CalSoc 2014

caledonian society for endocrinology and diabetes

Dunkeld Hilton
November 28th/29th

calsoc.org

Contents

Welcome to CalSoc 2014

Thank you for joining us in Dunkeld for the 34th winter meeting of the Caledonian Society for Endocrinology. The demand for places has been incredible and is testament to the undoubted demand for a Scottish forum dedicated to promoting education and fostering collaboration in clinical endocrinology.

We have assembled an impressive array of speakers from across the United Kingdom, supplemented by presentations showcasing current endocrine research taking place in Aberdeen, Glasgow and Edinburgh.

This year we also wish to explore the possibility of using CalSoc as a focus for collaborative clinical research and audit within Scotland. The first step in this process will be a discussion of potential projects, with the intention of establishing a rolling programme, the results of which would be reported at subsequent CalSoc meetings.

Thanks again for your support.

Dr Fraser Gibb
On behalf of the CalSoc Committee

<u>CalSoc Committee 2014</u>

Dr Fraser Gibb (Secretary-Treasurer): Edinburgh
Dr Russell Drummond: Glasgow
Prof Graham Leese: Dundee
Dr Sam Philip: Aberdeen

Attendees I

Name		Role	Post	Centre
Ganesh	Arunagirinathan	Delegate	Consultant	Edinburgh
Satinder	Bal	Delegate	Consultant	Inverness
Steve	Ball	Speaker	Consultant	Newcastle
Linda	Buchanan	Delegate	Consultant	Forth Valley
Tom	Chambers	Delegate	SpR	Edinburgh
Zhuo Min	Chong	Delegate	SpR	Glasgow
Catriona	Clarke	Delegate	Biochemist	Edinburgh
Andrew	Collier	Delegate	Consultant	Ayr
Alan	Connacher	Delegate	Consultant	Perth
Jenna	Cowan	Delegate	SpR	Glasgow
Gemma	Currie	Speaker	SpR	Glasgow
Janet	Darling	Delegate	Biochemist	Edinburgh
Anna	Dover	Delegate	Consultant	Edinburgh
Russell	Drummond	Committee	Consultant	Glasgow
Catriona	Farrell	Delegate	CMT 2	Glasgow
Miles	Fisher	Delegate	Consultant	Glasgow
Marie	Freel	Delegate	Consultant	Glasgow
Nazim	Ghouri	Delegate	SpR	Glasgow
Fraser	Gibb	Committee	Consultant	Edinburgh
Robert	Gifford	Delegate	SpR	Edinburgh
Jackie	Gilbert	Speaker	Consultant	London
Derek	Gordon	Delegate	Consultant	Glasgow
Sheila	Grecian	Delegate	SpR	Edinburgh
Fiona	Green	Delegate	Consultant	Dumfries
Isabel	Howat	Delegate	Consultant	Monklands
Kate	Hughes	Speaker	Lecturer	Edinburgh
Alan	Jaap	Delegate	Consultant	Edinburgh
Pauline	Jones	Delegate	Consultant	Edinburgh
Chris	Kelly	Delegate	Consultant	Forth Valley
Brian	Kennon	Delegate	Consultant	Glasgow
Chris	Kueh	Delegate	SpR	Glasgow
Heather	Laing	Administrator	Administrator	Edinburgh
Graham	Leese	Committee	Consultant	Dundee

Attendees II

Name		Role	Post	Centre
Rachel	Livingstone	Delegate	CMT 2	Glasgow
Marcus	Lyall	Delegate	SpR	Edinburgh
David	Macfarlane	Delegate	Consultant	Inverness
Gerard	Mackay	Delegate	Consultant	Glasgow
Alison	Mackenzie	Delegate	Consultant	Forth Valley
Scott	Mackenzie	Speaker	SpR	Edinburgh
Alasdair	Mackie	Delegate	Consultant	Dundee
Supriya	Mathur	Delegate	SpR	Edinburgh
Laura	McCreight	Delegate	SpR	Glasgow
Martin	McIntyre	Delegate	Consultant	Paisley
Laura	Mclaren	Delegate	SpR	Glasgow
Emily	McMurray	Delegate	Consultant	Edinburgh
Caroline	Millar	Delegate	Biochemist	Glasgow
Azhar	Mohammed	Delegate	SpR	Glasgow
Kenneth	Muir	Speaker	SpR	Aberdeen
Babu	Mukhopadhyay	Delegate	Consultant	East Kilbride
Bala	Muthukrishnan	Delegate	SpR	Edinburgh
Paul	Newey	Delegate	Consultant	Dundee
Colin	Perry	Delegate	Consultant	Glasgow
Sam	Philip	Committee	Consultant	Aberdeen
Anne	Pollock	Delegate	Biochemist	Inverness
Lorna	Rashid	Delegate	Biochemist	Edinburgh
Stuart	Ritchie	Delegate	Consultant	Edinburgh
Robert	Semple	Speaker	Consultant	Cambridge
Catherine	Shearing	Delegate	Biochemist	Edinburgh
Chris	Smith	Delegate	Consultant	Paisley
Mark	Strachan	Speaker	Consultant	Edinburgh
Nyo Nyo	Tun	Delegate	SpR	Edinburgh
Emma	Turtle	Delegate	SpR	Edinburgh
Debbie	Wake	Delegate	Consultant	Dundee
Brian	Walker	Speaker	Consultant	Edinburgh
Sharon	White	Delegate	SpR	Glasgow
Anna	White	Speaker	SpR	Glasgow
Rachel	Williamson	Delegate	Consultant	Borders

Programme – day 1

Friday 28th November

Chair: Dr Fraser Gibb

Registration	13:30 – 14:30
The challenges of diabetes drug development in academia *Prof Brian Walker, University of Edinburgh*	14:30 – 15:15
New BTA Thyroid cancer guidelines: changes and controversies *Dr Jackie Gilbert, King's College Hospital, London*	15:15 – 16:00
Coffee	16:00 – 16:15
2014: The year in endocrinology *Prof Mark Strachan, Edinburgh Centre for Endocrinology & Diabetes*	16:15 – 17:00
Drinks	17:00 – 18:15
Pre-dinner talk *Prof Graham Leese, University of Dundee*	18:15 – 19:00
Dinner	19:00

Programme – day 2

Saturday 29th November

Chair: Dr Russell Drummond

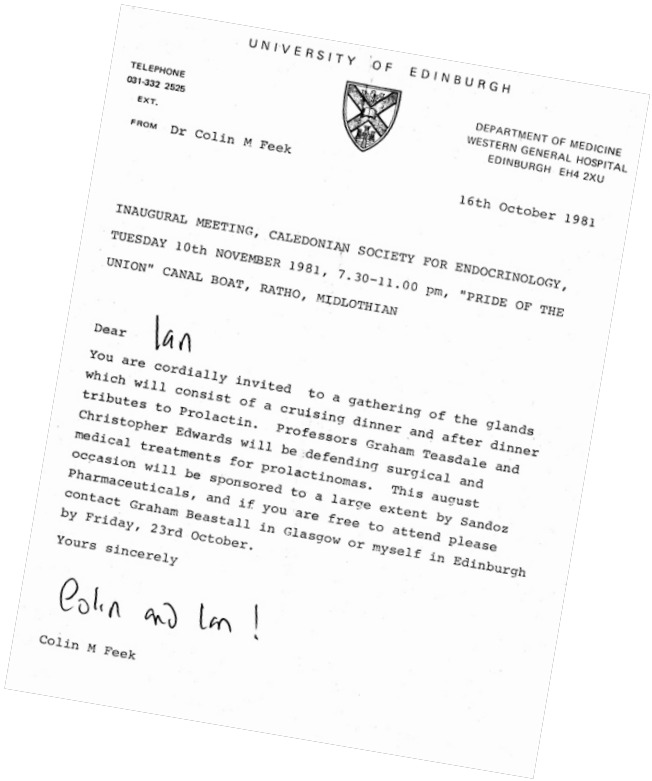
CalSoc AGM	08:45 – 09:00
European hyponatraemia guidelines: an insider's view *Dr Steve Ball, Newcastle University*	09:00 – 09:45
Abstract presentations • *Dr Kate Hughes, University of Edinburgh* • *Dr Gemma Currie, University of Glasgow* • *Dr Scott Mackenzie, University of Edinburgh*	09:45 – 10:45
Coffee	10:45 – 11:00
Abstract presentations • *Dr Kenneth Muir, University of Aberdeen* • *Dr Anna White, University of Glasgow*	11:00 – 11:45
Acquired Disorders of Insulin Action - Autoimmunity and "Late Effects" *Dr Robert Semple, University of Cambridge*	11:45 – 12:30
Lunch and announcement of abstract prizes	12:30 – 13:30
CalSoc Network meeting	13:30

CalSoc: the beginning

CalSoc was founded in 1981 by Ian Hay and Colin Feek, with the principal aim of promoting research and education in the field of endocrinology as stated in article 2 of the constitution:

The society shall promote the study of endocrine diseases by meeting for discussion and demonstration and shall provide for the dissemination of the results of studies undertaken.

The inaugural CalSoc meeting was held on a canal boat on the 10th November 1981 where Professor Graham Teasdale debated with the recently appointed Edinburgh Professor of Medicine, Christopher Edwards, in relation to the optimal management of prolactinoma.



UNIVERSITY OF EDINBURGH

TELEPHONE 031-332 2525 EXT.

FROM Dr Colin M Feek

DEPARTMENT OF MEDICINE
WESTERN GENERAL HOSPITAL
EDINBURGH EH4 2XU

16th October 1981

INAUGURAL MEETING, CALEDONIAN SOCIETY FOR ENDOCRINOLOGY, TUESDAY 10th NOVEMBER 1981, 7.30-11.00 pm, "PRIDE OF THE UNION" CANAL BOAT, RATHO, MIDLOTHIAN

Dear Ian

You are cordially invited to a gathering of the glands which will consist of a cruising dinner and after dinner tributes to Prolactin. Professors Graham Teasdale and Christopher Edwards will be defending surgical and medical treatments for prolactinomas. This august occasion will be sponsored to a large extent by Sandoz Pharmaceuticals, and if you are free to attend please contact Graham Beastall in Glasgow or myself in Edinburgh by Friday, 23rd October.

Yours sincerely

Colin and Ian !

Colin M Feek

Professor Graham Teasdale (above), on the "Pride of the Union", delivering the first CalSoc lecture. First CalSoc invite letter (right).

CalSoc: the beginning

CALEDONIAN SOCIETY FOR ENDOCRINOLOGY

INAUGURAL MEETING 10 NOVEMBER 1981

ORDER OF EVENTS

7.00 pm	Welcome reception at Bridge Inn, Ratho
7.30	Departure of "Pride of the Union"
7.35	Cruising Dinner
9.00	Aqueductal Promenade at Lins Mill
9.15	Piping aboard of Paul Padfield
9.25	Business Meeting
9.30	After Dinner Tributes to Prolactin Chris Edwards and Graham Teasdale
10.10	Discussion
10.30	Initiation of new members
10.40	Even more liquid refreshments
11.00	Return to Bridge Inn, Ratho

Programme for the inaugural CalSoc meeting

CALEDONIAN SOCIETY FOR ENDOCRINOLOGY

1981 MEMBERSHIP

E.A.S. Al-Dujaili	H.A. Kellett
D.T. Baird	F.C. Logue
G.H. Beastall	D.C. McCruden
I.T. Boyle	J.H. McKillop
P.C. Butler	D.J. Marante
P.H. Carr	P.L. Padfield
R.S. Chapman	W.A. Ratcliffe
H.N. Cohen	J.S.A. Sawers
R.A. Cowan	C.G. Semple
D.L. Davies	R.M. Sutherland
R. Eastell	G.M. Teasdale
C.R.W. Edwards	J.A. Thomson
C.M. Feek	A.D. Toft
I. Fogelman	J.J. Walker
B.M. Frier	A.M. Wallace
C.E. Gray	B.C. Williams
I.D. Hay	F.C.W. Wu

CalSoc founding members

Delegates at the 2nd CalSoc meeting (Albany Hotel, Glasgow – April 1982)

Prof Brian Walker – Drug Development

Developing new drugs for diabetes in academia

Excessive activity of glucocorticoids causes obesity, type 2 diabetes, cardiovascular disease and cognitive impairment. The enzyme 11b-HSD1 converts inert cortisone into the active cortisol, thereby amplifying intra-cellular cortisol concentrations and increasing glucocorticoid receptor activation. We proposed that inhibition of 11b-HSD1 would reduce intracellular cortisol levels and hence glucocorticoid action without interfering with the normal stress response, providing a novel therapeutic approach in type 2 diabetes, obesity, and cognitive dysfunction. Proof of concept was confirmed in a series of mouse transgenic models and in humans using a prototype 11b-HSD inhibitor, carbenoxolone.

These findings stimulated a number of pharmaceutical companies to develop selective 11b-HSD1 inhibitors, demonstrating their efficacy in phase II studies in type 2 diabetes. However, a small magnitude of effect on blood glucose, and the challenging regulatory environment that now requires early evidence of vascular protection for diabetes drugs, has halted commercial development of 11b-HSD1 inhibitors for the primary indication of type 2 diabetes.

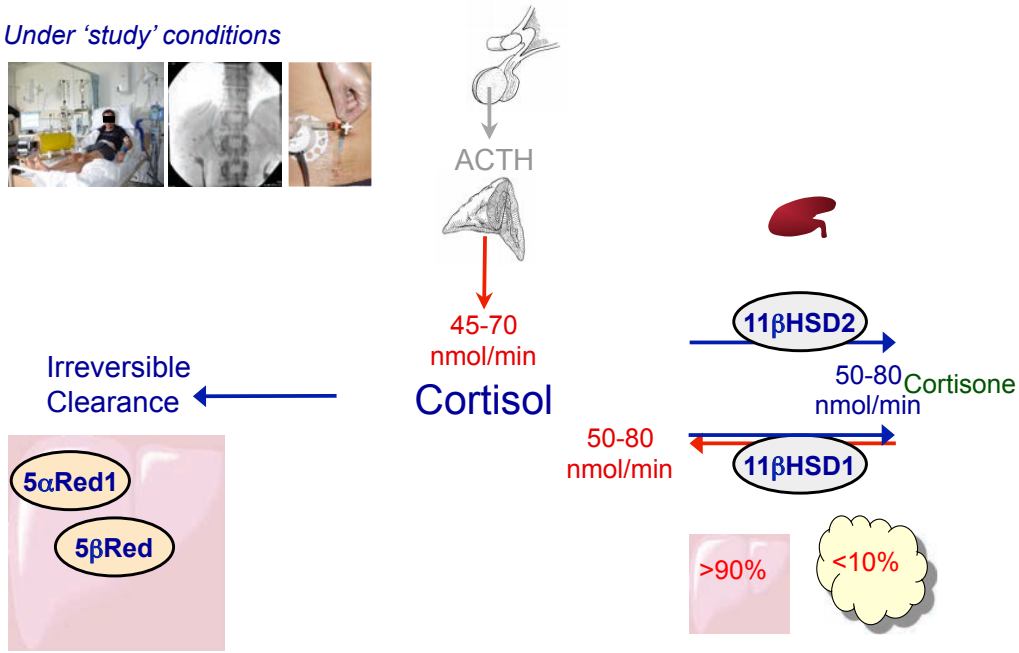
Meanwhile, we created an in-house drug discovery team within the University of Edinburgh, working closely with University researchers and with external contractors. We have developed potent selective 11b-HSD1 inhibitors, shown efficacy in a wide range of pre-clinical models, and have progressed a clinical candidate (UE2343) into first-in-man studies. We used our compounds to demonstrate utility of 11b-HSD1 inhibitors not only to lower blood glucose, but also for additional therapeutic indications, including reperfusion following myocardial infarction and peripheral arterial occlusion. In 2014, we licenced UE2343 to an Australian biotech company with whom we are now developing it in partnership.

Funded by the British Heart Foundation and the Wellcome Trust.

Speaker biography:
Brian Walker obtained his clinical training in Edinburgh and Glasgow and held a MRC Training Fellowship followed by a Senior Fellowship from the BHF from 1996-2006. He is now Professor of Endocrinology and Head of the 170-strong University/BHF Centre for Cardiovascular Science at the University of Edinburgh. His research over the last 25 years has spanned rodent models, experimental medicine, drug discovery, and epidemiology to demonstrate the contributions of endogenous cortisol and exogenous glucocorticoids to cardiovascular disease risk, discover novel determinants of tissue glucocorticoid action, and target these with new drugs. He has edited 3 editions of Davidson's Principles and Practice of Medicine, co-directs the Edinburgh Clinical Academic Track (ECAT) programme, and chairs the Wellcome Trust Clinical Interview Committee. He has supervised >40 PhD students and published >200 original papers which have attracted >12,000 citations.

Drug Development in Diabetes

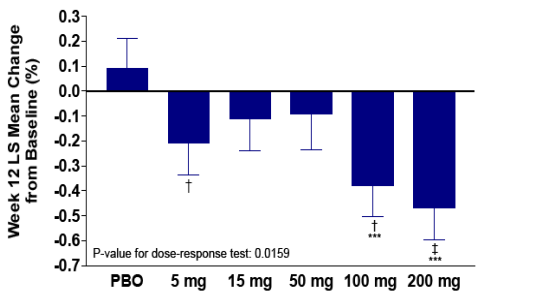
Contributions to the cortisol pool in humans



Efficacy of 11βHSD1 inhibition in patients with type 2 diabetes

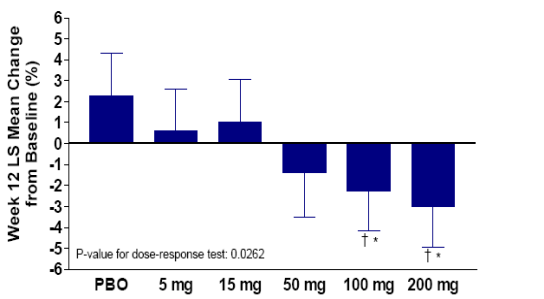
Incyte INCB13739
12 wk Rx
Groups of 46-53
T2DM on Metformin
BMI 25-45

HbA1c



†P<0.05; ‡P<0.01, Week 12 vs. Baseline
***P<0.01, Active vs. PBO

Cholesterol

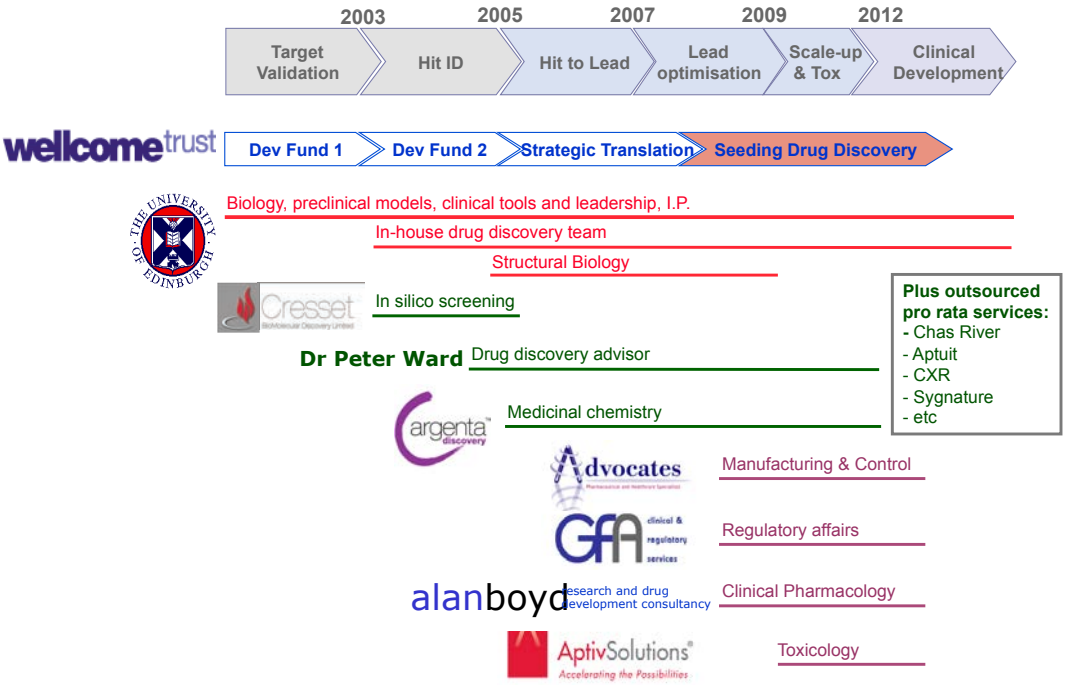


†P<0.05, Week 12 vs. Baseline
*P≤0.1, Active vs. PBO

Rosenstock Diabetes Care 2010

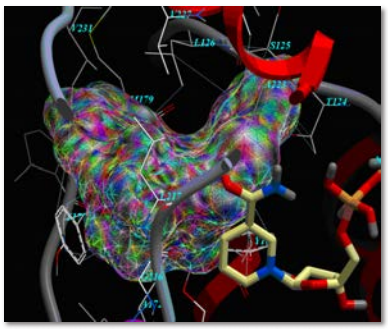
Drug Development in Diabetes

Drug Discovery Team

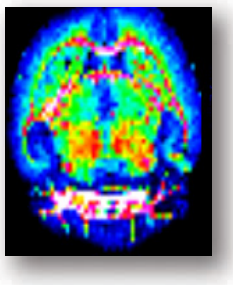


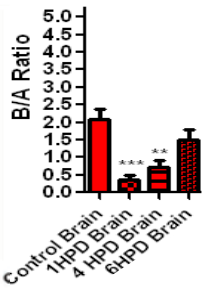
University of Edinburgh 11βHSD1 inhibitors

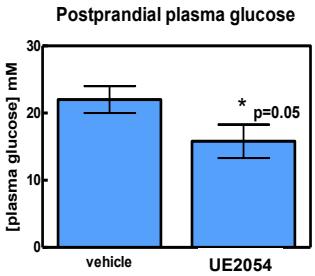
UE2343



UE inhibitor in murine brain by MALDI FTICR-MS imaging

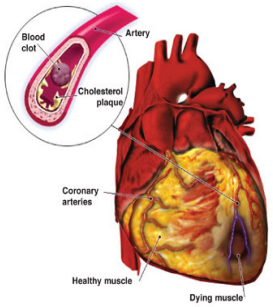


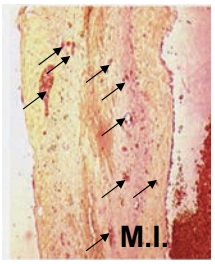


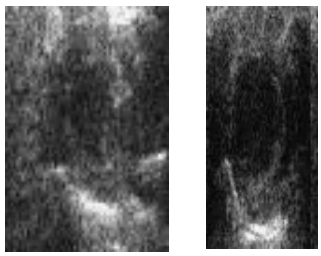


Drug Development in Diabetes

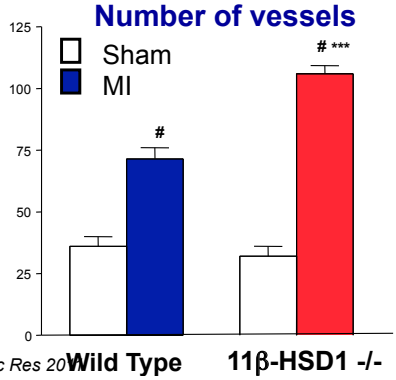
11β-HSD1 and outcome from myocardial infarction



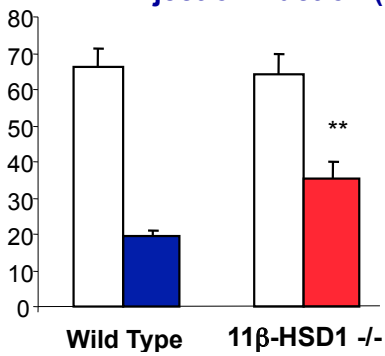




Number of vessels



LV Ejection fraction (%)



Small et al. PNAS 2005
McSweeney et al Cardiovasc Res 20

Dr Jackie Gilbert – Thyroid Cancer

The British Thyroid Association Guidelines for the Management of Thyroid Cancer were revised in 2014, recognising that the principles of personalised medicine are increasingly being applied to the management of patients with thyroid cancer. This edition incorporates recent evidence and promotes the survivorship agenda. There is emphasis on the importance of quality of life and sparing patients with a low risk of recurrence or mortality, unnecessary treatments. Patient engagement and participation in the decision making process is strongly encouraged.

The importance of ultrasound evaluation of the neck being performed by an expert operator, is highlighted and the use of the U1-U5 scoring/grading system is recommended for assessing risk of malignancy and guiding fine needle aspiration cytology.

Post-operative TNM staging predicts the risk of death from disease, and is a valuable indicator of overall prognosis. However, it does not take into account individual responses to treatment, which may alter prognosis. It also does not predict recurrence. The use of a three tier static risk assessment adapted from the American Thyroid Association (ATA) guidelines is recommended to assign risk for persistent or recurrent disease. This is useful for determining whether patients should undergo radioiodine remnant ablation (RRA) and the intensity and method of follow-up in the post-operative setting. Three categories: definite indications for RRA, uncertain indications for RRA and no indication for RRA are defined.

For patients who have undergone a total thyroidectomy with a R0 resection and RRA, a 9–12 months post-RRA stimulated thyroglobulin (sTg) and neck ultrasound (US),
allows potential modification of the initial static risk estimate based on the patient's response to RRA. This generates a dynamic risk category allowing a more personalised approach to
treatment, degree of TSH suppression and frequency of follow-up.

The revised guidelines address the role of new and emerging treatments in advanced disease and additional chapters include microcarcinoma, anaplastic thyroid cancer and survivorship. The patient information leaflets have been revised and extended and formally assessed for readability calculating the Flesch Readability Score (FRS) and the Flesch-Kincaid Grade Level (FKGL). This work has been undertaken in close collaboration with patient-led support organisations.

Reference:

Perros P et al, Clinical Endocrinology 2014, 8, S1, 1-122.

Also available to download: www.british-thyroid-association.org

Speaker biography:

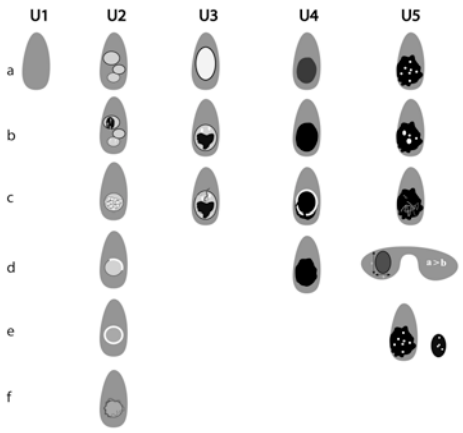
I am a Consultant in Endocrinology and General Medicine at King's College Hospital in London. I am the Lead for Undergraduate Education and Training Lead for Specialist Registrars in Diabetes and Endocrinology. I convene the thyroid strand of the Society for Endocrinology clinical update programme. I am a member of the Thyroid Cancer Guidelines Update Group and the current Secretary of the British Thyroid Association.

Guidelines Development

3rd Edition 2014

- Majority of patients have long life expectancy
- Focus on quality of life
- Survivorship
- Patient engagement and participation in decision making

Ultrasound assessment



- U1-U5 grading system
- Benign USS appearance permits reassurance
- Nodules detected by PET-CT with focal avidity

(BTA guidelines 2014)

Thyroid Cancer

Post operative risk of persistent/ recurrent disease

Low risk	Intermediate risk (any)	High risk (any)
No local/distant metastases	Microscopic tumour invasion (peri-thyroidal soft tissues T3)	Extrathyroidal invasion
All macroscopic tumour resected (R0/R1)	Cervical lymph node metastases N1a/N1b	Incomplete tumour resection (R2)
No locoregional tumour invasion		
No aggressive histological features	Aggressive histology eg. Tall cell, insular or angioinvasion	Distant metastases (M1)

(BTA guidelines 2014)

Radioiodine remnant ablation

NO INDICATIONS (all met)

Tumour ≤1cm uni- or multifocal

Histology classical PTC, follicular variant PTC or FTC

Min invasive, no vascular invasion

No extra thyroidal extension

⇨ RRA NOT RECOMMENDED (2++,C)

DEFINITE INDICATIONS (any)

Tumour >4cm

Gross extra thyroidal extension

Distant metastases

⇨ RRA RECOMMENDED (2++,C)

(BTA guidelines 2014)

Dynamic Risk Stratification

Excellent Response	Indeterminate Response	Incomplete Response
All the following: -Suppressed and stimulated Tg<1mcg/L -Neck USS without evidence of disease -Cross-sectional and/or nuclear medicine imaging negative (if performed)	Any of the following: -Suppressed Tg<1mcg/L and stimulated Tg ≥1 and <10mcg/L -Neck USS with nonspecific changes or stable sub-cm l. nodes -Cross-sectional and/or nuclear medicine imaging with nonspecific changes, not completely normal	Any of the following: -Suppressed Tg≥1mcg/L or stimulated Tg≥10mcg/L -Rising Tg values -Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging
Low risk	Intermediate Risk	High Risk

(Adapted ATA guidelines 2009 and BTA guidelines 2014)

TSH suppression

- Post initial treatment TSH<0.1mU/L (all)
- Post dynamic risk stratification

Response	TSH suppression
Excellent	TSH 0.3-2mU/L
Indeterminate	TSH 0.1-0.5mU/L (5-10 yrs)
Incomplete	TSH<0.1mU/L indefinitely

- "Historical" patients not dynamic risk stratified: TSH<0.1mU/L (5-10 yrs)

(Adapted BTA guidelines 2014)

Prof Mark Strachan – 2014 Review

This has been a tricky topic to prepare for presentation. For starters, it does not exist in any format in my library of slides and so this talk has been created entirely from scratch…never a good place to start! Choosing the papers to include is fraught with difficulty – does one choose the most widely read papers, those in the highest impact journals or those likely to be of most clinical impact? There is surprisingly little overlap between some of these categories. Should it be entirely my own work, or should I seek consensus from other colleagues? The inherent bias of the former is obvious, but one does not wish to trouble colleagues unnecessarily!

In the end, I have opted for a mixed approach and have chosen papers that I have found interesting and which I think will make an impact on our clinical practice. In fact, I shall be starting with some guidelines and not papers, as these are likely to have the greatest impact of all: the European guidelines on hyponatraemia and the British guidelines on the assessment and management of thyroid nodules and thyroid cancer. 2014 saw the publication of two important randomized trials in endocrine oncology: the first report of a new, effective treatment for differentiated thyroid cancer since 1946 and a trial showing therapeutic benefit of somatostatin analogues in non-functioning neuroendocrine tumours. There was even a randomized showing the benefits of Vitamin D supplementation before surgical treatment of hyperparathyroidism…something I thought was completely ludicrous the first time I saw it done.

At the 2014 Associations of Physicians meeting, Morris Brown from Cambridge University gave a fantastic presentation on his work on the genetics of aldosterone-producing adenomas and imaging of these tumours with novel PET isotopes. These studies have the potential to alter the way we look at 'low-renin' hypertension and our diagnostic approach to mineralocorticoid excess.

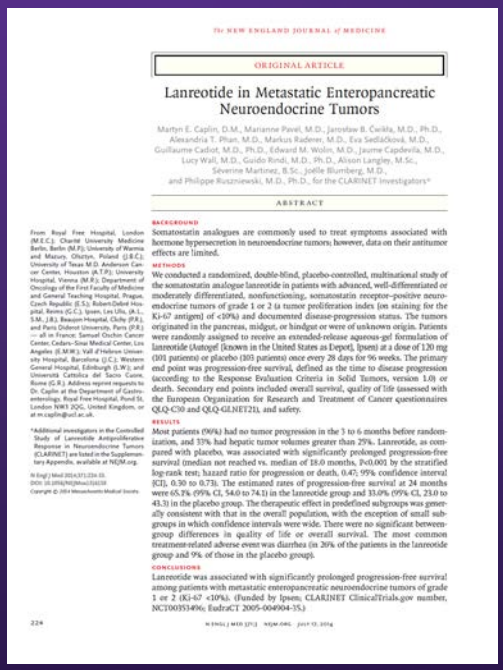
…and to cap off the last 12 months in endocrinology, some of the Glasgow endocrinologists produced a NEJM paper…on a kindred with a mutation in the Prolactin receptor. Their friends in the East were very pleased.

Speaker biography:

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

2014: The Year in Endocrinology

CLARINET Trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jaroslaw B. Ćwikła, M.D., Ph.D., Alessandra T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

ABSTRACT

BACKGROUND

Somatostatin analogues are commonly used to treat symptoms associated with hormone hypersecretion in neuroendocrine tumors; however, data on their antitumor effects are limited.

METHODS

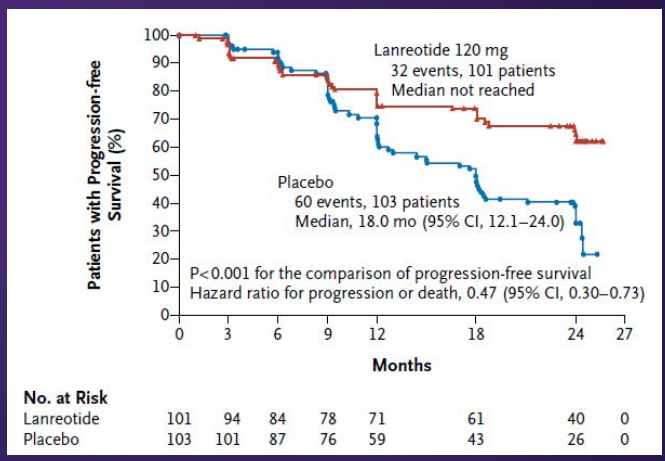
We conducted a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive neuroendocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of <10%) and documented disease-progression status. The tumors originated in the pancreas, midgut, or hindgut or were of unknown origin. Patients were randomly assigned to receive an extended-release aqueous-gel formulation of lanreotide (Autogel® [known in the United States as Depot], Ipsen) at a dose of 120 mg (101 patients) or placebo (105 patients) once every 28 days for 96 weeks. The primary end point was progression-free survival, defined as the time to disease progression (according to the Response Evaluation Criteria in Solid Tumors, version 1.0) or death. Secondary end points included overall survival, quality of life (assessed with the European Organization for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-GINET21), and safety.

RESULTS

Most patients (96%) had no tumor progression in the 3 to 6 months before randomization, and 33% had hepatic tumor volumes greater than 25%. Lanreotide, as compared with placebo, was associated with significantly prolonged progression-free survival (median not reached vs. median of 18.0 months, P<0.001 by the stratified log-rank test; hazard ratio for progression or death, 0.47; 95% confidence interval [CI], 0.30 to 0.73). The estimated rates of progression-free survival at 24 months were 65.1% (95% CI, 54.0 to 74.1) in the lanreotide group and 33.0% (95% CI, 23.0 to 43.3) in the placebo group. The therapeutic effect in predefined subgroups was generally consistent with that in the overall population, with the exception of small subgroups in which confidence intervals were wide. There were no significant between-group differences in quality of life or overall survival. The most common treatment-related adverse event was diarrhea (in 26% of the patients in the lanreotide group and 9% of those in the placebo group).

CONCLUSIONS

Lanreotide was associated with significantly prolonged progression-free survival among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 <10%). (Funded by Ipsen; CLARINET ClinicalTrials.gov number, NCT00353496; EudraCT 2005-004904-35.)



DECISION Trial

Articles

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

Summary

Background Patients with radioactive iodine (131I)-refractory locally advanced or metastatic differentiated thyroid cancer have a poor prognosis because of the absence of effective treatment options. In this study, we assessed the efficacy and safety of orally administered sorafenib in the treatment of patients with this type of cancer.

Methods In this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (DECISION), we investigated sorafenib (400 mg orally twice daily) in patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months. Adult patients (≥18 years of age) with this type of cancer were enrolled from 77 centres in 16 countries. To be eligible for inclusion, participants had to have at least one measurable lesion by CT or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST). Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0·5 mU/L. An interactive voice response system was used to randomly allocate participants in a 1:1 ratio to either sorafenib or matching placebo. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival, assessed every 8 weeks by central independent review. Analysis was by intention to treat. Patients in the placebo group could cross over to open-label sorafenib upon disease progression. Archival tumour tissue was examined for BRAF and RAS mutations, and serum thyroglobulin was measured at baseline and at each visit. This study is registered with ClinicalTrials.gov, number NCT00984282, and with the EU Clinical Trials Register, number EudraCT 2009-012007-23.

Findings Patients were randomly allocated on a 1:1 basis to sorafenib or placebo. The intention-to-treat population comprised 417 patients (207 in the sorafenib group and 210 in the placebo group) and the safety population was 416 patients (207 in the sorafenib group and 209 in the placebo group). Median progression-free survival was significantly longer in the sorafenib group (10·8 months) than in the placebo group (5·8 months; hazard ratio [HR] 0·59, 95% CI 0·45–0·76; p<0·0001). Progression-free survival improved in all prespecified clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of 207 (98·6%) patients receiving sorafenib during the double-blind period and in 183 of 209 (87·6%) patients receiving placebo. Most adverse events were grade 1 or 2. The most frequent treatment-emergent adverse events in the sorafenib group were hand-foot skin reaction (76·3%), diarrhoea (68·6%), alopecia (67·1%), and rash or desquamation (50·2%).

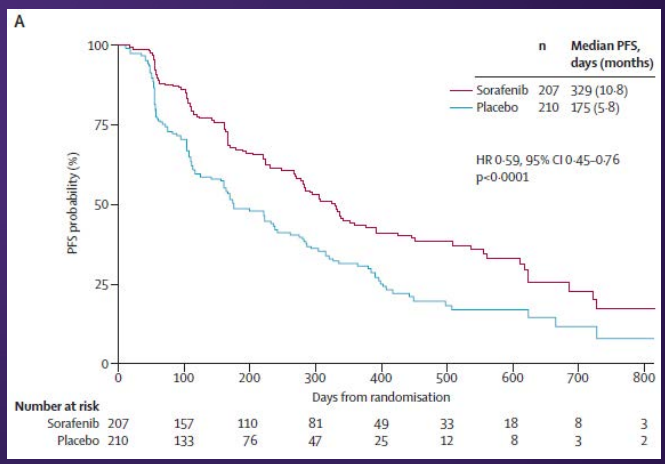
Interpretation Sorafenib significantly improved progression-free survival compared with placebo in patients with progressive radioactive iodine-refractory differentiated thyroid cancer. Our results are consistent with the known safety profile of sorafenib. These results suggest that sorafenib is a new treatment option for patients with progressive radioactive iodine-refractory differentiated thyroid cancer.

Funding Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals (an Amgen subsidiary).

Introduction

Differentiated thyroid cancer accounts for about 95% of all thyroid carcinomas worldwide. Differentiated thyroid cancer arises from aberrant follicular cells and is classified histologically as either papillary, follicular (including Hürthle cell), or poorly differentiated.[1,2] Generally, the cancer can be treated effectively with surgery, radioactive iodine, and a thyroxine therapy.[1,2] However, 7–23% of patients develop distant metastases,[3] two-thirds of whom become refractory to radioactive iodine.[4] These patients have a poor prognosis,[5] and the absence of effective therapy (including chemotherapy) makes their clinical management difficult.[6]

Several genetic alterations have been identified in the molecular pathogenesis of thyroid cancer, most frequently RET–PTC translocations and BRAF[V600E] point mutations in papillary thyroid carcinoma, and RAS point mutations in follicular and poorly differentiated thyroid carcinoma.[7] BRAF[V600E] has been associated with poor pathological features and poor clinical outcomes in papillary thyroid carcinoma, although not in all studies.[7,8] Increased expression of vascular endothelial growth



Dr Steve Ball – Hyponatraemia

Hyponatraemia (serum Na+ <135 mmol/L) is common and associated with increased mortality and morbidity across a range of clinical contexts. Over the last 20 years there have been divergent centre and speciality-specific approaches to the diagnosis and management of the problem. This reflects the diverse clinical settings in which the problem is found; the difficulties translating the evidence-base into clinical practice; and speciality-specific differences in perceived clinical priorities.
This presentation will focus on the development and detail of recent European Guidelines in Hyponatraemia, focusing on methodology, validity and how they may help support practice in specific settings. The talk will balance reference to the guidelines with insights into their development and application.

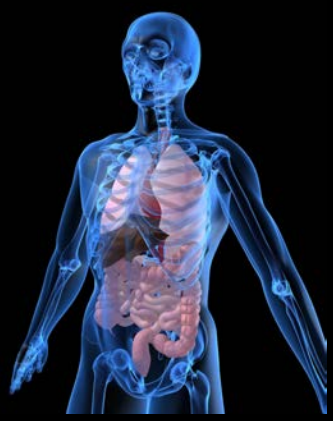
Speaker biography:
Steve studied basic science as an undergraduate at Birmingham University, where he went on to complete a PhD in Molecular Endocrinology before pursuing undergraduate and postgraduate medical studies in London. He completed middle grade training in Diabetes and Endocrinology before spending 2 years in the USA as a Medical Research Council (UK) and Howard Hughes Fellow, subsequently returning to his current post.

Steve combines clinical medicine, research and teaching in Newcastle where he is the head of the Endocrine Unit. He has recently completed work with the multi-disciplinary European Hyponatraemia Guideline Group. Steve has served on the Clinical Committee and Council of the Society for Endocrinology (UK) and is currently a Senior Editor of Clinical Endocrinology.

Hyponatraemia

assessment, management & guidance

- Context
- Guideline development
- Recommendations on diagnosis
- Recommendations on treatment
- Challenges & future work



Newcastle Endocrinology

Hyponatraemia & mortality

epidemiology

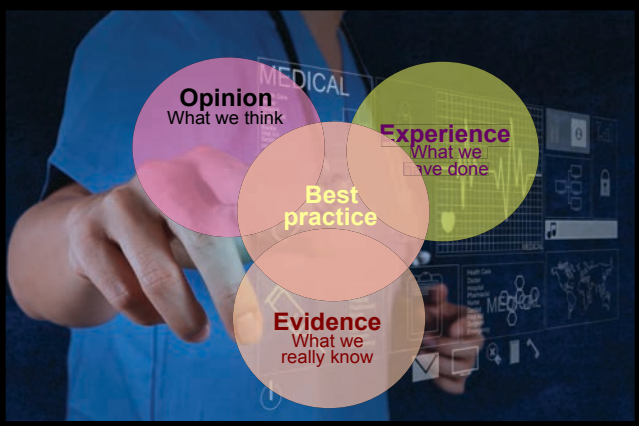
The American Journal of Medicine

Waiker SS, Mount DB, Curhan GC 2009.
Mortality after hospitalisation with mild, moderate & severe hyponatraemia
The American Journal of Medicine 122: 857-865

Newcastle Endocrinology

Hyponatraemia

Evidence in medicine
what determines clinical practice?



Newcastle Endocrinology

Guidance methodology
grade system for recommendations

Recommendation

Strength of recommendation	1	Strong
	2	Weak

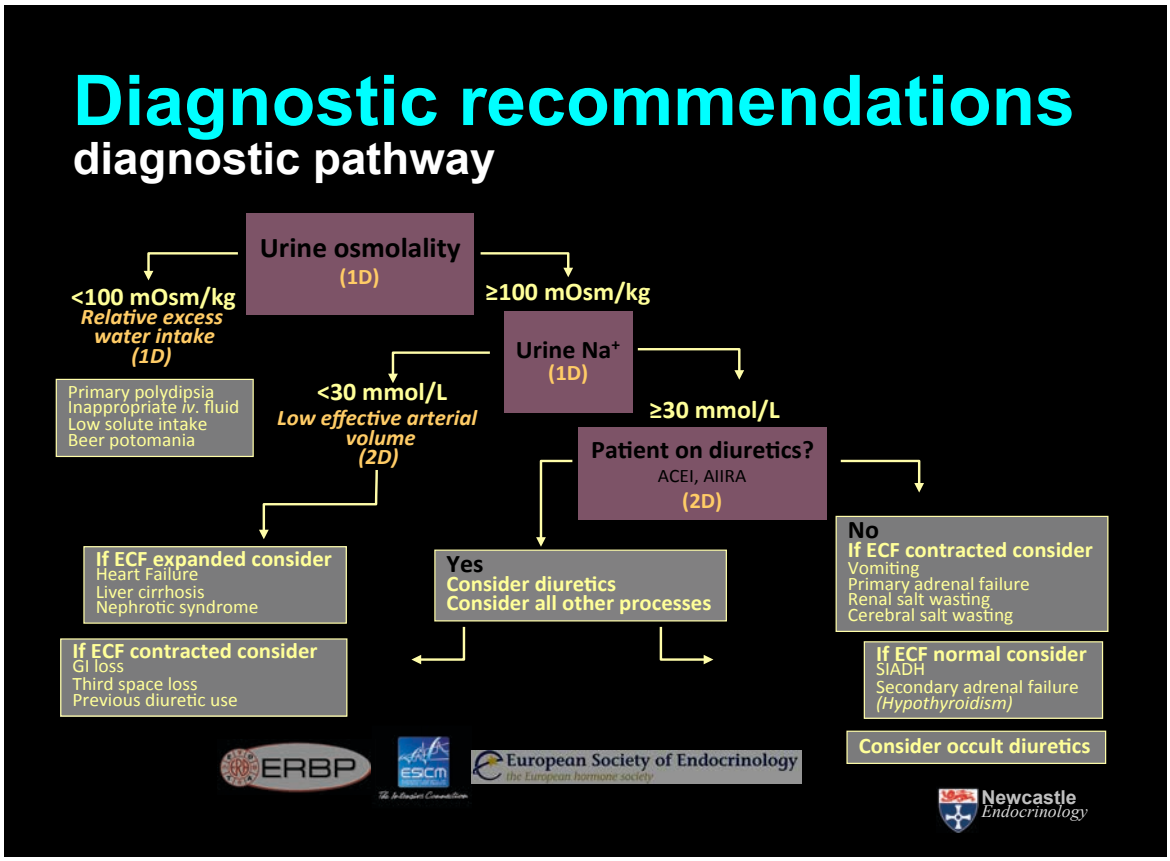
Quality of evidence	A	High
	B	Moderate
	C	Low
	D	Very low

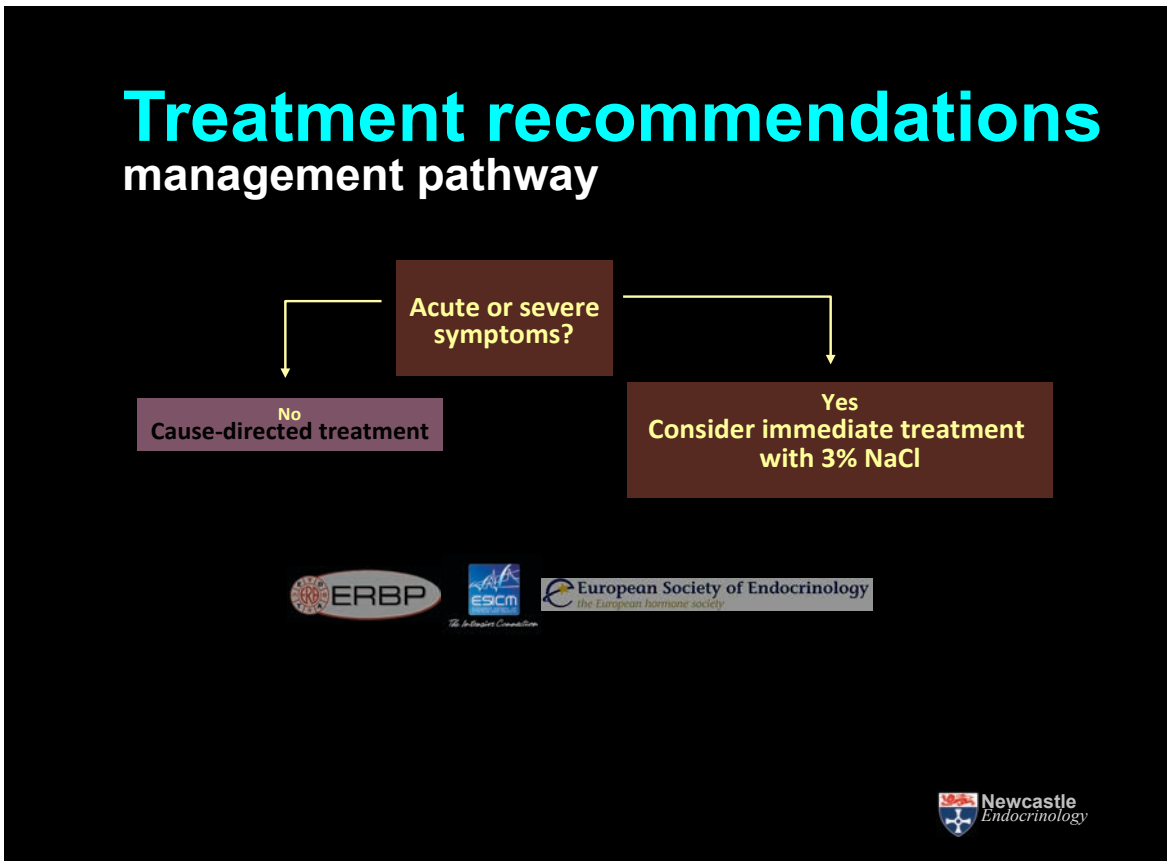
BMJ Guyatt GH *et al.* 2008.
GRADE: an emerging consensus on rating quality of evidence & strength of recommendations
British Medical Journal 336: 924-926.

ERBP ESICM European Society of Endocrinology

Newcastle Endocrinology

Hyponatraemia





Dr Robert Semple – Insulin Resistance

Insulin exerts effects on tissues by activating a complex network of intracellular signalling events. When insulin action goes awry, life-threatening hypoglycaemia or insulin resistant diabetes may ensue. Insulin resistance is also associated with major pathologies including type 2 diabetes mellitus, the fatty liver disease spectrum, atherogenic dyslipidaemia, ovulatory dysfunction, hyperandrogenism and cancer. I shall briefly reveiw known genetic causes of severe insulin resistance, with an emphasis on insulin resistance subgroups that give insights into common disease mechanism. I shall then go on to discuss the presentation, diagnosis and treatment of acquired, severe disorders of insulin action seen as a late effect of childhood irradiation, or caused by anti-insulin or anti-insulin receptor antibodies.

References 1.Parker VE, Semple RK. Genetic Forms of Severe Insulin Resistance: What Endocrinologists Should Know. Eur J Endocrinol. 2013 Sep 12;169(4):R71-80.

2.Parker VER, Savage DB, O'Rahilly S, Semple RK Mechanistic Insights into Insulin Resistance in the Genetic Era Diabetic Medicine 2011 Dec;28(12):1476-86

3.Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S Genetic Syndromes of Severe Insulin Resistance Endocrine Reviews, 2011 Aug;32(4):498-514

4.Malek R, Chong AY, Lupsa BC, Lungu AO, Cochran EK, Soos MA, Semple RK , Balow JE, Gorden P Treatment of Type B Insulin Resistance: A Novel Approach to Reduce Insulin Receptor Auto-antibodies J Clin Endocrinol Metab. 2010 Aug;95(8):3641-7

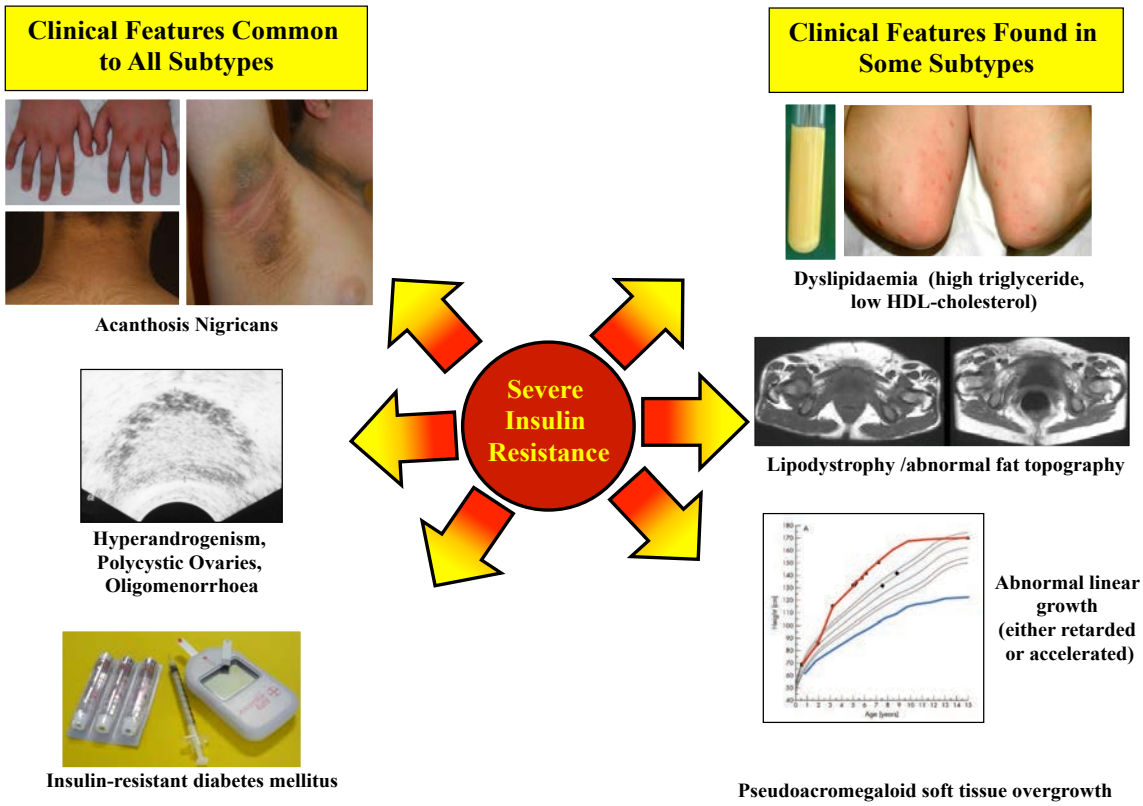
5.Mayson SE, Parker VE, Schutta MH, Semple RK, Rickels MR. Severe Insulin Resistence and Hypertriglyceridemia After Childhood Total Body Irradiation. Endocr Pract. 2012 Nov 27:1-22.

6.Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore). 2009 May;88(3):141-53.

Speaker biography:

Robert Semple is a Wellcome Trust Senior Research Fellow and Honorary Consultant Endocrinologist at the University of Cambridge. He read Biochemistry 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 Stephen O'Rahilly, focussing on genetic regulation of adipose tissue metabolism. For the past 12 years he has focussed on rare disorders of insulin action and growth. His research aims to identify novel genetic defects underlying insulin resistance and related conditions, both to accelerate diagnosis and to enhance treatment of affected patients, and to draw inferences, through physiological study of affected patients, about the pathobiology of common forms of metabolic disease. This work has played a key part in the establishment of a National NHS Severe Insulin Resistance Service in Cambridge.

Insulin Resistance



Principles of Management of Lipodystrophy

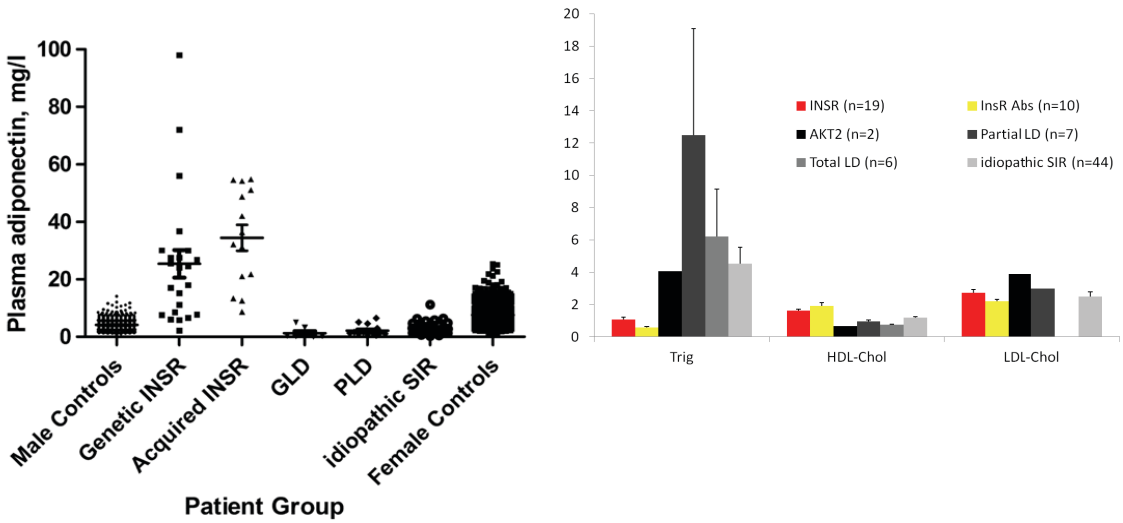
Lipodystrophy = "Adipose Failure"

1. Offload adipose tissue
   - Low fat, hypocaloric diet
   - "obesity therapies" – orlistat, GLP1 agonists, bariatric surgery
   - leptin
2. Maximise insulin sensitivity
   - Exercise
   - Metformin, (pioglitazone)
3. Rationally targeted therapy (for the future)
   - Anti-lipolytic agents in "lipid droplet" LD?
4. Treat dyslipidaemia, hypertension

Therapeutic Options for Insulin Receptoropathy

- Diet
- Metformin
- Insulin, possibly at high doses
- Acarbose, especially if hypoglycaemic
- rhIGF1
- rhleptin
- (Pioglitazone)
- (GLP-1 agonists, DPPIV inhibitors)
- Management of ovulatory dysfunction/hyperandrogenism

Insulin Receptoropathy: Distinct from Prevalent Insulin Resistance



Insulin Resistance

Severe Insulin Resistance – Summary I

	Presenting prepubertally	Presenting postpubertally
Lipodystrophic	**Congenital generalised LD** **Acquired LD** (Familial partial LD)	**Familial partial LD** **Acquired LD** (Congenital generalised LD)
Non lipodystrophic	**Donohue syndrome** **Rabson Mendenhall syndrome** **SHORT syndrome** Dyslipidaemic IR (mostly of unknown cause) (Acquired)	**Generalised or "Type A" IR** Acquired or "Type B" IR **Dyslipidaemic IR** (mostly of unknown cause)
Complex/syndromic	Alström Syn Werner Syn Bloom Syn MOPDII MDP Syn. Mandibuloacral dysplasia Other	Formes frustes?

Summary II: Investigation

Initial

- Fasting glucose, insulin*, OGTT
- Fasting lipids
- Testosterone
- Leptin, adiponectin, IGFBP-1, SHBG
- Clinical photography/MRI/DXA

**Consider type of insulin assay, and ability to pick up native and analogue insulins*

More targeted

- Genetic testing (most commonly LMNA, PPARG, INSR)
- Anti-Ins Abs ("macroIns")
- Anti-InsR Abs
- C3, C4, C3 nephritic factor

Dr Kate Hughes– Abstract

Stress Hyperglycaemia in Hospitalised Patients and Their 3-Year Risk of Diabetes: A Scottish Retrospective Cohort Study

McAllister DA, Hughes KA, Lone N, Sattar N, Mills NL, McKnight J and Wild SH on behalf of the Scottish Diabetes Research Network.

Background

Hyperglycaemia in people without diabetes who have been admitted to hospital is common and associated with adverse outcomes, but the subsequent risk of type 2 diabetes is unknown.

Aim

To describe the association between admission venous glucose level and the subsequent 3-year risk (cumulative incidence) of type 2 diabetes.

Methods

We linked a national register of patients with diabetes (SCI-Diabetes), a national hospitalisation database and regional biochemistry results databases. Patients aged 40 years or older with an emergency admission to hospital between 2004 and 2008 without prevalent diabetes were included. Incident diabetes was defined in patients diagnosed between 31 days and 3 years after the date of discharge from hospital.

The predicted 3-year risk of type 2 diabetes by level of admission glucose, age and sex were obtained from logistic regression models.

Results

87,078 (70.5%) of patients had glucose measured on admission. The 3-year risk of type 2 diabetes was <1% for a glucose ≤5mmol/L increasing linearly to approximately 15% at 15mmol/L. The 3-year risks at 7mmol/L and 11.1mmol/L were 3% and 10% respectively. 1 in 4 and 1 in 40 patients had glucose levels above these respective cut-points. Risk of diabetes also varied according to age and sex.

Conclusions

Patients with glucose levels of 11.1mmol/L on admission to hospital have a 10% risk of type 2 diabetes, should be informed of this risk and offered follow-up testing. We have provided a risk calculator to allow clinicians to estimate the age-sex specific 3-year risk of type 2 diabetes (Glucose on Unselected Admissions and Risk of Diabetes [GUARD]: Type 2 Diabetes Risk Calculator available at www.cphs.mvm.ed.ac.uk/diabetes-risk/).

Reference

Stress hyperglycaemia in hospitalised patients and their 3-year risk of diabetes: a Scottish retrospective cohort study. McAllister DA, Hughes KA, Lone N, Mills NL, Sattar N, McKnight J, Wild SH. PLoS Med. 2014 Aug 19;11(8):e1001708

Dr Kate Hughes– Abstract

Speaker biography:

Kate Hughes is a Clinical Lecturer in Endocrinology at the University of Edinburgh and an Honorary Specialist Registrar in Diabetes and Endocrinology, currently based at the St John's Hospital, Livingston. She graduated from the University of Glasgow in 2001 with Commendation and embarked on her early general medical training in Glasgow. She moved to Edinburgh for her specialist training post in Diabetes and Endocrinology in 2006 and from there undertook a period of research leading to a PhD, under the supervision of Prof Brian Walker at the University of Edinburgh (2007-2010). Since graduating her PhD, Kate has become a Clinical Lecturer and her research-interest is tissue glucocorticoid physiology.

Kate was a member of the YDEF committee between 2013-14 and held the post of Secretary of the Caledonian Society for Endocrinology between 2011-2014 and ran YDF Caledonia 2012, 2013, and 2014, the joint meeting of the Caledonian Society for Endocrinology and YDF in Scotland.

Hyperglycaemia in acute illness: 3-year risk of type 2 diabetes

THE UNIVERSITY of EDINBURGH

University of Glasgow

Glucose, mmol/L

Men

Age, years	6	6.5	7.1	8	9	10	11.1	13	15
45	2%	2%	3%	5%	7%	10%	12%	17%	20%
55	2%	3%	4%	7%	9%	12%	16%	21%	25%
65	2%	3%	4%	6%	9%	12%	15%	20%	24%
75	2%	2%	3%	4%	6%	8%	11%	14%	18%
85	1%	1%	1%	2%	3%	4%	5%	7%	9%

Women

Age, years	6	6.5	7.1	8	9	10	11.1	13	15
45	2%	2%	3%	4%	6%	8%	10%	14%	17%
55	2%	3%	4%	6%	8%	10%	13%	18%	22%
65	2%	3%	4%	5%	7%	10%	13%	17%	21%
75	1%	2%	2%	4%	5%	7%	9%	12%	15%
85	1%	1%	1%	2%	2%	3%	4%	6%	8%

Advice and testing

This tool allows clinicians to interpret (random) hospital admission glucose levels for patients requiring an emergency medical or surgical admission to hospital, and who are not known to have diabetes.

Low risk <5%	Risks comparable to those in the general population. Offer brief advice on the risks of developing diabetes, the benefits of a healthy lifestyle and modifying risk factors.
High-risk 5% to 15%	At elevated risk of type 2 diabetes. Offer a blood test, either fasting plasma glucose measurement following recovery from acute illness, or HbA1c, depending on local guidance.
Very high-risk > 15%	As for high-risk, although clinicians may wish to give a higher priority to reaching a definitive diagnosis prior to discharge from hospital.

This chart indicates the 3-year risk of incident type 2 diabetes based on age, sex and (random) glucose in mmol/L. It was developed and validated in patients who had an emergency medical or surgical admission to a Scottish hospital.
The advice provided above modifies the recommendations provided in National Institute for Health and Care Excellence (NICE) guidance on the risk assessment and identification of patients with type 2 diabetes (www.nice.org.uk/guidance/PH38/) so that they are applicable for patients who have been admitted to hospital with an acute illness.
Patients assigned to the high-risk category based on this tool have a similar risk of type 2 diabetes to patients similarly assigned on the basis of the tools endorsed in the NICE guidance.
This tool was developed and validated in a predominantly white population and has not been validated in groups at increased risk of type 2 diabetes.

This work was funded by The Chief Scientist Office (CSO) of the Scottish Government (Grant number CZH-4-836).
David A. McAllister, Katherine A. Hughes, Nazir Lone, Nicholas L. Mills, Naveed Sattar, John McKnight, Sarah H. Wild (2014). Stress Hyperglycaemia in Hospitalised Patients and Their 3-Year Risk of Diabetes: A Scottish Retrospective Cohort Study. PLoS Med 11(8): e1001708. doi:10.1371/journal.pmed.1001708

PLOS | MEDICINE

CHIEF SCIENTIST OFFICE

SDRN Scottish Diabetes Research Network

Dr Gemma Currie - Abstract

Urinary Proteomics in Diabetic Nephropathy

Biomarker research is a rapidly evolving field and a multitude of markers with potential for early prediction of DN have been described in recent years. Despite this, none have outperformed microalbuminuria to the extent that would support their transition from research tools into clinical practice. It is perhaps unrealistic to expect that in conditions such as DN with complex underlying pathogenic mechanisms a single marker would be adequate for diagnosis, staging and prognosis. Proteomics involves the separation and quantification of peptides in a biological sample, producing a multimarker panel that is resistant to changes in any of its individual components. This technique has attracted attention in recent years as a potentially important tool for early, pre-clinical disease detection. Proteomic analysis can be performed on human tissue, cultured cells or bodily fluids. Urine offers a stable modality for proteomic work as it is stored in the bladder for a number of hours prior to voiding, meaning that any proteolytic processes are complete prior to sample collection. In addition it can be collected non-invasively, obtaining large volume samples is not generally problematic and it can be stored for several years without significant alterations in the proteome(1). Glomerular filtration, lysosomal proteolytic activity at the brush border and tubular absorption all impact upon the peptide composition of urine, consequently urinary peptide analysis has the potential to provide a signature for multiple systemic disease processes. Clinical research has uncovered a variety of potential applications for urinary proteomics as a pre-clinical diagnostic tool in a number of disease processes including coronary artery disease, pre-eclampsia and stroke.

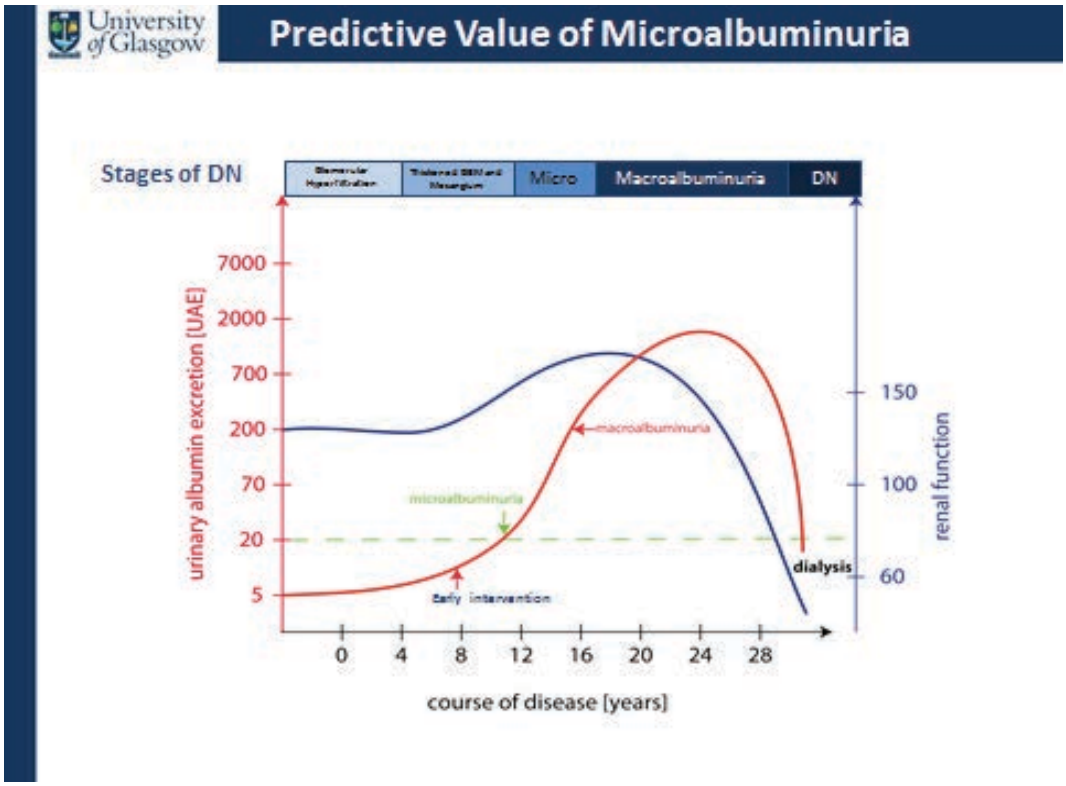
CKD273 is a panel of 273 urinary peptides which shows promise as a tool for early detection of DN. First described in 2010, the panel was initially shown to distinguish between chronic kidney disease (CKD) of any aetiology and healthy controls with 85.5% sensitivity and 100% specificity (2). It has also recently been shown to predict adverse outcomes including death or end-stage renal disease in CKD patients(3). Two further studies have demonstrated the predictive power of CKD273 in identifying diabetic patients at risk of progression to overt DN(4;5). Further to this CKD273 has recently been validated in a multicentre setting. In 165 urine samples obtained from 87 cases of DN and 78 controls at 9 centres worldwide the classifier distinguished cases from controls with high consistency across all centres (areas under the curve ranging from 0.95 to 1.00)(6). A classification factor cut-off of 0.343 was established in the biomarker discovery cohort to highlight individuals “at risk” of later DN (2) and this has been confirmed by other studies (4;5).
Although these initial results are promising, in order for a biomarker to transition from bench to bedside its clinical utility and ability to inform treatment decisions in comparison to the current state-of-the-art needs to be evaluated prospectively in a representative population. With regard to CKD273, this is currently being tested in the multicentre EU PRIORITY study **(www.eu-priority.org).**

(1) Dakna M et al. Biomedical Sciences and Applications 2009; 877:1250-1258.
(2) Good D et al. Molecular and Cellular Proteomics 2010; 9:2424-2437.
(3) Argiles A et al. PLoS ONE 2013; 8(5):e62837.
(4) Zurbig P et al. Diabetes 2012; 61(12):3304-3313.
(5) Roscioni S et al. Diabetologia 2013; 56:259-267.
(6) Siwy J et al. Nephrology Dialysis Transplantation 2014; 0(1):8.

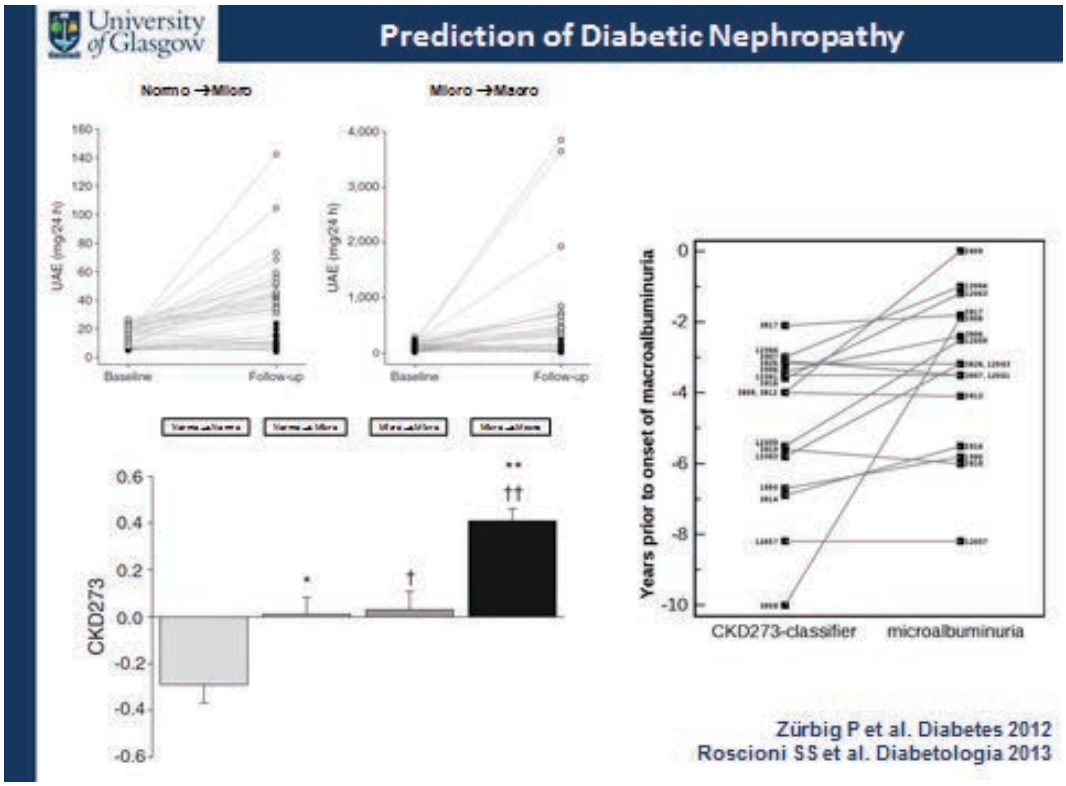
Dr Gemma Currie - Abstract

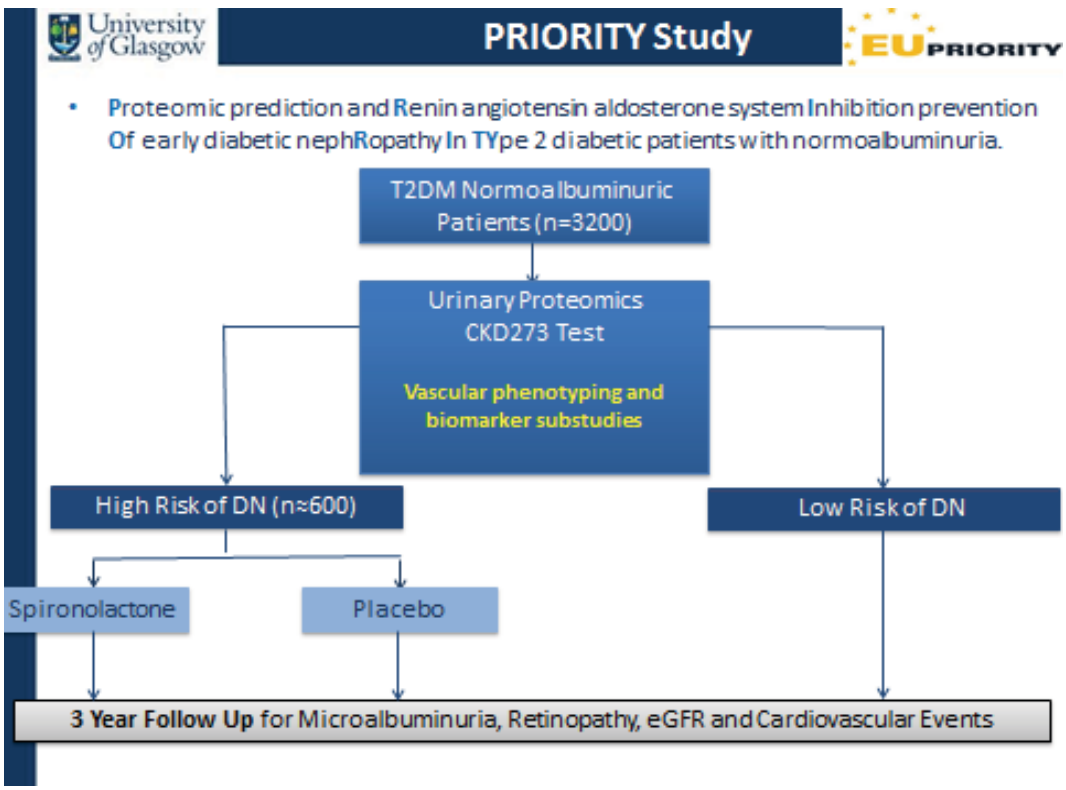
Speaker biography:

I have been a specialty trainee in Diabetes and Endocrinology in the West of Scotland Deanery since 2009 and am currently working as a clinical research fellow at the University of Glasgow BHF Cardiovascular Research Centre under the supervision of Prof Christian Delles, Prof John Petrie and Dr Marie Freel. My research interests include use of urinary proteomics for nephropathy and vascular risk stratification in type 2 diabetes and the role of aldosterone in both healthy and hypertensive pregnancy.



Dr Gemma Currie - Abstract





Dr Scott Mackenzie – Abstract

When two glucocorticoids are better than one: 'relative corticosterone deficiency' in human metabolic syndrome

Scott D Mackenzie, Mark Nixon, Ashley I Taylor, Rebecca M Reynolds, Jennifer L Bolton, Caroline E Hayward, James F Wilson, David I W Philips, Natalie ZM Homer, Ruth Andrew and Brian R Walker

Human plasma contains cortisol (F) and corticosterone (B) at a ratio of ~10:1. Rats and mice produce B but not F because they lack CYP17 in their adrenals. Although B is usually neglected in humans, previous reports suggest differential transmembrane export of F>B by the ATP-binding cassette (ABC) transporter ABCB1 may account for accumulation of B in the CNS, where the ratio of F:B is ~3: 1[1,2]. We recently discovered another transporter, ABCC1, which conversely exports B>F from adipose tissue; deletion of ABCC1 in mice increases intra-adipose accumulation of B but not F. Here we tested in humans the hypotheses that: (i) negative feedback suppression of the hypothalamic-pituitary-adrenal (HPA) axis is disproportionately sensitive to B; (ii) adipose tissue is disproportionately sensitive to F; and (iii) low plasma B, due to increased adrenal CYP17 activity, contributes to impaired HPA axis negative feedback and increased F action in metabolic syndrome.

We validated the stable isotope tracer D8-corticosterone (D8-B) in vitro and determined its kinetics in vivo in healthy men. In a randomised crossover study, patients with Addison's disease (n = 10) who had omitted steroid replacement therapy underwent ramped steady state infusion of D8-B or D4-F over 4.5 hours. Maximum achieved concentrations of F (424 nM) tended to be higher than B (324 nM), but were equally effective at suppressing ACTH (by 28 % vs 23%, respectively). Although markers of peripheral glucocorticoid action (glucose, insulin, glycerol, and non-esterified fatty acids) were not different during B and F infusion, glucocorticoid-responsive transcripts in subcutaneous adipose tissue were much higher following F than B (*PER1* 2.2-fold and *LPL* 1.3-fold; $p<0.05$).
To study associations of CYP17 activity with features of metabolic syndrome, we measured plasma B and F in males (08:30 hrs; n=279) following dexamethasone suppression (0.25 mg) and ACTH (1 µg) stimulation. Glucose tolerance was relatively impaired with higher cortisol (β=0.146, p=0.01) but lower corticosterone (β=-0.056, p=0.05). In a second cohort (n = 2018), we showed that lower B:F ratios was associated with SNPs in *CYP17* which have previously been associated with obesity.
These data support the concept of differential tissue sensitivity to B and F, whereby B suppresses the HPA axis more effectively than it induces adverse effects in adipose tissue. Enhanced CYP17 activity, causing 'relative corticosterone deficiency', may contribute to HPA axis activation and enhanced cortisol action in adipose tissue. Corticosterone therapy might allow control of HPA axis activation without inducing adverse metabolic effects.

1 Karssen, A.M. *et al.* (2001). *Endocrinology*, **142**, 2686-2694.
2 Raubenheimer, P.J. *et al.* (2006) *Clin.Endocrinol.(Oxf)*, **65**, 22-26.

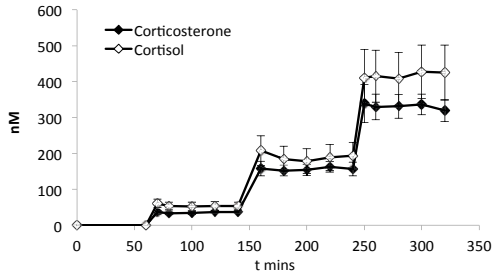
Dr Scott Mackenzie – Abstract

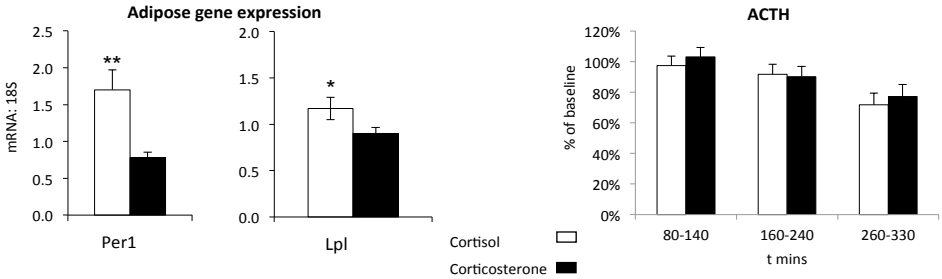
Speaker Biography:

Dr Scott Mackenzie graduated from the University of Glasgow in 2004 and is currently a specialty trainee (ST6) in diabetes and endocrinology in South-East Scotland. He recently completed a clinical research fellowship at the BHF Centre for Cardiovascular Science, University of Edinburgh, sponsored by the Wellcome Trust Scottish Translational Research and Therapeutics Initiative (STMTI). Dr Mackenzie's research examines a novel area of glucocorticoid physiology, assessing the role of the neglected second endogenous glucocorticoid, corticosterone, in human health and disease.

RESULTS

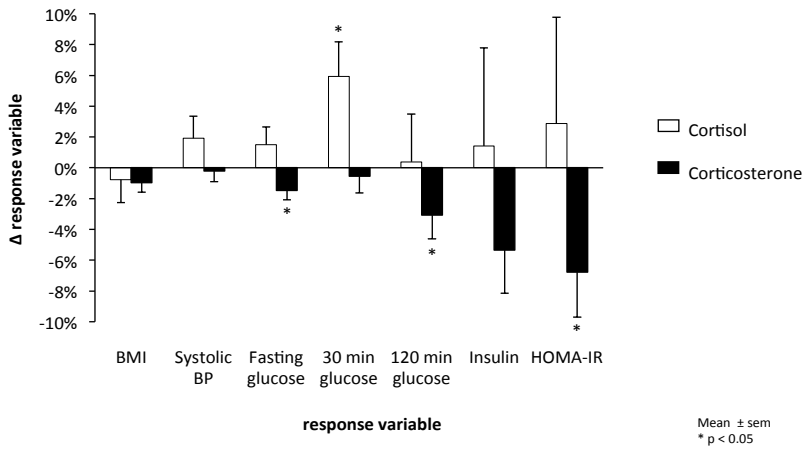
Glucocorticoid infusion in patients with Addison's diseas





RESULTS

Associations of stimulated cortisol and corticosterone with cardiovascular risk factors



Mean ± sem
* p < 0.05

Dr Kenneth Muir – Abstract

GENERATION OF INSULIN PRODUCING CELLS BY REVERSING THE EPITHELIAL TO MESENCHYMAL TRANSITION

Muir, KR. Lima MJ. Docherty, HM. Forbes, SF, Docherty, K
School of Medical Sciences, University of Aberdeen, Aberdeen, UK, and Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, UK.

Since the advent of the Edmonton protocol, Islet cell transplantation has become a viable and effective treatment modality for type 1 diabetes, particularly for individuals with recurrent severe hypoglycaemia. Lack of donor material and the requirement for lifelong immunosuppression are two key factors preventing its widespread adoption.
A replenishable source of insulin-producing cells has the potential to cure type 1 diabetes. Attempts to culture and expand pancreatic beta cells *in vitro,* results in their transition from insulin-producing epithelial cells to mesenchymal stromal cells (MSCs) with high proliferative capacity but devoid of any hormone production. The aim of this research was to determine whether the transcription factor, Krüppel-like factor 4 (Klf4), can induce a mesenchymal-to-epithelial transition (MET) i.e. reversal of the dedifferentiation process that takes place in cell culture.

Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230–238

Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663-676.

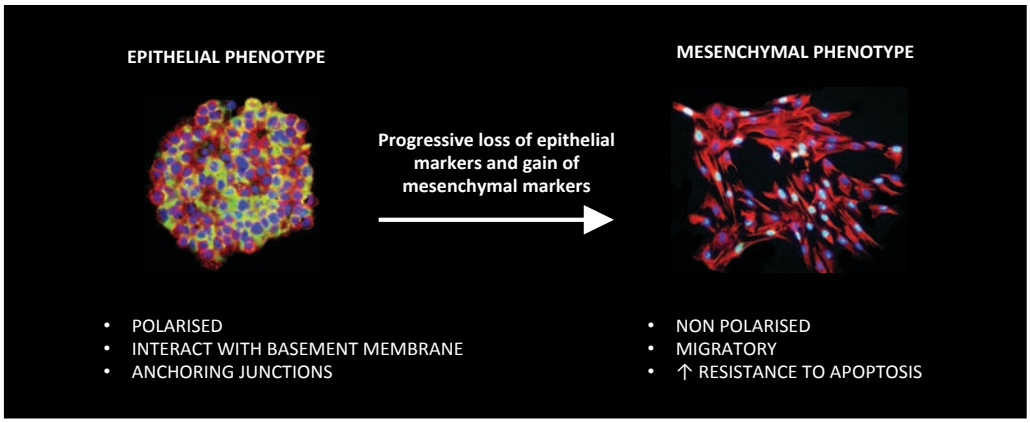
Muir KR, Lima MJ, Docherty HM, Docherty K. Cell therapy for type 1 diabetes. QJM. doi: 10.1093/qjmed/hcu025

Biography
Kenneth Muir graduated in Medicine at the University of Dundee in 2002 having also completed an intercalated degree in Physiological Sciences. He began training in Diabetes and Endocrinology in 2009. Since 2011 he has been working with Professor Kevin Docherty at the University of Aberdeen as part of the Scottish Translational Medicine and Therapeutics Initiative (STMTI) looking at alternative sources of insulin producing cells.

Dr Kenneth Muir – Abstract

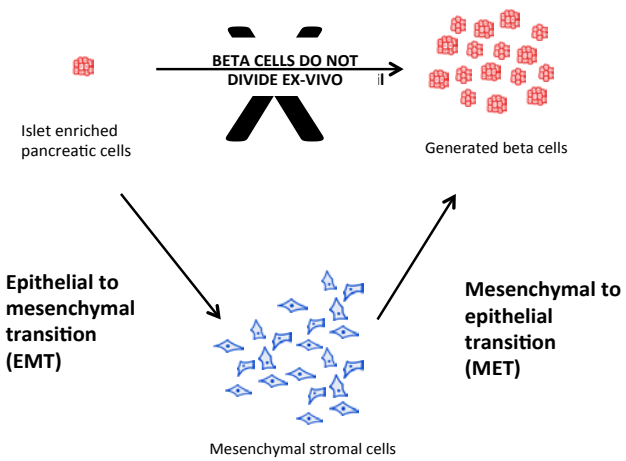
GENERATION OF INSULIN PRODUCING CELLS BY REVERSING THE EPITHELIAL TO MESENCHYMAL TRANSITION

Pancreatic beta cells undergo a process of dedifferentiation in standard adherent cell culture conditions



The resultant cells do not produce insulin but can be significantly expanded in number

If these cells can then be induced to redifferentiate once expanded, by induction of a mesenchymal to epithelial transition, there is potential to generate clinically meaningful numbers of insulin producing cells



Dr Anna White – Abstract

Regulation of the renin angiotensin aldosterone system in adipose tissue by AMP-activated protein kinase

Anna White, Aurelie Nguyen Dinh Cat, Augusto Montezano, Ian Salt, Rhian M Touyz
Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom.

Background
Adipose tissue plays an important role in the development of metabolic disorders including type 2 diabetes. Overactivity of the local renin angiotensin aldosterone system (RAAS) in adipocytes has been implicated in the low level inflammation associated with obesity. Recently, the energy regulator AMP-activated protein kinase (AMPK) has been shown to have anti-inflammatory properties in adipose tissue and therefore we hypothesise that AMPK activators will down-regulate local RAAS effects in adipocytes.

Methods
3T3-L1 (mouse) and SW872 (human) cells were differentiated into adipocytes and stimulated with AMPK activators AICAR (1mM), A769662 (300µM) and metformin (2mM). RT-PCR, immunoblotting and ELISA were used to assess effects on components of RAAS.

Results
Mature adipocytes had two-fold higher mineralocorticoid receptor (MR) gene expression compared to pre-adipocytes. Stimulation of differentiated adipocytes with AICAR, A769662 and metformin activated AMPK as assessed by increased phosphorylation of the AMPK substrate, acetyl-CoA carboxylase. Stimulation of adipocytes with AICAR or A769662, but not metformin, decreased MR gene expression (50% decrease, $p<0.05$). Aldosterone secretion was increased by AICAR in 3T3-L1 (40% increase, $p<0.05$) but not SW872 adipocytes. In SW872 adipocytes however, stimulation with A769662 increased aldosterone secretion by 200% ($p<0.01$) with an associated increase in gene expression of the steroid precursor StAR (1.35 fold increase, $p<0.01$).

Conclusions
We found that adipocyte MR expression was down-regulated by AMPK activators with associated increase in aldosterone biosynthesis. This may reflect a compensatory feedforward response secondary to MR downregulation. Decreased MR signalling by AMPK activators in adipocytes may provide potential metabolic benefit.

Key References

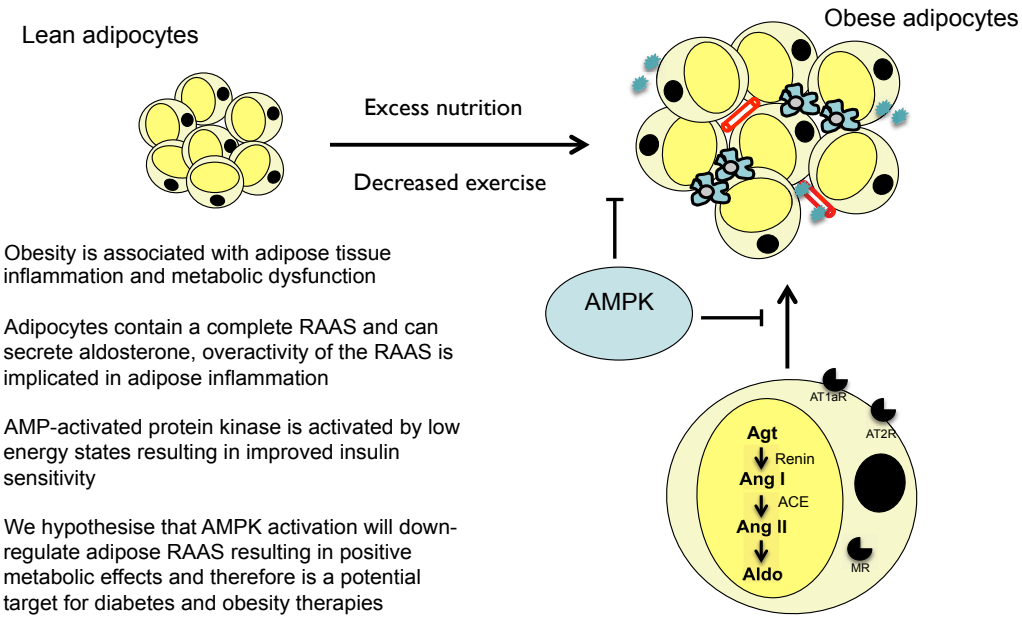
1. Bijland S et al Clin Sci (Lond). 2013 Apr;124(8):491-507.
2. Briones AM et al. Hypertension. 2012 May;59(5):1069-78.
3. Feraco A et al. J Steroid Biochem Mol Biol. 2013 Sep;137:99-106.

Speaker Biography:

I graduated from the University of Glasgow in 2006 and currently hold a specialty training number in Diabetes and Endocrinology in the West of Scotland. I am interested in the associations linking obesity, diabetes and the renin-angiotensin-aldosterone system and am investigating this area at a molecular level. I was awarded the Sir George Alberti Research Training Fellowship from Diabetes UK and am undertaking a translational research project leading to a PhD with supervision from Professor Rhian Touyz and Dr Ian Salt.

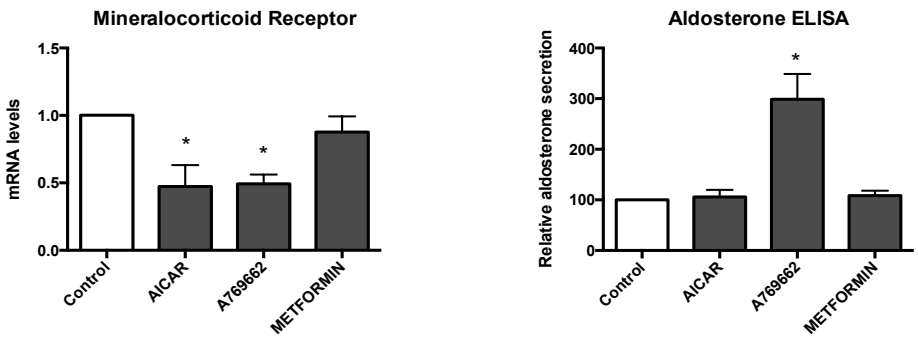
Dr Anna White – Abstract

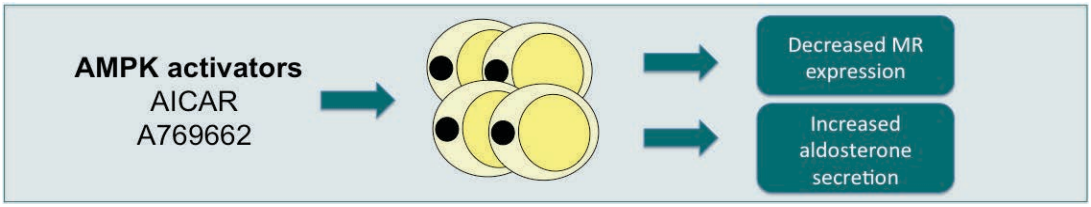
University of Glasgow | College of Medical, Veterinary & Life Sciences



- Obesity is associated with adipose tissue inflammation and metabolic dysfunction
- Adipocytes contain a complete RAAS and can secrete aldosterone, overactivity of the RAAS is implicated in adipose inflammation
- AMP-activated protein kinase is activated by low energy states resulting in improved insulin sensitivity
- We hypothesise that AMPK activation will down-regulate adipose RAAS resulting in positive metabolic effects and therefore is a potential target for diabetes and obesity therapies

University of Glasgow | College of Medical, Veterinary & Life Sciences



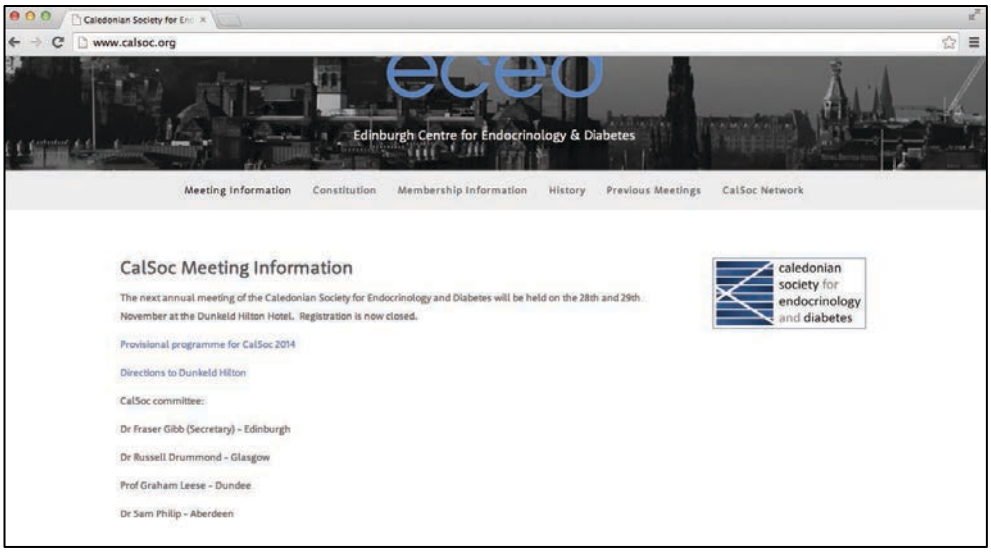


www.calsoc.org

The new CalSoc website currently sits within the Edinburgh Centre for Endocrinology & Diabetes website. It will contain details of further meetings and updates on CalSoc network projects. It also contains an archive of previous meeting programmes, a section on the history of CalSoc and the relevant forms for membership.

We hope to expand and develop the content over time and would welcome any suggestions in this regard.

We are also keen to complete the archive and would welcome any programmes from previous meetings which are not currently on the site.



caledonian society for endocrinology and diabetes

CalSoc 2014 registration, meals and accommodation were covered by unrestricted educational grants from our sponsors: