royal Victoria Infirmary, Newcastle / Newcastle University

17.00 – 17.30 **Developing a Scottish Endocrine IT system**

19.30 Dinner

Programme of Events

Saturday 25th November

08.45 – 09.00 CalSoc Annual General Meeting

Session 2

Chair: Dr Marie Freel
Consultant Endocrinologist / Honorary Associate Clinical Professor
Queen Elizabeth University Hospital, Glasgow / University of Glasgow

09.00– 09.45 **Utility and Challenges of Genetic Testing in Endocrinology**
Dr Paul Newey
Senior Lecturer in Endocrinology
School of Medicine, University of Dundee

09.45 – 10.45 **Abstract Presentations**
Dr Dhruti Bhatt
Dr Laura Reid
Dr Sharon Mackin
Dr Nyo Nyo Tun

10.45 – 11.00 Coffee

11.00 – 11.45 **Abstract Presentations**
Dr Catriona Farrell
Dr Marcus Lyall
Dr Catriona Kyle

11.45 – 12.30 **Update on insulin resistance**
Professor Robert Semple
Professor of Translational Molecular Medicine
University of Edinburgh

Welcome to CalSoc 2017

Welcome to Crieff for the 37th 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.

A recurring question at recent meetings has been 'How can we use CalSoc to harness the enthusiasm and expertise of the Scottish endocrine community to deliver a national programme of clinical research?' This has involved exploring the possibility of developing an endocrine equivalent of our world-leading SCI-Diabetes system. Part of this year's meeting will be devoted to providing an update on progress and canvassing opinion about what such a system would look like and how we might achieve it.

Many thanks to our growing number of supporters from the pharmaceutical industry. This year we welcome NAPP and Pfizer, as well as long-term sponsors Novo Nordisk, Lilly, Sanofi, MSD 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
Dumfries and Galloway Royal Infirmary

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	Grade	Location	Role
Prakash	Abraham	Cons	Aberdeen	Attendee
Melisande	Addison	Trainee	Edinburgh	Attendee
Ganesh	Arungirinathan	Cons	Edinburgh	Attendee
Mohammed	Azharuddin	Cons	Greenock	Attendee
Dhruti	Bhatt	Trainee	Aberdeen	Oral
Chad	Bisambar	Trainee	Ayr	Attendee
Luke	Boyle	Trainee	Edinburgh	Attendee
Geraldine	Brennan	Cons	Monklands	Attendee
Linda	Buchanan	Cons	Forth Valley	Attendee
David	Carty	Cons	Glasgow	Attendee
Tom	Chambers	Trainee	Edinburgh	Attendee
Louise	Clark	Cons	Dumfries	Attendee
Catriona	Clarke	Biochemist	Edinburgh	Attendee
Alan	Connacher	Cons	Perth	Attendee
Jenna	Cowan	Cons	Crosshouse	Attendee
Marion	Devers	Cons	Monklands	Attendee
Anna	Dover	Cons	Edinburgh	Attendee
Jane	Dymott	Cons	Aberdeen	Attendee
Catriona	Farrell	Trainee	Dundee	Oral
Marie	Freel	Cons	Glasgow	Attendee
Priya	George	Trainee	Dundee	Attendee
Fraser	Gibb	Cons	Edinburgh	Attendee
Saket	Gupta	Cons	Fife	Attendee
Kate	Hughes	Cons	Glasgow	Attendee
Emma	Johns	Trainee	Glasgow	Attendee
Chris	Jones	Cons	Greenock	Attendee
Pauline	Jones	Cons	Edinburgh	Attendee
Brian	Kennon	Cons	Glasgow	Attendee
Chris	Kueh	Trainee	Glasgow	Attendee
Catriona	Kyle	Trainee	Edinburgh	Oral
Graham	Leese	Cons	Dundee	Attendee
Robert	Lindsay	Cons	Glasgow	Attendee
Rachel	Livingstone	Trainee	Glasgow	Attendee
Marcus	Lyall	Trainee	Edinburgh	Oral

First name	Second Name	Grade	Location	Role
Alison	MacEwen	Cons	Ayrshire	Attendee
David	Macfarlane	Cons	Inverness	Attendee
Scott	Mackenzie	Cons	Edinburgh	Attendee
Alasdair	Mackie	Cons	Dundee	Attendee
Sharon	Mackin	Trainee	Glasgow	Oral
Hannah	Macpherson	Trainee	Edinburgh	Attendee
Iqbal	Malik	Cons	Dundee	Attendee
Susan	McGeoch	Cons	Aberdeen	Attendee
Louise	McKenna	Trainee	Glasgow	Attendee
Frances	McManus	Cons	Glasgow	Attendee
Emily	McMurray	Cons	Edinburgh	Attendee
Kenneth	Muir	Cons	Inverness	Attendee
Paul	Newey	Cons	Dundee	Speaker
Rose	Norton	Student	Edinburgh	Attendee
Mo	Oroko	Trainee	Glasgow	Attendee
Simon	Pearce	Cons	Newcastle	Speaker
Petros	Perros	Cons	Newcastle	Speaker
Colin	Perry	Cons	Glasgow	Attendee
Sam	Philip	Cons	Aberdeen	Attendee
Laura	Reid	Trainee	Edinburgh	Oral
Rebecca	Reynolds	Cons	Edinburgh	Speaker
Robert	Semple	Cons	Edinburgh	Speaker
Anne	Sillars	Trainee	Glasgow	Attendee
Lee	Sit	Trainee	Edinburgh	Attendee
Karen	Smith	Biochemist	Glasgow	Attendee
Alison	Stewart	Cons	Glasgow	Attendee
Roland	Stimson	Cons	Edinburgh	Attendee
Mark	Strachan	Cons	Edinburgh	Attendee
Sandeep	Thekkepat	Cons	Monklands	Attendee
Chris	Thompson	Cons	Dublin	Attendee
Joe	Timmons	Trainee	Glasgow	Attendee
Nyo Nyo	Tun	Trainee	Edinburgh	Oral
Liesbeth	Van Look	Cons	Livingston	Attendee
Min Chong	Zhuo	Trainee	Glasgow	Attendee

Prof Rebecca Reynolds

Biography

Professor Reynolds is Professor of Metabolic Medicine, University of Edinburgh and Honorary Consultant Physician in Diabetes & Endocrinology, NHS Lothian and Deputy Head of the Centre for Cardiovascular Sciences, University of Edinburgh. Her main research interest is in the early life origins of health and disease and she was awarded the Nick Hales Award in 2011 by the International Society for the Developmental Origins of Health and Disease and the Curt Richter Award in 2012 by the International Society of Psychoneuronendocrinology in recognition of this work. She is Chair of the Diabetes UK Clinical Studies Group 'Causes of Diabetes'. Her research spans 'process to population' eg experimental medicine studies in pregnant women and their children, detailed mechanistic studies using placental tissue, randomised controlled trials testing interventions in pregnancy to improve outcomes and epidemiological data-linkage studies using 'big data' in Scotland. Her clinical work includes general and antenatal diabetes and endocrinology, and reproductive endocrinology. She is module lead for University of Edinburgh MBChB Endocrinology & Diabetes.

Abstract

Obesity and Diabetes in Pregnancy: Highlights in 2017

Obesity and diabetes represent the most common pregnancy complications in developed countries. Both of these conditions have short term risks during pregnancy for both mother and child (1), with increasing evidence demonstrating that there are also longer term risks of these exposures in pregnancy impacting on health across the lifespan (2, 3). Researchers and clinicians in Scotland have contributed to some of the landmark clinical trials published in 2017. All these trials aimed to improve treatment and clinical outcomes for women with obesity and/or diabetes in pregnancy. This presentation will discuss the results of these key trials including the CONCEPTT trial testing the utility of continuous glucose monitoring in pregnant women with type 1 diabetes (4), the GRACES trial, testing whether the combination of oral hypoglycaemic agents metformin + glibenclamide would be preferable to standard care of metformin + insulin for women with gestational diabetes (5) and trials of interventions in obese pregnancy with metformin (EMPOWAR and MOPS) (6,7), diet/lifestyle interventions (8), or bariatric surgery (9). Participation in these studies has demonstrated our ability to participate in/ and/or lead important clinical trials in pregnancy, chiming with the Chief Medical Officer for England's vision to optimise women's health.

References

Kalliala I et al Obesity and gynaecological and obstetric conditions: umbrella review of the literature. BMJ. 2017 Oct 26;359:j4511. doi: 10.1136/bmj.j4511.

Lee K et al Maternal Obesity During Pregnancy Associates With Premature Mortality and Major Cardiovascular Events in Later Life. Hypertension. 2015 Nov;66(5):938-44. doi: 10.1161/HYPERTENSIONAHA.115.05920

Reynolds RM et al Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ. 2013 Aug 13;347:f4539. doi: 10.1136/bmj.f4539.

Feig DS et al Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017 Sep 15. pii: S0140-6736(17)32400-5. doi: 10.1016/S0140-6736(17)32400-5

Reynolds RM et al Glibenclamide and metfoRmin versus stAndard care in gEstational diabeteS (GRACES): a feasibility open label randomised trial. BMC Pregnancy Childbirth. 2017 Sep 22;17(1):316. doi: 10.1186/s12884-017-1505-3.

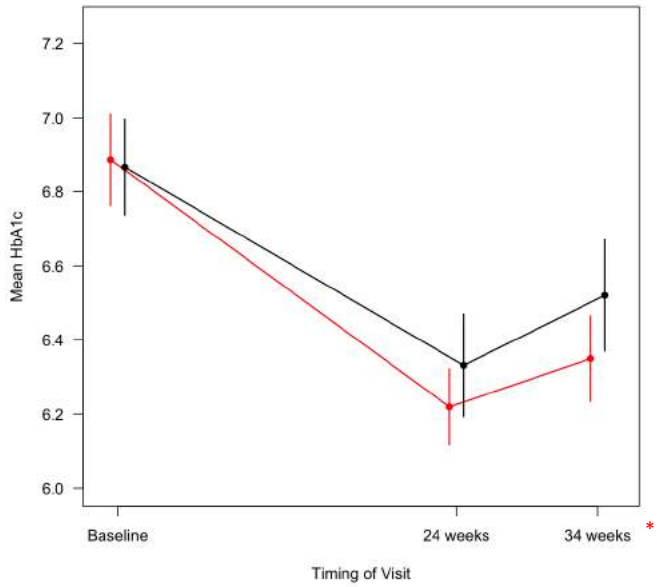
Chiswick C et al Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2015 Oct;3(10):778-86. doi: 10.1016/S2213-8587(15)00219-3. Epub 2015 Jul 9.

Syngelaki A et al Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus.N Engl J Med. 2016 Feb 4;374(5):434-43. doi: 10.1056/NEJMoa1509819.

Rogozińska E et al Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. Health Technol Assess. 2017 Aug;21(41):1-158. doi: 10.3310/hta21410.

Johansson K et al Outcomes of pregnancy after bariatric surgery. N Engl J Med. 2015 Feb 26;372(9):814-24. doi: 10.1056/NEJMoa1405789.

Primary outcome



CONCEPTT

*mean difference -0.19%; 95% CI -0.34—0.03; p = 0.0207

Summary of neonatal outcomes

- LGA
  53% CGM vs 69% control;
  Odds ratio 0.51; 95%CI 0.28—0.90, p=0.0210
  NNT 6
- Neonatal hypoglycaemia requiring iv treatment
  15% vs 28%;
  Odds ratio 0.45; 95%CI 0.22—0.89, p=0.0250
  NNT 8
- NICU admission>24hrs;
  27% CGM vs 43% control;
  Odds ratio 0.48; 95% CI 0.26-0.86; p=0.0157
  NNT 6

CONCEPTT

Prof Rebecca Reynolds

Obesity and obstetric conditions:
umbrella review of 144 meta-analyses of cohort studies

Strong evidence for increased risk of :

Maternal adverse outcomes

- Pre-eclampsia
- Gestational Diabetes
- Antenatal depression
- Total and emergency caesarean section

Fetal adverse outcomes

- Fetal macrosomia
- Low Apgar score at 1 minute
- Stillbirth

Kalliala et al BMJ 2017; 359; j4511

Conclusions

- A randomised trial of glibenclamide v insulin in women with GDM and who need a second line therapy in addition to metformin would be “feasible” but would require 30-60 centres recruiting for 3 years
- In this small sample, no woman had a symptomatic hypoglycaemic episode
- Preference for glibenclamide over insulin is not universal
- Preliminary data suggests that insulin gives superior control, with fewer excursions < 3.3 mmol/l

Tommy’s

GRACES

Effect of diet and lifestyle interventions :
IPD and meta-analysis and health economic evaluation

Evidence from 36 RCTs of over >12,000 women shows that lifestyle interventions have :

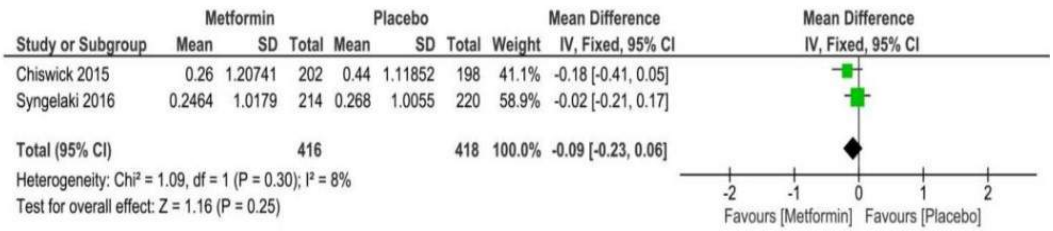
- 0.70 kg (95% CI 0.92 to 0.48 kg) reduction in gestational weight gain

- No effect on birth weight
- No effect on the incidence of large for gestational age, or small for gestational age infants
- No effect on maternal composite outcomes
- No evidence of cost benefit

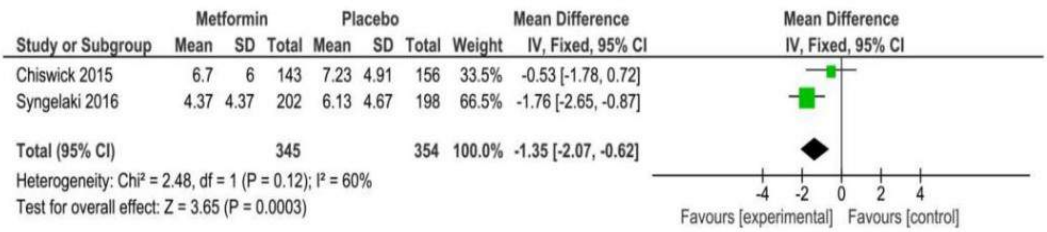
Rogozinska et al HTA 2017 21(41): 1-158

Metformin: bwt and GWG

Birthweight



Gestational weight gain



Elmaraezy et al Int J Reprod Biomed 2017 15(8): 461

Prof Simon Pearce

Biography

Simon Pearce qualified in Medicine MB,BS 1st class honours from Newcastle University. Following internal medicine training, he undertook postgraduate education in endocrinology in Raj Thakker's lab at Hammersmith, followed by spells at Brigham & Women's Hospital, Boston; and latterly back in Newcastle, UK. He was appointed as Senior Lecturer in Endocrinology in 2001 at Newcastle University, and promoted to Professor in 2007, affiliated to the Institute of Genetic Medicine and the Royal Victoria Infirmary. He has published more than 170 papers over the last 25 years, mainly on parathyroid calcium-sensing, thyroid disease and Addison's disease.

Summary of talk

•The first presentation of a patient with adrenal insufficiency is frequently overlooked by healthcare professionals.
•Food poisoning and gastroenteritis are the commonest cause of Addisonian crisis.
•Salt depletion due to (relative) mineralocorticoid deficiency is responsible for much of the pathophysiology of adrenal crisis.
•Excellent patient engagement and steroid education is key to allowing people with Addison's disease to safely manage their condition, day-to-day.
•Small and often doses of hydrocortisone give better steroid exposure profiles.
•Fine-tuning of mineralocorticoid replacement and salt intake in Addison's patients is important for adrenal crisis prevention and optimal wellbeing, and is often neglected by physicians.
•Both modified-release hydrocortisone tablets and continuous subcutaneous hydrocortisone infusions offer closer approximations to healthy plasma cortisol rhythms than multidose, immediate-release oral hydrocortisone.
•Greater clinical experience with these novel replacement therapies needs to be gained for their role in the management of adrenal insufficiency to be established.
•There is durable residual adrenal function in a proportion of patients with Addison's disease, and this is a future therapeutic target.

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Gan EH, MacArthur K, Mitchell AL, Hughes BA, Perros P, Ball SG, James RA, Quinton R, Chen S, Furmaniak J, Arlt W, Pearce SH. Residual adrenal function in autoimmune Addison's disease: improvement after tetracosactide (ACTH1-24) treatment. J Clin Endocrinol Metab 2014; 99:111-8. doi: 10.1210/jc.2013-2449

Prof Simon Pearce

Delayed Diagnosis of Adrenal Insufficiency Is Common: A Cross-Sectional Study in 216 Patients

- 67% of patients had 3 or more encounters with features of adrenal failure before Δ
- 50% of men, 70% of women had complained of symptoms > 6 months
- 68% had a different initial diagnosis
  - Mental health
  - Gastrointestinal

Bleicken B et al. Am J Med Sci 2010

Patient Education

- Steroid card & Medical alert jewellery
- iPhone medic alert home screens
- "Sick day rules"
  - Fever, diarrhoea
  - Minor procedures (dentist, gastroscopy)
  - Vomiting
- How & when to inject with IM hydrocortisone
- www.addisons.org.uk

Prof Simon Pearce

Patient Education

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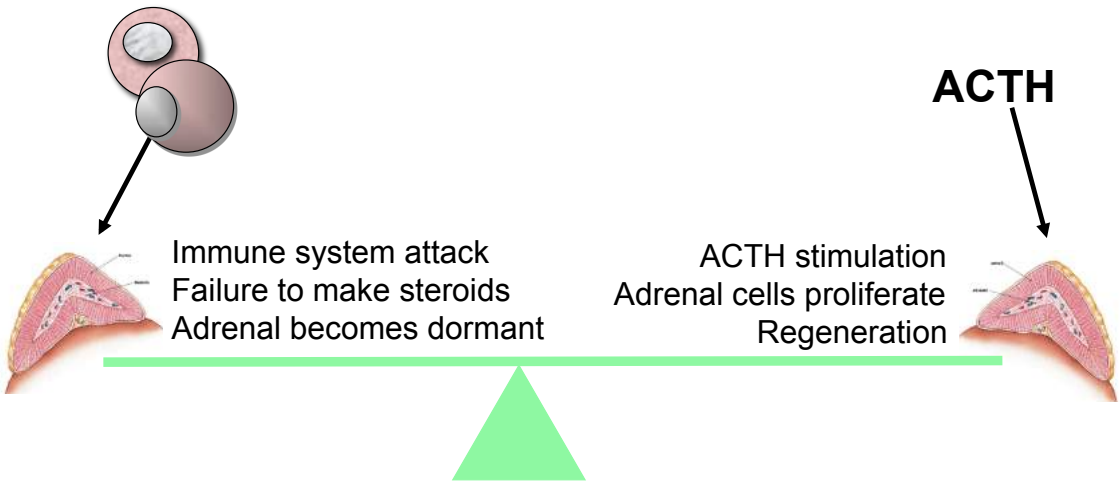
Ask the patient 10 questions

1. Do you have low spots during the day?
2. Are you clock-watching for one particular dose?
3. Do you often miss a dose because you haven't noticed the time?
4. What time is bedtime?
5. Do you sleep okay?
6. How do you feel first thing in the morning?
7. How are your general energy levels/ get up & go?
8. Are you napping during the day?
9. Changes in pigmentation?
10. Changes in weight?

Chronic Management: mineralocorticoid

- Fludrocortisone 50-500mcg daily
- Younger people need more
- Discuss salt cravings, including typical foods
- Consider salt tablets (NaCl 1.8-3.6 g/d)
- Titrate according to Na^+/K^+, BP, renin

Model of evolving Addison's disease



- Insidious onset of disease
- ACTH vs Immune destruction

Dr Petros Perros

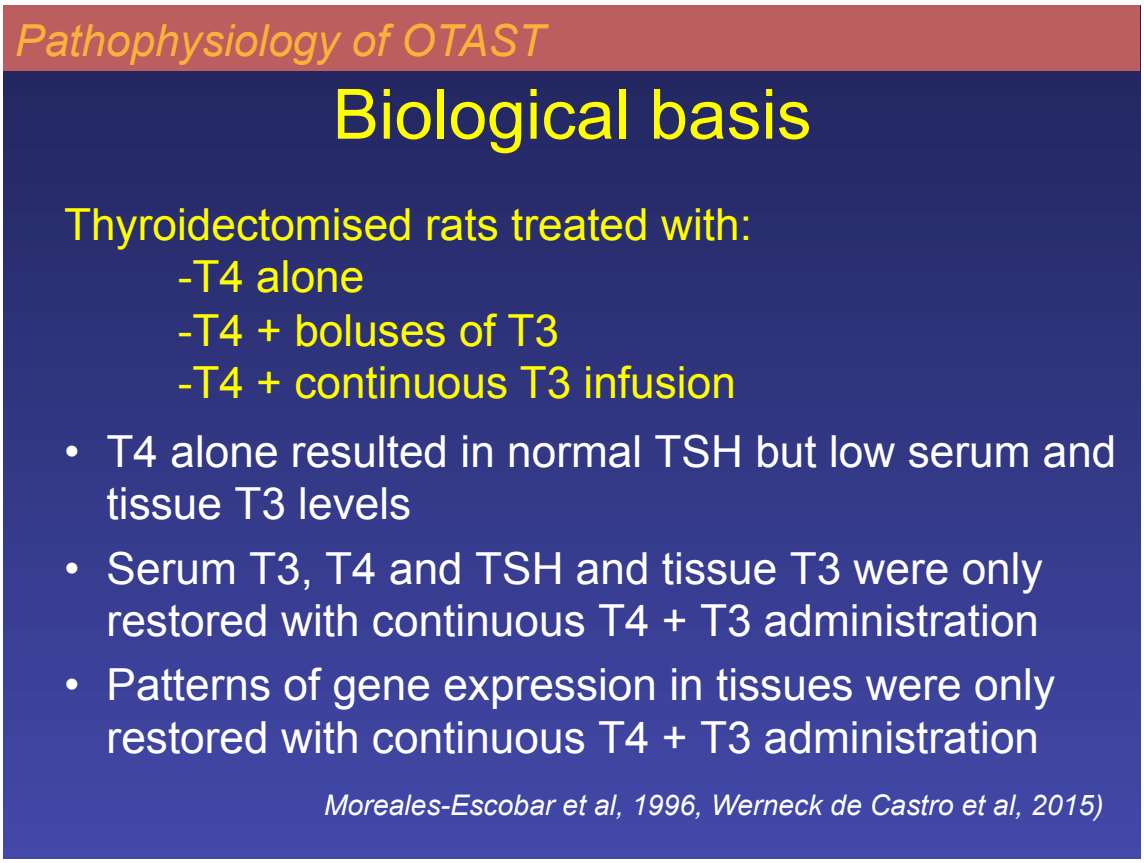
Biography

Petros Perros is a consultant endocrinologist at the Royal Victoria Infirmary, Newcastle and honorary senior lecturer, Newcastle University. He qualified from Newcastle University and trained in Newcastle, Glasgow and Edinburgh. His clinical and research interests include thyroid cancer, thyroid eye disease and neuroendocrine tumours. He is a past president of the European Group on Graves' Orbitopathy and is currently convenor of the Society for Endocrinology thyroid network.

Abstract

Hypothyroidism goes to the Scottish Parliament

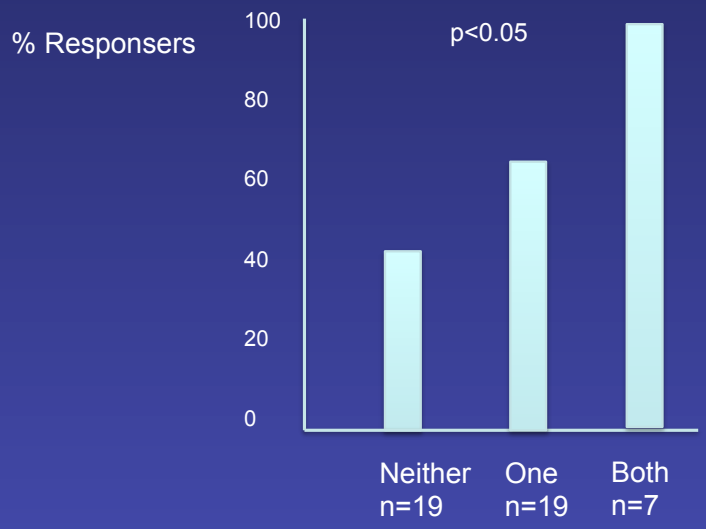
Somatic and cognitive symptoms are found about 10% of the general population and in patients with hypothyroidism. Claims that treatment with T3-containing preparations in combination with T4 are superior to T4 alone have not been confirmed by several randomised clinical trials. Some patient groups are campaigning for wide use of T3 in combination with T4 or desiccated animal thyroid extract. Two plausible hypotheses have been put forward to explain persistent symptoms in treated hypothyroid patients: functional somatoform disorder, and inability of available thyroid hormone replacement therapies to restore normal physiology. Concerns about long-term safety of combination therapies persist.



Pathophysiology of OTAST

Biological basis

MCT10 and D2 Gene Polymorphisms:
preference for T4+T3 treatment

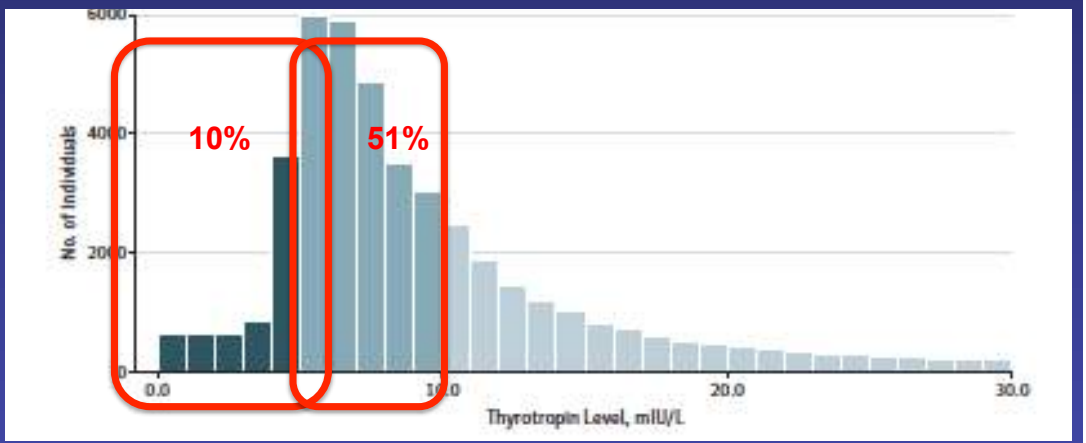


Carle et al, 2017

Pathophysiology of OTAST

Trends in diagnosis and treatment of hypothyroidism

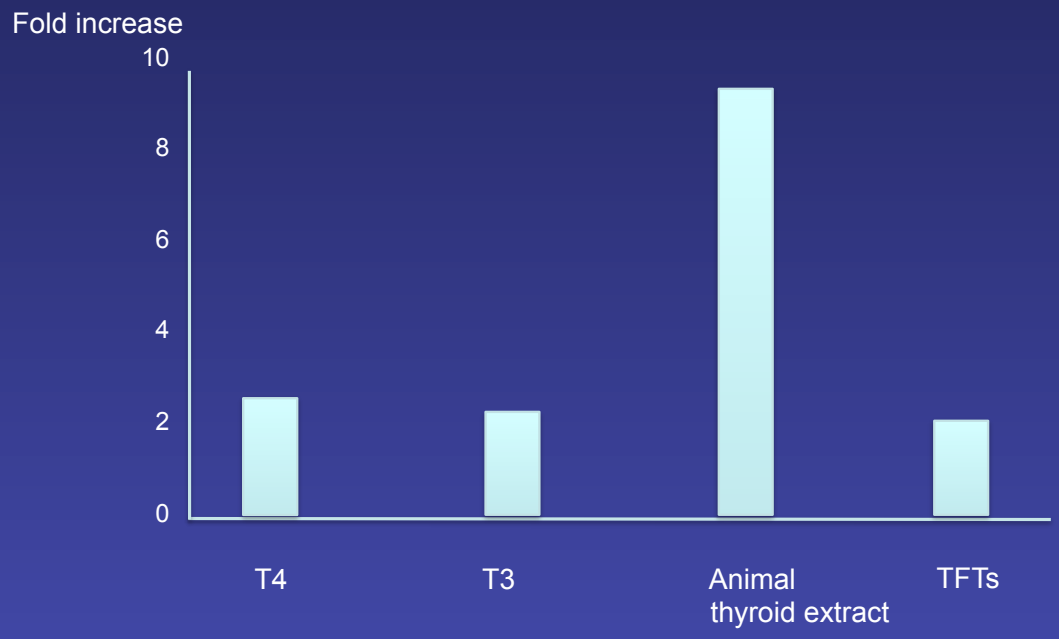
TSH threshold for starting treatment



Taylor et al, 2014

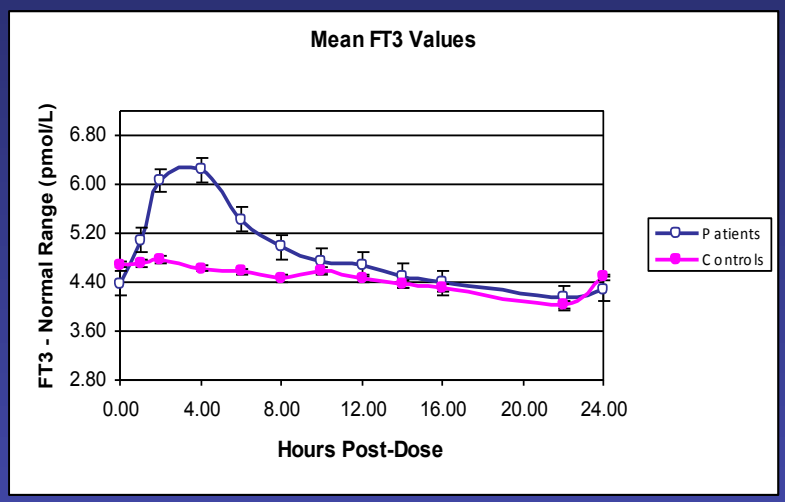
Dr Petros Perros

Pathophysiology of OTAST



Potential harm of T3 + T4 treatments

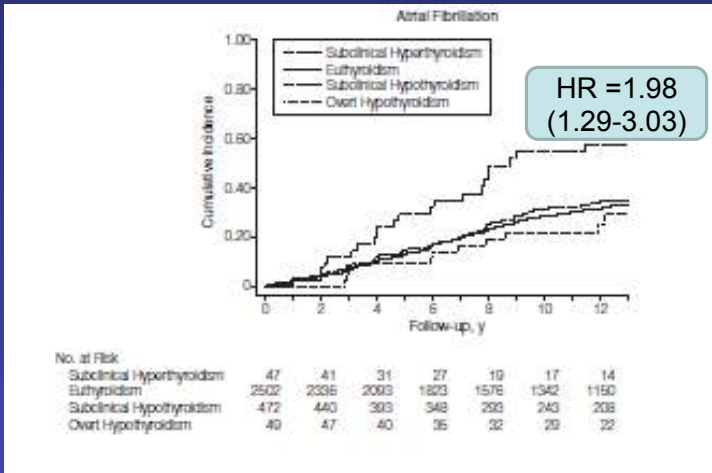
Biochemical thyrotoxicosis almost inevitable in T3 treated patients



Potential harm of T3 + T4 treatments

Extrapolations from subclinical hyperthyroidism paradigm

Risk of future AF

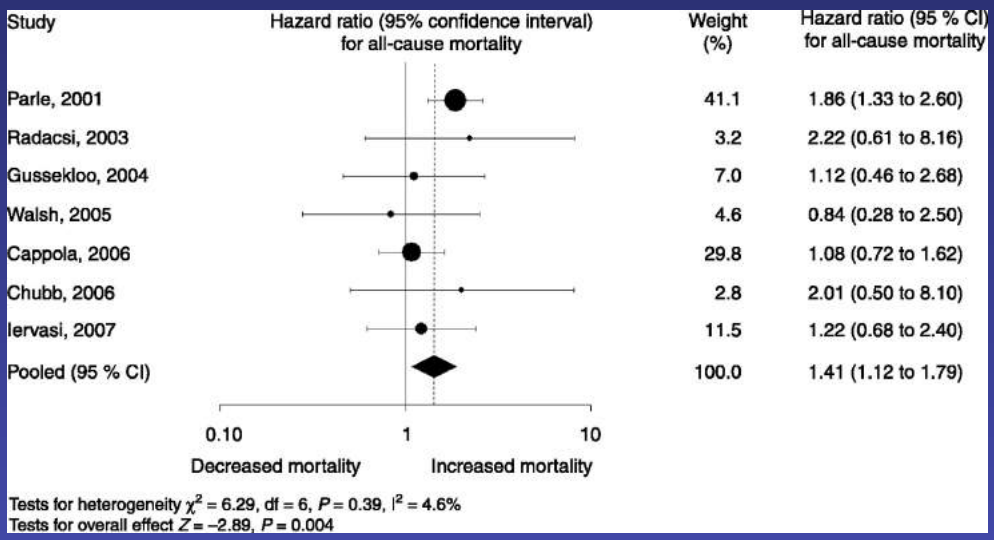


Cappola et al 2006

Potential harm of T3 + T4 treatments

Extrapolations from subclinical hyperthyroidism paradigm

Mortality



Haemtkens et al 2008

Dr Paul Newey

Biography

Dr Paul Newey is a Senior Lecturer in Endocrinology and Honorary Consultant Physician at the University of Dundee, Scotland. He undertook his medical studies at the University of Edinburgh before moving to Oxford for his Specialty Training. During this period he was awarded a DPhil for his studies on hereditary endocrine disorders including Multiple Endocrine Neoplasia Type 1 (MEN1). He was subsequently appointed a NIHR Clinical Lecturer in Oxford undertaking post-doctoral research in the field of endocrine tumourigenesis. In 2014, Dr Newey moved to the University of Dundee to establish his own research group continuing his interest in endocrine tumourigenesis. In 2015, he was awarded a NRS Scottish Senior Clinical Fellowship. Dr Newey's main area of research is understanding the genetic basis of endocrine disease with a focus on neuroendocrine tumours and disorders of calcium homeostasis.

Abstract

Utility and Challenges of Genetic Testing in Endocrinology

The advent of high-throughput DNA sequencing technology has accelerated the identification of genes responsible for both hereditary and sporadic endocrine diseases and is increasingly applied in the clinical setting to guide patient management. However, this accessibility and scope of genetic testing brings many challenges, including inherent difficulties in data interpretation. These challenges, which include establishing accurate estimates of variant pathogenicity and penetrance, may result in diagnostic confusion. This talk will provide an overview of the current approaches to clinical genetic testing in endocrinology and highlight many of the contemporary challenges faced.

The Genetic Testing Workflow – Pre-Test Considerations

Pre-genetic test

Indicators of possible genetic disease; *consider*

- Childhood/early-onset disease
- Familial setting
- Presence of features consistent with genetic sydrome (e.g. MEN1, MEN2)
- Disease-specific indications (e.g. PPGL)

Value of genetic test: *consider*

- Disease severity and 'typical' penetrance of disorder
- Potential 'utility' of result
  - Intervention/screening based on result
  - Value of test result to first-degree relatives
  - Pre-natal diagnosis/genetic counselling

The Genetic Testing Workflow – Which Test?

Which genetic test?

Sanger sequencing

- Single/pauci-gene testing

NGS approaches

- Disease-Targeted gene panel
- Whole-exome sequecing (WES)
- Whole-genome sequecning (WGS)

Increasing likelihood of identifying rare SNVs including 'variants of uncertain significance' (VUS) and/or 'incidental findings' (IFs)

Informed Consent

For NGS approaches, pre-test discussion with patient should include:

- Pre-test estimates of identifying variant(s)
- Possibility of ambiguous/uncertain results (e.g. VUS)
- Potential for 'actionable' incidental findings
- Limitations of genetic test employed (false-positive, false-negative rates)

Dr Paul Newey

The Genetic Testing Workflow – Intepretation

Genetic Test Interpretation

Support for potential pathogenicity of SNV(s) should take account of:

A. Variant-specific considerations:

- SNV type (i.e. LOF vs missense)
- SNV frequency in relevant control population (although absence in control populations typically provides low specificity for pathogenicity)
- Segregation of variant in affected family members or clear enrichment in disease cohort relative to control population
- Utility of computational prediction tools - low specificity
- Utility of disease/mutation databases - ?reduced accuracy/low reliability
- Biological plausibility/ functional evaluation in relevant model systems

B. Gene-specific / Test-level considerations:

- Pre-test probability of identifying rare variant(s)
  - Number / size / evolutionary conservation of genes being sequenced
  - Background rates of rare coding-region variation in gene(s) of interest
- Gene-specific constraint metrics (e.g. tolerance of LOF/missense variation)

The Genetic Testing Workflow – Communicating Results

Post-genetic test / Patient feedback

Positive test - i.e. pathogenic variant(s): *consider*

- Clinical utility to patient (implementation of treatment/screening)
- Consider need for tracing first-degree relatives / genetic counselling (i.e. consider mode of inheritance, severity and/or penetrance of disorder)

Inconclusive test: i.e. variant(s) of uncertain significance: *consider*

- Strength of evidence supporting association
- Relate to pre-test estimates of identifying rare coding SNV(s)
- Consider need for ongoing patient follow up/surveillance/contact tracing

Negative test: e.g. benign variant(s) only: *consider*

- Potential reassurance to patient and wider family
- ? Role of alternate/additional genetic testing

Appropriate framework for assessing and communicating IFs

SNV reporting: requirement for accurate reporting of variant(s) and phenotypes in clinical repositories and scientific literature

Prof Robert Semple

Biography

Robert Semple is an errant Scot who, until October, had spent his entire professional career in England. He read Natural Sciences and then Medicine at the University of Cambridge before internal medical posts in London. He returned to Cambridge for specialist training in Diabetes and Endocrinology, interrupted by doctoral studies with Prof Sir Stephen O'Rahilly, focusing on transcriptional regulation of adipose tissue metabolism. For the past 12 years his research has focused on rare human disorders of insulin action and/or growth, with the aim of identifying novel acquired or genetic defects underlying insulin resistance and related conditions, both to accelerate diagnosis and treatment of affected patients, and to gain insights into disease mechanism. In October he took up a chair of Translational Molecular Medicine at the University of Edinburgh, and as well as re-establishing a research group focusing on causes and consequences of insulin resistance, he aims to provide a clinical route of referral in Scotland for patients with related problems.

Abstract

Acquired and genetic disorders of adipose tissue development or function and/or severe insulin resistance are a heterogenous group of conditions which are underdiagnosed yet impose a huge burden of premature morbidity and mortality on affected patients. Drawing on experience of 15 years of research, translational and clinical experience in Cambridge, encompassing the English NHS Severe Insulin Resistance Service, a practical account will be given of the conditions most likely to be seen in endocrine/diabetes practice, with a focus on the requirements for specific diagnosis and management.

Prof Robert Semple

Dr Dhruti Bhatt

Biography

I graduated from the University of Sheffield in 2009 and moved to North of Scotland for foundation and core medical training. I commenced specialist training in Diabetes and Endocrinology in 2014 and am currently in my penultimate year of training at Aberdeen Royal Infirmary.

Abstract

Is ^{11}C-methionine PET co-registered with MRI a game changer for challenging functioning pituitary tumours – Aberdeen experience in Acromegaly and Cushing's disease.

Dhruti Bhatt[1], Jack Straiton[2], Mahmoud Kamel[3], Alex Graveling[1], Sam Philip[1], Prakash Abraham[1]. *Department of Endocrinology[1], Department of Clinical Radiology and Nuclear Medicine[2], Department of Neurosurgery[3], Aberdeen Royal Infirmary, Aberdeen, U.K.*

Aims: ^{11}C-methionine positron emission tomography co-registered with MRI (met-PET/MRI) is a new imaging technique used for functioning pituitary adenomas. In patients with persistent acromegaly after primary therapy and other functioning pituitary adenomas, met-PET/MRI can help identify the site(s) of residual pituitary adenoma when MRI appearances are inconclusive and direct further targeted intervention (Trans-sphenoidal surgery-TSS or radiotherapy).

Methods: Prospective study of patients with acromegaly under active follow-up in a teaching hospital. Data was collected from paper and electronic records (2009 onwards). An arbitrary age cut-off of 75 was used when considering suitability for repeat TSS. Remaining patients were divided into three categories. P1: poorly controlled on somatostatin analogue (SSA) therapy and/or pegvisomant. P2: well controlled on SSA. P3: poorly controlled on dopamine agonist (DA) therapy. For Cushing's disease targeted patients were referred from other centres.

Results: Acromegaly cohort: Out of the fifty-one patients included, twenty-three patients under the age of 75 were on active treatment (P1: 10, P2:8 and P3:3). Annual cost (BNF 2017) of medical endocrine therapy for P1 category patients was £150,829 and P2 category patients was £73,466. Nine P1 category patients, willing for further intervention, have agreed to met-PET/MRI and 2 patients have undergone TSS. Illustrative case: A young female patient with acromegaly on SSA+DA (P1) and DM(diabetes mellitus) on 120 units of insulin/day, both poorly controlled, underwent redo TSS influenced by met-PET/MRI (fused images). She was discharged off insulin and with intact steroid axis.

Cushing's disease cohort: So far 3 patients (1 each from Aberdeen/Dundee/Inverness) with Cushing's disease have had positive outcomes following TSS influenced by met-PET/MRI. Illustrative cases 1: A 67 year old woman with previous right adrenalectomy and subsequent ACTH dependant Cushing's syndrome via suppression and CRH tests. BIPSS and MRI x 2 negative, met-PET/MRI confirmed an adenoma and underwent surgery; 2 A 28 year old man with recurrent Cushing's disease and Type 2 DM underwent TSS after the met-PET/MRI clarified the functioning area from post surgical change.

Comment: So far, our patients who have undergone met-PET/MRI have shown identifiable residual functioning pituitary adenoma. It has influenced our decision to put these patients forward for TSS. There are potential cost savings involved if they are able to come off medical therapies or even decrease frequency of these injections.

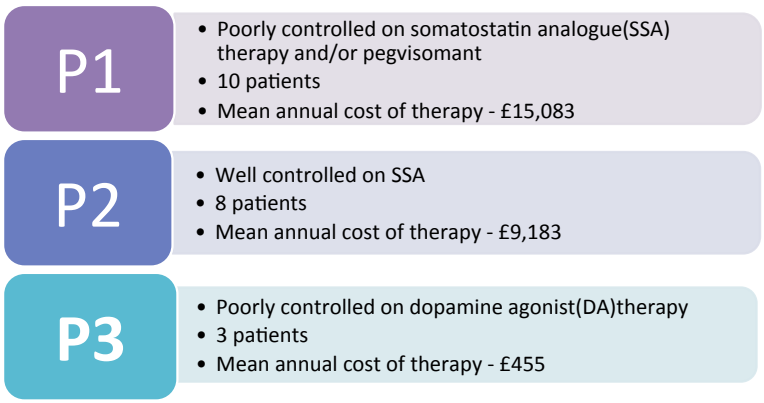
Acknowledgements – Cambridge team for assistance setting up met-PET/MRI. Eur J Endocrinol. 2016 Nov; 175(5): 485-498. Prof Graham Leese, Dundee and Dr Satinder Bal, Inverness for referral and information about their patients.

Dr Dhruti Bhatt

Outline

- MET-PET
- Potential applications
  - Cambridge experience since 2011 – 200+
  - Aberdeen startup Dec 2016 – 9 cases (6 pipeline)
    - Acromegaly – 4 (2 illustrative cases discussed)
    - Cushings – 3 (1 each from Aberdeen/Dundee/Inverness – 2 illustrative cases discussed)
    - TSHoma - 1
    - Ectopic ACTH - 1

Figure 1: Patient category and total annual cost



Acromegaly – Illustrative case -1

- 26, F, presented in 2011

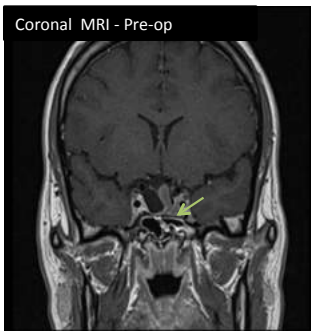
- IGF1 - 150 (9-42nmol/l) at diagnosis, OGTT lowest GH 83mcg/l and new diagnosis of DM
- TSS - 2011 – Improved vision, but remnant

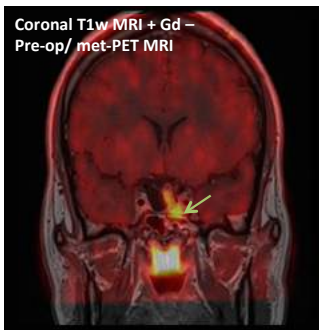
- Radiotherapy – 2013; Pegvisamont allergy, On Lanreotide 120mg 4 weekly and Cabergoline
- Single parent, Smoker, Poor compliance

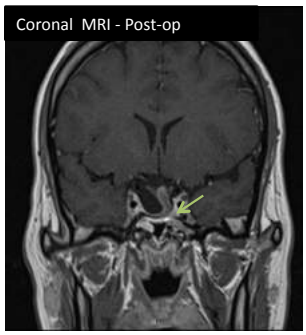
- 2016: IGF1 45-60(15-40nmol/L);
  HBA1c: 127-151mmol/mol on Humalog Mix 25 – 60units bd

Case 1:-

Radiology – Pre and Post-op







Case 1: results continued

Biochemical profile	Pre-op (Feb'17)	Post-op (Jul'17)
IGF-1 (15-40nmol/L)	63.2	16.9
GH ug/L	1.55	1.31
Cortisol, nmol/L	-	894
HbA1c (20-42mmol/mol)	120	88
Prolactin (59-619mu/l)	<40	<40
FT4 (10-25pmol/L)	17	22

Dr Laura Reid

Biography

Laura studied medicine at Clare College, Cambridge, graduating in 2010. She completed her foundation and core medical training in Northern Ireland, before spending a year working in Melbourne, Australia. She moved to Edinburgh in 2015 to commence training in diabetes and endocrinology. She has recently started work on an MD, focusing on glycaemic variability and diabetic retinopathy progression in people with type 1 diabetes pre and post commencement of insulin pump therapy or treatment with islet cell transplantation.

Abstract

Predictors of nephrolithiasis, osteoporosis and mortality in primary hyperparathyroidism
Laura J Reid, Bala Muthukrishnan, Fraser W Gibb

Introduction: Primary hyperparathyroidism (PHPT) is one of the commonest endocrine disorders with a prevalence of at least 1 in 1000. Nephrolithiasis and osteoporosis are more common in people with primary hyperparathyroidism, although the clinical factors associated with this risk are not well characterised. Recent evidence has suggested parathyroid hormone concentration, but not calcium, is associated with mortality in PHPT.

Objectives:
To review prevalence of nephrolithiasis and osteoporosis in patients with PHPT in Edinburgh, and assess factors associated with these complications.
To assess factors associated with mortality in PHPT.

Methods: All patients assessed at the Edinburgh Centre for Endocrinology & Diabetes, between 2006 – 2014, with a diagnosis of PHPT were identified (n = 611). Presenting clinical features, biochemistry results and imaging results were obtained from the electronic patient record.

Results: In total, 85/611 (13.9%) of patients had a diagnosis of nephrolithiasis. Adjusted calcium at diagnosis (2.76 [2.65 – 2.91] vs. 2.72 [2.65 – 2.82], p = 0.08) and PTH (12.7 [9.9 – 19.6] vs. 12.0 [9.3 – 16.7], p = 0.07) were not significantly different in those with a history of renal stones compared to those with no renal stones. Only age (OR 0.97, p <0.001) and male gender (OR 2.32, p = 0.003) were significantly associated with nephrolithiasis in logistic regression analysis. Bone Mineral Density (BMD) data was available in 461 patients of whom 223 had osteoporosis; 184 osteopenia and 54 normal BMD. Age (p<0.001), BMI (p<0.001), Gender (p=0.044) and PTH at diagnosis (p=0.047) were significantly associated with osteoporosis. Parathyroid surgery (HR 0.25, p = 0.005), Vitamin D deficiency (HR 1.23, p=0.007) adjusted calcium at diagnosis (HR 1.15, p = 0.03) were independently associated with mortality; PTH was not (HR 0.99, p = 0.74).

Conclusions:
- Nephrolithiasis is most common in younger men with PHPT.
- Osteoporosis is common in PHPT but this is, in part, a consequence of the age and gender of those presenting with this condition.
- PTH, rather than calcium, is more strongly correlated with bone mineral density.
- Parathyroid surgery is associated with lower rates of mortality but this is almost certainly a reflection of selection bias (*i.e.* less surgery in frail patients).
- Higher PTH is associated with higher mortality, but this is most likely a reflection of lower vitamin D levels, which are more robustly associated with mortality.
- Contrary to earlier reports, these data suggest adjusted calcium and not PTH is the most significant biochemical signal for mortality risk in PHPT.

Nephrolithiasis –Associated Factors

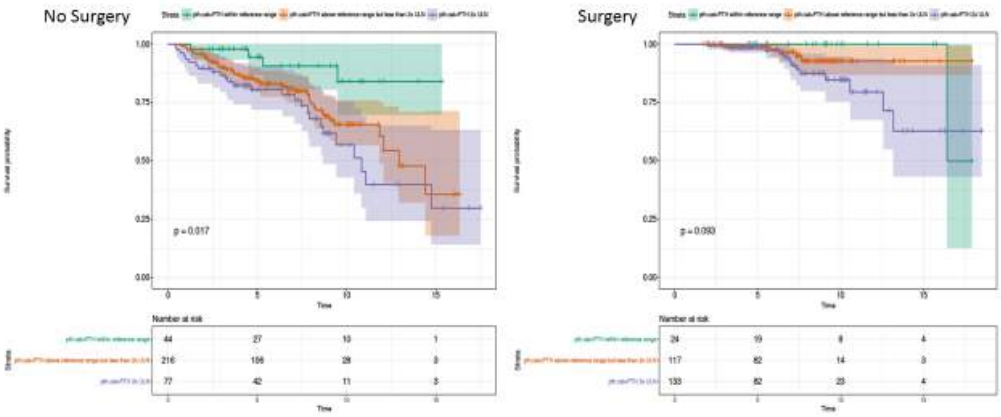
	Renal stones (n = 85)	No renal stones (n = 526)	p =
Age	**61 (49 – 72) (n = 59)**	**69 (59 – 77) (n = 386)**	**<0.001**
BMI	27.8 (25.8 – 30.9)	27.7 (24.0 – 31.8)	0.377
Adjusted calcium	2.76 (2.65 – 2.91)	2.72 (2.65 – 2.82)	0.075
PTH	12.7 (9.9 – 19.6)	12.0 (9.3 – 16.7)	0.067
Vitamin D	32 (22 – 48) (n = 56)	31 (22 – 48) (n = 357)	0.896
Creatinine	73 (63 – 88)	71 (63 – 87)	0.382
Urine calcium / litre	4.3 (1.9 – 5.4) (n = 50)	3.4 (1.9 – 5.1) (n = 284)	0.087
Urine CCCR	0.016 (0.009 – 0.021) (n = 36)	0.016 (0.009 – 0.021) (n = 184)	0.265
Male	**27/108 (25.0%)**	**81/108 (75.0%)**	**<0.001**
Female	**58/503 (11.5%)**	**445/503 (88.5%)**	

Osteoporosis – Associated Factors

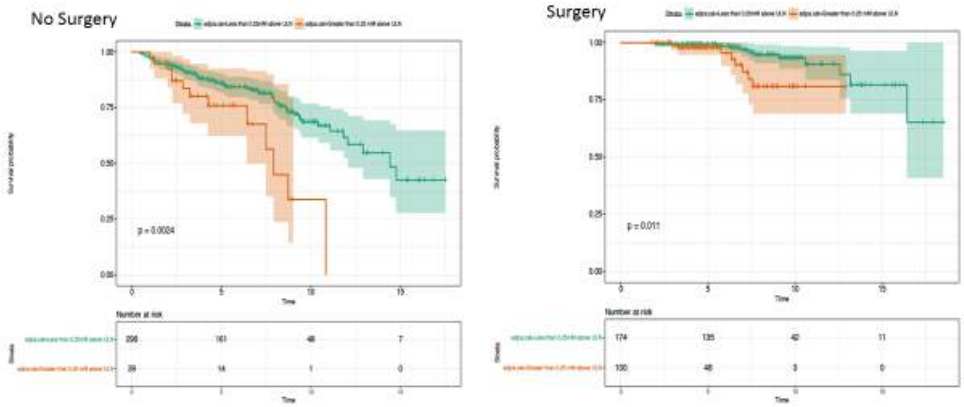
	Osteoporosis (n = 223)	No osteoporosis (n = 238)	P
Age at diagnosis	**72 (66 – 79)**	**65 (57 – 73)**	**<0.001**
BMI	**26.3 (22.7 – 29.9) (n = 201)**	**28.6 (25.8 – 32.5) (n = 214)**	**<0.001**
Calcium	2.73 (2.66 – 2.83)	2.72 (2.66 – 2.81)	0.486
Peak calcium	2.85 (2.75 – 2.97)	2.84 (2.76 – 2.96)	0.894
PTH	**12.1 (9.7 – 16.9)**	**11.5 (8.4 – 14.2)**	**0.047**
Phosphate	0.91 (0.80 – 1.03)	0.90 (0.77 – 1.00)	0.322
Vitamin D	29 (22 – 51) (n = 166)	34 (23 – 48) (n = 172)	0.447
Creatinine	69 (62 – 84)	72 (64 – 88)	0.068
Urine CCCR	0.018 (0.010 – 0.023) (n = 75)	0.015 (0.010 – 0.020) (n = 107)	0.076
Urine calcium/litre	3.2 (1.9 – 5.2) (n = 115)	3.7 (2.0 – 5.1) (n = 161)	0.492
Female	**196/389 (50.4%)**	**193/389 (49.6%)**	**0.044**
Male	**27/72 (37.5%)**	**45/72 (62.5%)**	

Dr Laura Reid

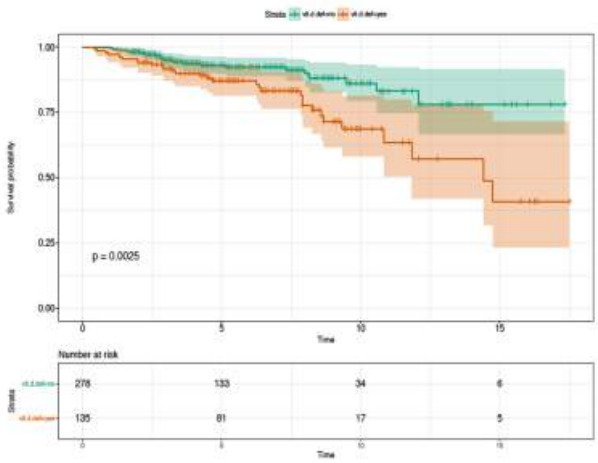
Mortality: PTH



Mortality - Calcium



Mortality: Vitamin D Deficiency



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

Kenney Caffey Syndrome 2: An extremely rare case of hypoparathyroidism and recurrent hypomagnesaemia
Sharon T Mackin, Rhian M Touyz, Colin Perry

We present a diagnostically challenging case of a 22-year old female with short stature and congenital hypoparathyroidism with recurrent admissions for severe hypocalcaemia, hypokalaemia and hypomagnesaemia.

Case
Our patient was born at 38 weeks gestation to unrelated, healthy parents of average height, following a pregnancy complicated by intrauterine growth restriction. She was a small infant with a birthweight of 2.4kg (-1.7 SD), a length that was almost 4 SD below expected and a small head circumference of 31cm (-2.2 SD). She had facial dysmorphic features of frontal bossing, microphthalmia and mid-facial hypoplasia.
Growth failure was a persistent problem during childhood despite normal stimulated GH and IGF-1 levels. Skeletal surveys revealed gracile bones with cortical thickening, hypoplastic mandibles and a j-shaped sella. Pituitary imaging and biochemistry were normal. GH therapy was trialled several times but complicated pre-existing hypermetropia with macular oedema.
Recurrent severe hypocalcaemia, hypomagnesaemia and hypokalaemia has resulted in frequent hospitalisation since infancy. Biochemical testing confirms persistent hypoparathyroidism, high urinary magnesium and potassium excretion but normal calcium:creatinine, renin and aldosterone. She is treated with alfacalcidol 1 microgram daily and varying doses of calcium carbonate, magnesium and potassium replacement.
Despite extensive investigation, no unifying diagnosis was achieved until at the age of 21 years, whole genomic sequencing confirmed a de-novo heterozygous c.1706G>A transition in the FAM111A gene diagnostic of Kenny-Caffey Syndrome 2.

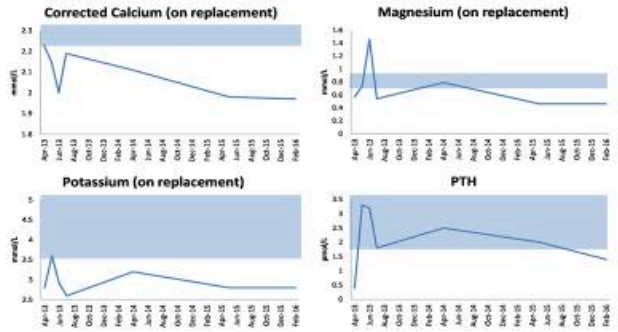
Kenny- Caffey Syndrome 2 (KCS2)
KCS2 is extremely rare with less than 60 cases reported in the English literature. The clinical features of short stature, skeletal abnormalities and hypoparathyroidism were first described in a mother and son in 1966 by Kenny and Linarelli.[1] In 2013, genomic sequencing of five unrelated, affected individuals identified a mutation in the FAM111A gene located on chromosome 11.[2] FAM111A codes for a 611 amino acid protein which bears homology to trypsin but its function is unclear.[3] Existing clinical case series' hypothesise an important role in parathyroid hormone regulation and bone growth. The recurrent hypomagnesaemia and hypokalaemia seen in our case suggests a potential mechanism involving magnesium regulation. We are conducting further research into understanding the role of FAM111A in magnesium homeostasis.

Kenny FM, Linarelli L (1966). Dwarfism and cortical thickening of tubular bones: transient hypocalcemia in a mother and son. *Am J Dis Child* 111: 201–207
Unger S, Gorna MW, Le Bechec A et al (2013). FAM111A mutations result in hypoparathyroidism and impaired skeletal development. Am J Hum Genet 92: 990–995
Fine DA, Rozenblatt-Rozen O, Padi M et al (2012) Identification of FAM111A as an SV40 host range restriction and adenovirus helper factor. *PLoS Pathog*. 8(10): e1002949

Dr Sharon Mackin

Biochemistry

- Hypoparathyroidism with recurrent hypocalcaemia, hypomagnasaemia and hypokalaemia since infancy



Alfacalcidol 1-1.5mcg/day
Varying doses of oral calcium, magnesium and potassium replacement

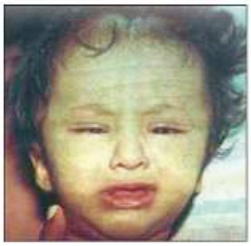
Biochemistry

Urine Ca:Creatinine ratio	0.43
Urine Magnesium fractional excretion	6.7% (<4%)
Urine Potassium	72 mEq/L (<40mEq/L)
Serum Potassium	3.3 mmol/L (3.5-5mmol/L)
Urine Creatinine	3.2 mmol/day
Serum Renin	165.6 pmol/L (100-800pmol/L)
Serum Aldosterone	207 pmol/L (100-800pmol/L)
TTG antibody	negative
Urine amino acids	normal

Colonoscopy: non-significant presence of occasional lymphoid aggregates

Kenney Caffey Syndrome 2

- Typical features:
  - Proportionate short stature
  - Thin, gracile bones with cortical thickening and medullary stenosis
  - Hypoparathyroidism
  - Hypermetropia
  - Normal cognition
- Autosomal dominant
- Osteocraniostenosis: perinatal death



Agarwal I et al. (2013

Kenney Caffey Syndrome 2

- Unger et al 2013
  - 4 individuals with KCS and 1 with OCS
  - Identified de-novo heterozygous FAMIIIa mutation
    - Chromosome 11
    - C.1706G>A most common
    - Severe phenotype assoc with p.Ser342del
- Isojima 2014 similar findings

Role of FAMIIIa gene

- Unknown function
- 611 AA protein
  - Trypsin-like peptidase structure
- LT antigen SV40 virus has strong affinity for FAMIIIa
  - Antiviral properties
- Other LT antigens have important role in regulation of gene transcription
  - ? FAMIIIa does too

Dr Nyo Nyo Tun

Biography

I graduated from University of Edinburgh in 2007. My foundation and core medical training years were spent in Glasgow and Aberdeen. I returned to Edinburgh in 2013 to undertake specialty training and took time out of programme to undertake an MD looking into predictive factors of androgen deficiency in men with type 2 diabetes under the supervision of Dr. Dawn Livingstone and Dr. Fraser Gibb.

Abstract

Testosterone Deficiency in T2DM is a Condition of Relative Estrogen Excess, Elevated Adipose Aromatase Expression and High Leptin

Dr Nyo Nyo Tun, Dr Dawn Livingstone & Dr Fraser W Gibb

Background:
Androgen deficiency (AD) is observed in up to 50% of men with T2DM. It has been proposed this is a consequence of elevated aromatase activity from an expanded adipose compartment, however this has been called into question as lower estradiol concentrations have been reported in men with T2DM related hypogonadism. A complementary hypothesis posits the pro-inflammatory state associated with T2DM as a potential contributor. We sought to investigate predictive factors for AD in a large cohort of men with T2DM.

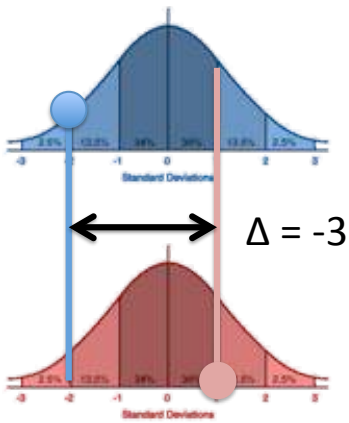
Methods:
228 men with T2DM under the age of 65 were recruited and underwent: fasting blood sampling, anthropometric measurements, bioimpedance body fat estimation, AMS and SF-36 questionnaires and subcutaneous adipose needle biopsy (n = 150). Sex steroids (including T and E2) were measured by LC MS/MS. 15 genetic variants related to sex-steroids were analysed and subcutaneous adipose mRNA expression of 23 genes of interest was assessed by RT-PCR. T and E2 were converted to z-scores and the difference between z-scores used as a measure of divergence.

Results:
AD (defined as total T < 10nM) was present in 34.3%. Individual factors associated with AD included BMI (33.2 vs. 30.5 mg/kg^2, P < 0.001), HbA1c (58 vs. 51 mmol/mol, P < 0.001), HOMA-IR (6.2 vs. 4.6, P = 0.008), difference between T and E2 z-score (-0.6, vs. 0.40, P < 0.001 – less than 0 indicates relative E2 excess), plasma leptin (21350 vs. 14600 pg/ml, P < 0.001) and adipose aromatase expression (2.45 vs. 1.87, P <0.05). Age, smoking, alcohol consumption, IL-6, IL-8, MCP-1 and TNF-α were not associated with testosterone deficiency. Modest associations with AD were observed in 5 of the 15 genetic variants assessed. Logistic regression identified T – E2 z-score difference (P < 0.001), insulin resistance (P = 0.03) and plasma leptin (P 0.05) as the strongest independent predictors of AD.

Conclusions:
Previous demonstration of lower E2 levels in hypogonadal men with T2DM is confounded by failure to adjust for lower substrate androgen levels. Our findings support the hypothesis that adiposity (high leptin), higher aromatase expression and relative estrogen excess are key determinants of hypogonadism in T2DM. In contrast circulating and adipose measures of inflammation were not associated with hypogonadism.

Relative T and E2 balance

Difference between z-scores



Less than 0 = relative estradiol excess

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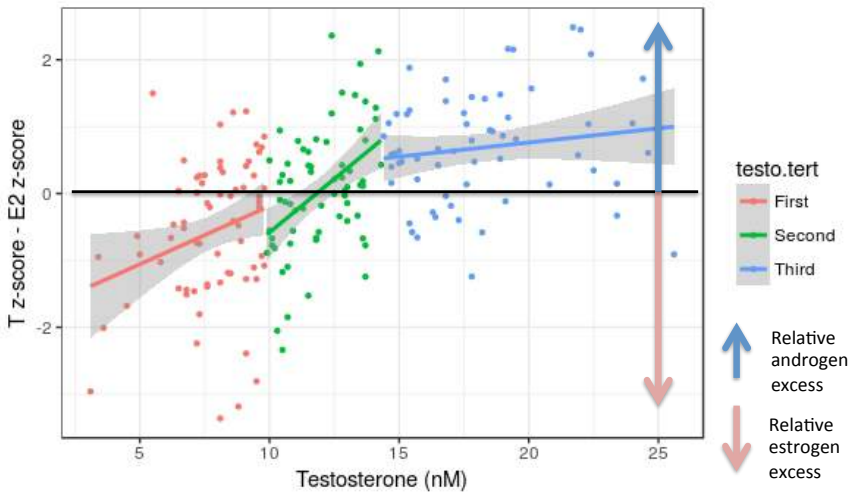
Relative T and E2 balance

Difference between z-scores



Limited to n = 196 men with normal range LH

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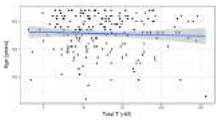
Dr Nyo Nyo Tun

Age

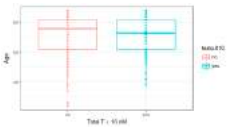
Associated with E, CFT but not total T

Total testosterone

R -0.023, P = 0.744

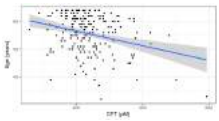


P = 0.820

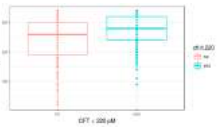


Free testosterone

R -0.218, P = 0.002

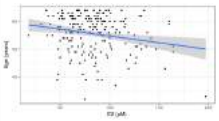


P = 0.019



Estradiol

R -0.157, P = 0.028



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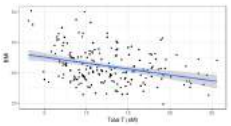
BMI

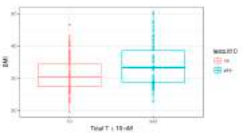
Divergent association with T and E2

Total testosterone

R -0.291, P < 0.001

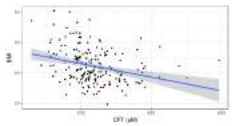


P = 0.002

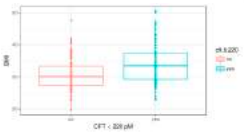


Free testosterone

R -0.332, P < 0.001

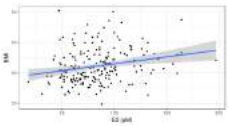


P < 0.001



Estradiol

R 0.257, P < 0.001



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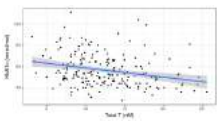
HbA1c

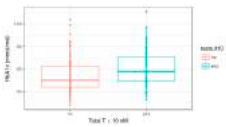
Lower T associated with higher HbA1c

Total testosterone

R -0.287, P < 0.001

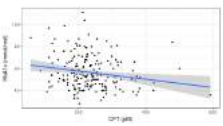


P < 0.001

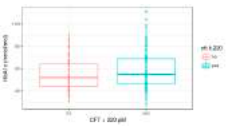


Free testosterone

R – 0.173, P = 0.016

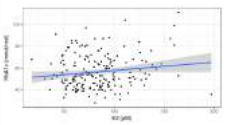


P = 0.108



Estradiol

R 0.085, P = 0.239



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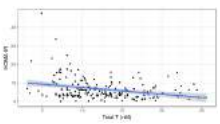
HOMA-IR

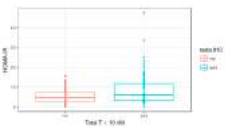
Insulin resistance associated with low T

Total testosterone

R -0.272, P < 0.001

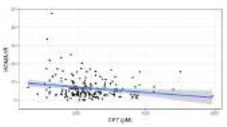


P = 0.011

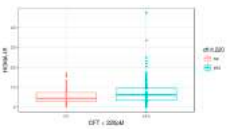


Free testosterone

R -0.167, P = 0.019

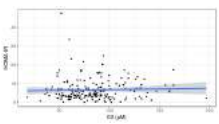


P = 0.025



Estradiol

R 0.086, P = 0.232



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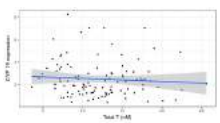
CYP19 expression

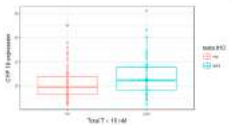
Associated with lower CFT and higher E2

Total testosterone

R -0.100, P = 0.308

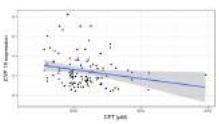


P = 0.090

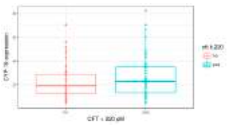


Free testosterone

R -0.205, P = 0.035

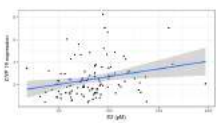


P = 0.266



Estradiol

R 0.301, P = 0.002



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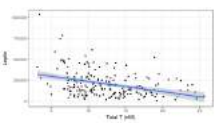
Leptin

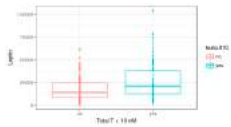
Associated with lower T and higher E2

Total testosterone

R -0.351, P < 0.001

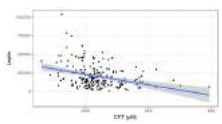


P = 0.002

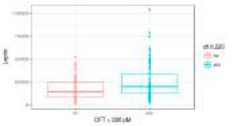


Free testosterone

R -0.331, P < 0.001

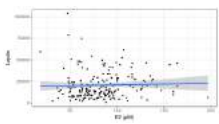


P = 0.002



Estradiol

R 0.143, P 0.046



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Dr Catriona Farrell

Biography

Catriona Farrell graduated in medicine from Glasgow University in 2010 where she went on to complete Foundation and Core Medical Training. She moved to the East of Scotland in 2015 to commence higher specialty training in Diabetes and Endocrinology. In 2017 Catriona was awarded the Diabetes UK Sir George Alberti Research Fellowship to undertake a PhD, she will be looking into the use of high intensity exercise as a novel treatment of impaired awareness of hypoglycaemia in type 1 diabetes under the supervision of Prof Rory McCrimmon at the University of Dundee.

Abstract

Pancreatic Neuroendocrine Tumour associated with Hypoglycaemia; Tumour, Treatment or Transformation?

Catriona Farrell, Asa Dahle-Smith, Graham Leese, Paul Newey

Pancreatic neuroendocrine tumours (PanNETs) occur infrequently, with an annual incidence of ~1/100,000 and are typically classified into functioning and non-functioning subgroups depending on the secretory profile of the tumour. For individuals presenting with advanced functional tumours (e.g. insulinoma, gastrinoma, glucagonoma) treatment strategies need not only address controlling disease progression but must also control symptoms associated with hormone excess. Failure to recognise or adequately treat such hormone secretion may result in significant morbidity and/or mortality. Here, we illustrate some of these challenges in a patient diagnosed with an advanced PanNET, who subsequently developed marked hypoglycaemia.

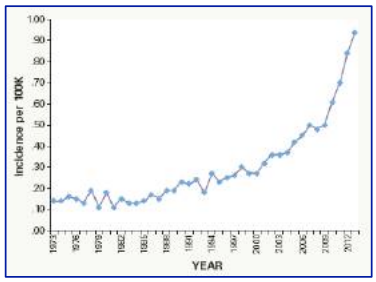
The 57-year old male patient initially presented with weight loss and jaundice. Imaging revealed the presence of a head-of-pancreas mass associated with multiple liver metastases. Subsequent pancreatic biopsy indicated a low-grade pancreatic neuroendocrine tumour, whilst further evaluation indicated marked elevation of serum chromogranin A, modest elevation of glucagon (X2 ULN), and avid uptake on octreotide scanning. In view of disease burden, medical management was recommended and he commenced long-acting somatostatin analogue (SSA) therapy. Three months after commencing SSA therapy, the patient developed symptoms suggestive of hypoglycaemia culminating in a road traffic accident associated with loss of consciousness. Subsequent referral to endocrinology confirmed endogenous hyperinsulinaemic hypoglycaemia and diazoxide was started with partial amelioration of symptoms. In view of minor disease progression on imaging, SSA therapy was discontinued and everolimus commenced, with excellent control of hypoglycaemia. Disease burden has remained stable on current therapy.

In this presentation we will review the use of everolimus as an insulinoma treatment and consider the three possibilities for the presentation of hypoglycaemia in this case: (1) missed diagnosis of metastatic insulinoma at presentation; (2) precipitation of hypoglycaemia by SSA therapy; or (3) tumour transformation to a secretory phenotype.

Dr Catriona Farrell

Background – Pancreatic Neuroendocrine Tumours (PanNETs)

- PanNETS are a heterogeneous group of neoplasms arising from endocrine cells of the pancreatic islets
- Incidence and prevalence increasing over past 20 years
- Functioning vs non-functioning
- Advanced disease is frequently evident at the time of diagnosis
- Current therapies aim to control disease progression and symptoms related to excess hormone secretion

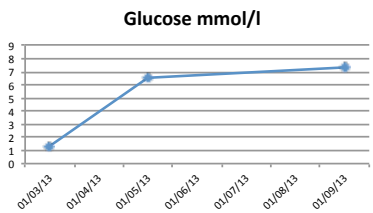


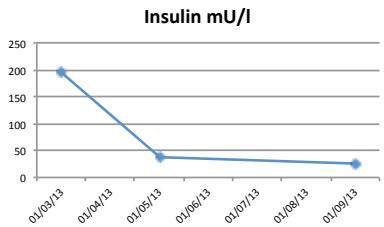
Age-adjusted incidence of Pancreatic NETS (Data from SEER Registry)

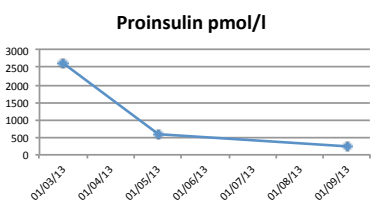
Management – Insulinoma

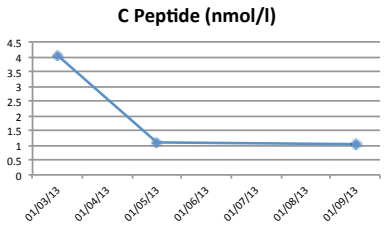
- **Surgical** – should be offered to all patients if non resectable metastatic disease is not present
  - Laparoscopic
  - Ablation (percutaneous, endoscopic)
- **Medical** – prior to surgery, or malignant or recurrent cases
  - Frequent small meals
  - Diazoxide
  - Somatostatin analogues
  - mTOR inhibitor (Everolimus)
  - Peptide Receptor Radionuclide Therapy (PRRT)
  - Chemoembolisation

Response to Everolimus









Dr Marcus Lyall

Biography

Marcus Lyall is a Clinical Lecturer at the BHF Centre for Cardiovascular Science 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 positon on the Edinburgh Clinical Academic Training (ECAT) Scheme in 2012. His PhD research under the supervision of Dr Mandy Drake and Professor Richard Meehan, focused on the interaction between glucose metabolism and the epigenome in metabolic liver disease. Other research interests include *in vitro* stem cell modelling of NAFLD and steroid induced hyperglycaemia in cancer therapy.

Abstract

Is Renin a Useful Marker of Mineralocorticoid Replacement in Addison's Disease?

Marcus J Lyall[1], Tarek Mohamed Elsayed Salem[2], Fraser W Gibb[3]

1 University/BHF Centre for Cardiovascular Science, Endocrinology Unit, University of Edinburgh. 2 Alexandria university, Egypt. 3 Edinburgh Centre for Endocrinology and Diabetes, Royal Infirmary of Edinburgh.

Introduction

The utility of renin measurement in guiding mineralocorticoid replacement is unclear. To address this, we retrospectively examined the parameters and treatment of 97 patients with Addison's disease over a five year period.

Methods

Adrenal replacement, blood pressure (BP), orthostatic blood pressure response, urea, sodium, potassium and renin levels of 97 patients attending our clinic were collected over the period 2012-2016. Data were analysed and graphical outputs generated in R version 3.3.2.

Results

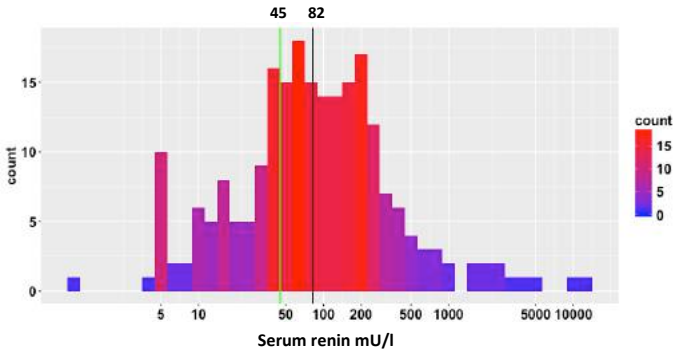
97 patients attending for 397 appointments were reviewed. Renin level was measured on 227 (57%) of attendances at an estimated cost of £5500. 68% of renin measurements were elevated (>45mU/L) with 48% above 90mu/L and a median level of 82mU/L. A weak but significant negative association with plasma sodium ($P<0.001$, R^2 0.072) was noted however no association was present between renin level and potassium level, systolic or diastolic blood pressure or orthostatic response. A renin level >90mu/L was 63% sensitive and 57% specific for detecting another feature of mineralocorticoid deficiency (Na < 135mmol/l, K > 5.0mmol/l, orthostatic hypotension). A renin level >45ml/l was 76% sensitive but only 36% sensitive. Receiver operating characteristic curve demonstrated that elevated renin was a valid but suboptimal test for identifying other features of mineralocorticoid deficiency (AUC 0.649, p value < 0.01). In patients with normal biochemistry and orthostatic blood pressure response, deranged renin level alone significantly influenced the incidence of fludrocortisone dose titration (renin < 5 or > 90mU/l, P< 0.001 chi-squared test).

Conclusion.

Our study suggests that serum renin minimally correlates with clinical and biochemical features of mineralocorticoid state and that high renin levels have only modest sensitivity and low specificity for detecting features of mineralocorticoid deficiency. Despite this, renin continues to be measured routinely at significant cost and treatment decisions continue to be made based only on renin level the clinical outcome of which remains unclear.

Dr Marcus Lyall

Renin distribution of patients on mineralocorticoid replacement.



- Renin level was measured on 227/397 (57%) of attendances
- The majority of patients with PAI remain hyper-reninaemic despite fludrocortisone replacement (Median 82mu/l).
- 68% of measurements were above the reference range (45mU/L) with 48% greater than 90mU/l.

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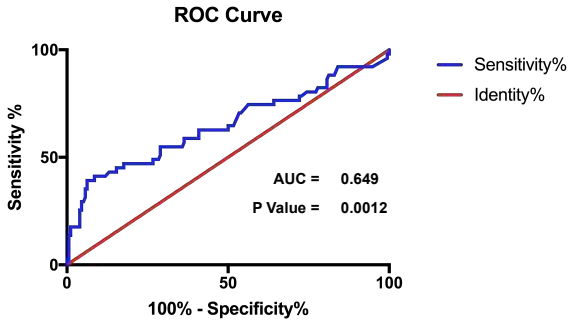
Does elevated serum renin predict other features of mineralocorticoid deficiency?

Statistic	>45mU/l	>90mU/l
Sensitivity	76.47%	62.75%
Specificity	34.09 %	56.82 %
Positive Predictive Value	25.16%	29.63%
Negative Predictive Value	83.33 %	84.03 %
Disease prevalence	22.47%	22.47%



- Renin renin is a valid but suboptimal test for identifying other features of mineralocorticoid
  - serum Na < 135mmol/l,
  - serum K+ >5.0mmol/l or
  - postural drop of ≥10mmHg diastolic or ≥20mmHg systolic

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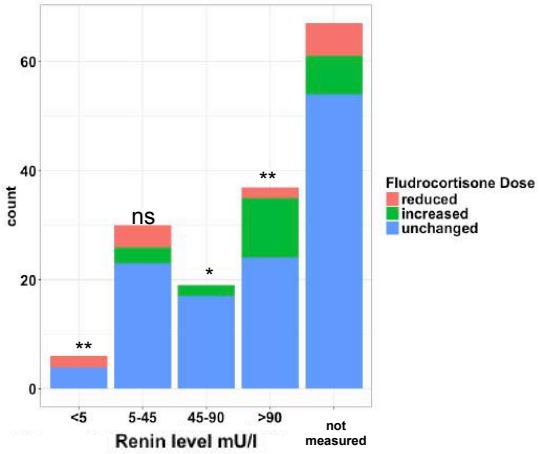
Are we making clinical decisions based on renin level alone?



Change in fludrocortisone dose in response to renin level in patients with normal electrolytes, blood pressure and orthostatic response, stratified by renin level.
* P < 0.01 ** P < 0.001 Chi squared test compared to ' not measured'.

- In patients with normal biochemistry and orthostatic blood pressure response, deranged renin level alone significantly influenced the incidence of fludrocortisone dose titration.

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Conclusions

- This study suggests that serum renin minimally correlates with clinical and biochemical features of mineralocorticoid state.
- Despite this, renin continues to be measured routinely, at significant cost, and treatment decisions continue to be made based on renin level alone
- How this impacts on clinical outcomes is unclear.
- Further work is required to investigate how renin level relates to incidence of hospital admission, antihypertensive treatment and cardiovascular outcome.

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Dr Catriona Kyle

Biography

I graduated from Aberdeen University in 2008 and completed my foundation and core medical training in Glasgow. In 2012, I moved to Edinburgh to undertake specialist training in Diabetes and Endocrinology. After 2 years, I took time out of programme to undertake a PhD with Professor Brian Walker and Dr Roland Stimson investigating the contributions of cortisol and corticosterone to metabolic regulation in humans. I returned to clinical training in August 2017 and am currently working in the Royal Infirmary of Edinburgh.

Abstract

Contributions of cortisol and corticosterone to metabolic regulation in humans

Catriona J Kyle[1], Mark Nixon[1], Alice Ostojic[1], Luke Boyle[1], Natalie Z Homer[1], Ruth Andrew[1], Roland H Stimson[1], Brian R Walker[1].

[1]BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Background Both cortisol and corticosterone circulate in human plasma however corticosterone has been relatively neglected in human research to date. There is evidence of distinct regulation within different tissues: the transmembrane ATP-binding cassette (ABC) transporter ABCB1, highly expressed in the brain, exports cortisol but not corticosterone, likely accounting for the relative accumulation of corticosterone in the central nervous system (CNS). In contrast, ABCC1, highly expressed in adipose tissue and skeletal muscle, exports corticosterone but not cortisol, suggesting cortisol has a disproportionately greater effect in these tissues. We hypothesized that corticosterone plays an important role in central hypothalamic-pituitary-adrenal axis feedback and that corticosterone might be a better glucocorticoid for replacement in congenital adrenal hyperplasia (CAH) due to an improved metabolic side effect profile.

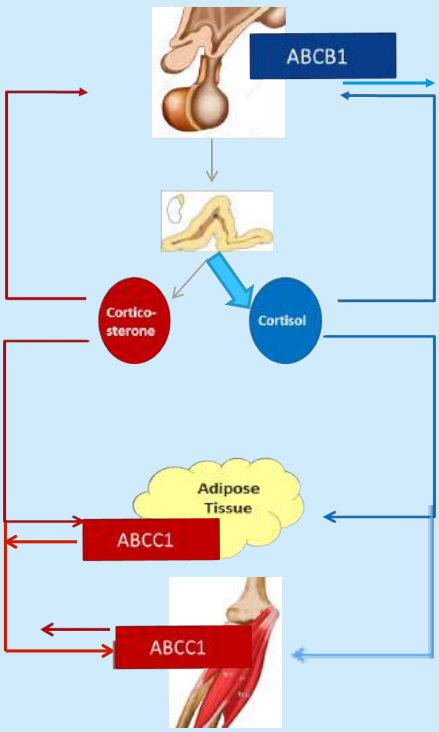
Methods To determine whether the ABCC1 transporter is responsible for differential binding of cortisol and corticosterone to GR/MR in adipose tissue and skeletal muscle, we examined corticosteroid receptor occupancy of glucocorticoids centrally and peripherally with and without ABCC1 inhibition in 14 healthy individuals in a randomised crossover design. To explore the efficacy of corticosterone as a novel treatment for CAH in humans, we compared the efficacy of corticosterone compared with hydrocortisone and placebo in suppressing the HPA axis in patients with CAH.

Results ABCC1 inhibition increased HPA axis activity but did not increase adipose tissue or skeletal muscle glucocorticoid receptor occupancy following combined glucocorticoid and mineralocorticoid receptor antagonism, highlighting a previously undiscovered central role for ABCC1. Corticosterone infusion suppressed ACTH and adrenal androgens to a similar extent as hydrocortisone in CAH patients, providing proof-of-concept of its efficacy.

Conclusions These data show that there are important differences between corticosterone and cortisol physiology in humans. This is in part due to the effects of ABCC1 which plays an important role in regulation of the HPA axis in addition to regulating peripheral glucocorticoid action. Corticosterone acutely suppresses the HPA axis in CAH, highlighting its potential as an alternative to hydrocortisone for glucocorticoid replacement therapy.

The alternative HPA axis

Raised CSF and brain tissue concentrations

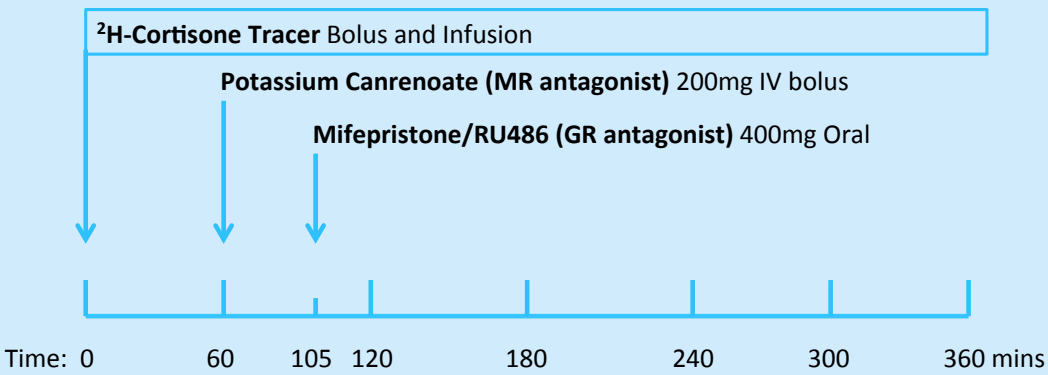


? Key role of corticosterone in HPA negative feedback

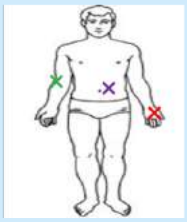
Nixon et al.
Sci Trans Med 2016

Does ABCC1 protect adipose tissue from excess corticosterone?

1. ABCC1 inhibition in adipose and skeletal muscle



- Blood was sampled regularly from 3 sites:



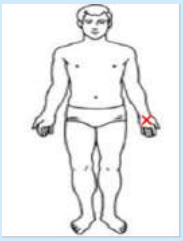
Arterialised (retrograde cannula in hand, heated to 60°C)

Skeletal muscle (deep vein, antecubital fossa)

Adipose tissue (superficial abdominal vein)

- Adipose tissue blood flow was measured by ^{133}Xenon washout and in skeletal muscle using venous occlusion plethysmography.

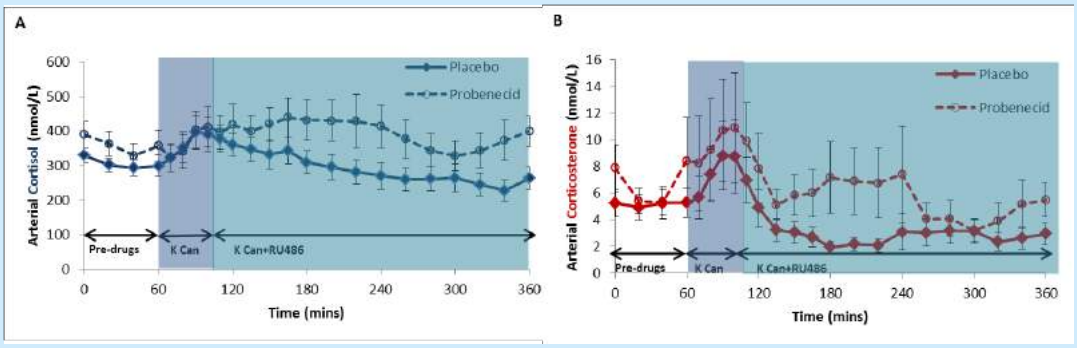
Dr Catriona Kyle



Results: Whole body

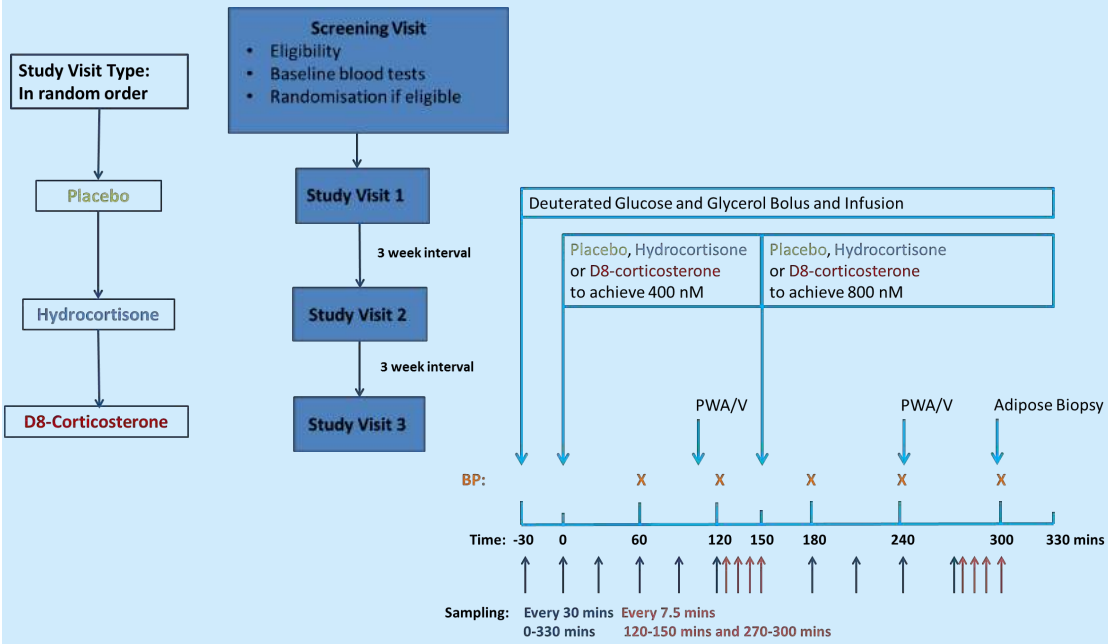
Arterialised plasma cortisol and corticosterone concentrations

Placebo and Probenecid



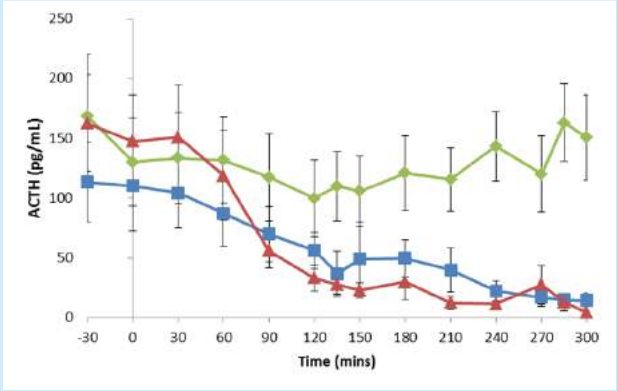
However, inhibition of ABCC1 with probenecid substantially enhanced this response

2. Corticosterone as an alternative glucocorticoid replacement therapy



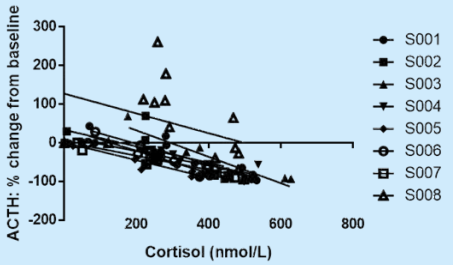
Results: Plasma ACTH

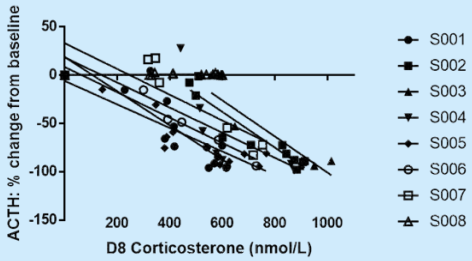
ACTH suppression apparent with both glucocorticoids



Placebo
Cortisol
D8-corticosterone

% ACTH suppression against GC concentration





Cortisol 333.1±31.0 nmol/L

D8-corticosterone: 535.2±53.6 nmol/L

Notes

Notes

caledonian society for endocrinology and diabetes

CalSoc 2017 registration, meals and accommodation were covered by our sponsors: