# Diabetes and endocrinology symposium: genes, environment and emerging therapies

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**ABSTRACT** This symposium provided an update in various areas within the fields of diabetes and endocrinology. Topics included the effects of diet and exercise on the metabolic syndrome and cardiovascular disease; programmes to decrease the incidence of diabetes; updates in the genetics of phaeochromocytoma, obesity and type 2 diabetes; the use of pegvisomant in acromegaly and incretin-based therapies in type 2 diabetes; and the relative strengths and weaknesses of bisphosphonates and HRT as treatment for post-menopausal osteoporosis.

**KEYWORDS** Acromegaly, diabetes, environment, genes, incretins, neuro-endocrine tumours, osteoporosis, phaeochromocytoma

**LIST OF ABBREVIATIONS** Body mass index (BMI), bone mineral density (BMD). computerised tomography (CT), Dipeptidyl Peptidase IV (DPP-IV), FINnish Diabetes RIsk SCore (FINDRISC), glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide (GLP-1), hormone replacement therapy (HRT), magnetic resonance imaging (MRI), multiple endocrine neoplasia 2 (MEN2), Scottish Medicines Consortium (SMC), succinate dehydrogenase (SDH)

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## MODIFYING ENVIRONMENTAL FACTORS IN DIABETES AND CARDIOVASCULAR DISEASE

Dr Alison Kirk, lecturer in sports biomedicine from the University of Dundee, discussed promoting and maintaining physical activity in people with type 2 diabetes. Exercise improves all components of the metabolic syndrome, but patients are often hampered by a lack of guidance, which should be individualised rather than standardised.

In 2004, the Chief Medical Officer suggested that in the absence of a reduction in energy intake, most people need 45–60 minutes of daily activity to prevent obesity,[1] but 80% of people with type 2 diabetes do not achieve this goal. Walking remains a popular and effective means of exercising[2] and individualized pedometer-set goals are more effective than minutes of physical activity goals.[2–3] Activity can also be increased by group exercise classes,[3] ecological approaches, such as signs encouraging stair use, and interpersonal approaches, employing techniques such as goal setting, feedback, stimulus control and relapse-prevention.

Long-term change is difficult to achieve and under-researched, although NICE, the Cochrane collaborative and other authors have reviewed the evidence for different methods of increasing physical activity.[2–4] The Time 2 ACT research trial, which is currently in progress, is designed to assess the effectiveness of a written self-instructional physical activity intervention compared to physical activity consultation and standard care. The issue of who should deliver guidance on exercise remains unresolved.

Dr Michael Burr from the department of epidemiology, statistics and public health at Cardiff University, discussed the potential for diet to modify cardiovascular disease. A systematic review of randomised trials has shown that modifying fat intake alters the risk of cardiovascular disease, with polyunsaturated fats conferring benefit.[5] Cohort studies have identified various other beneficial factors, including, fruit, vegetables, whole grain foods, nuts, moderate amounts of alcohol and dark chocolate. Salt reduction lowers blood pressure and reduces cardiovascular events,[6] while folic acid[7] and antioxidants[8] appear ineffective. However, delivering dietary factors as isolated supplements does not have the same benefits as the consumption of these factors within a balanced diet.

This session closed with the Marjory Robertson lecture, delivered by Professor Jaako Tuomilehto, professor of public health from the University of Helsinki, who discussed the challenges of translating lifestyle advice into clinical practice. Given the relentless increase in the incidence of type 2 diabetes, prevention is of paramount importance. The Finnish Diabetes Prevention Trial[9] was a randomised controlled trial to assess whether lifestyle interventions could prevent or delay the development of type 2 diabetes in middle-aged subjects with impaired glucose tolerance. The study involved dietary counselling sessions every three months, individualised advice on exercise and annual glucose tolerance tests.

The programme achieved improvements in all metabolic parameters with a relative risk reduction of developing diabetes of 58% in the intervention group. The study closed at six years, but differences between the two groups were statistically significant at two years. Other studies have also demonstrated the benefits of lifestyle interventions.[10–12] Patients who may benefit from such interventions can be identified using risk calculations such as the FINDRISC score.[13] In 2003, using the principles of the Finnish Diabetes Prevention Trial,[9] Finland implemented a programme for the prevention of type 2 diabetes in high-risk individuals from five hospital districts (FIN-D2D)[14] with the long-term aim of implementing it nationally.

## HOW GENETICS ALTERS CLINICAL PRACTICE

Professor Eamonn Maher, head of medical and molecular genetics at the University of Birmingham, opened this session with a discussion on the genetics of phaeochromocytoma. While traditional dogma states that 10% of phaeochromocytomas are inherited, the true figure could be closer to 25%.[15] He discussed genetic conditions associated with phaeochromocytoma, including MEN2 (A and B), neurofibromatosis type 1, von Hippel-Lindau disease and SDH subunit mutations. Head and neck paragangliomas can also be associated with germline mutations in SDH. Alternative screening approaches were discussed, including genetic testing for the above conditions in every case of phaeochromocytoma versus targeted screening of higher-risk individuals, such as those less than 40 years old and those with malignant, multicentric or extra-adrenal phaeochromocytomas.

Professor Tim Frayling from the Institute of Biomedical and Clinical Science, Peninsula Medical School Exeter, discussed how gene-chip technology has advanced our understanding of the genetics of type 2 diabetes. Genome-wide association studies have identified six new genes relevant to type 2 diabetes over the last year, including FTO,[16] IGF2BP2,[17] CDKAL1,[17–18] CDKN2A/B,[17, 19] HHEX/IDE[20] and SLC30A8[20]. The FTO gene, located on chromosome 16, increases the risk of type 2 diabetes by increasing fat mass. FTO AA carriers have 67% higher odds of being obese than TT carriers and each copy of the A allele is associated with a 1·4 kg increase in weight.[16]

## EMERGING THERAPIES IN ENDOCRINOLOGY

Dr Peter Trainer, consultant endocrinologist at the Christie Hospital in Manchester, reviewed the established treatments for acromegaly, emphasising that surgery is the gold standard and that dedicated pituitary surgeons are vital for success. Somatostatin analogues are the mainstay of pharmacological treatment, employed either before or after surgery. Dopamine agonists occasionally have a role as adjunctive therapy. Radiotherapy is indicated if surgery does not achieve a cure. Pegvisomant, a growth hormone receptor antagonist, is the latest addition to the pharmacological armamentarium. It achieves biochemical control in approximately 97% patients[21] and is licensed in Europe for patients with resistance or intolerance to somatostatin analogues. Earlier theoretical concerns about tumour growth with this therapy appear unfounded. Cost remains an on-going consideration and pegvisomant has not been approved by the SMC, although it is in use in England and Wales.

Updates in the management of neuroendocrine tumours were discussed by Dr Val Lewington, consultant physician in nuclear medicine at the Royal Marsden Hospital. The importance of a multi-modality approach was emphasised. Both the malignant potential of these tumours and the feasibility of primary resection need to be assessed early on in management, as surgery is the only potentially curative treatment. If surgery is not possible and the tumour has a low proliferation index (as assessed by Ki67 expression), watchful waiting is reasonable. Other useful biochemical prognostic indicators include chromogranin A and B. Localisation and staging may involve endoscopy and endoscopic ultrasound, CT, diffusion weighted MRI and functional imaging. There is a limited role for chemotherapy as neuroendocrine tumours are relatively chemo-resistant. Other treatment options include symptom control with somatostatin analogue therapy, loco-regional treatment such as intra-arterial embolisation and brachytherapy, radio-frequency ablation, interferon alpha and radio-peptide targeted therapy. Researchers are currently turning their attention to anti-angiogenesis drugs and growth factor inhibitors as potential treatments.

## EMERGING THERAPIES IN DIABETES

Professor Anthony Barnett, professor of medicine at the University of Birmingham, discussed the use of incretin-based therapies in the management of type 2 diabetes. Incretins were discovered followed the observation that an oral glucose load produces a greater insulin response than an equivalent intravenous glucose load. Incretins are gut-derived peptides secreted in a glucose-dependent manner. The two main incretins are GLP-1 and GIP. GLP-1 increases insulin release and reduces beta cell workload by slowing gastric emptying, decreasing postprandial glucose secretion and promoting satiety. GLP-1 has a short half-life (two minutes) due to breakdown by the enzyme DPP-IV. Incretin-based therapies currently take the form of injectable incretin mimetics resistant to breakdown by DPP-IV (Exenatide and Liraglutide) which lower HbA1c by around 1%[22] or orally administered DPP-IV inhibitors (Sitagliptin, Vildagliptin and Saxagliptin), which lower HbA1c by 0·5–0·8%.[23] The major advantage of these therapies is that they do not cause hypoglycaemia or weight gain.[22–23] Sitagliptin and exenatide are licensed as add-on therapy to existing oral hypoglycaemic agents. SMC approval has recently been granted to exenatide, while a

verdict is awaited on sitagliptin. GLP-1 mimetics are likely to be introduced at the point of oral agent failure before introduction of insulin, whereas the DPP-IV inhibitors are likely to be used as second or third line oral agents.

## DEBATE: *This house believes that in patients with post-menopausal osteoporosis, HRT is better first line therapy than bisphosphonates*

Prof David Purdie argued the case for oestrogen use in post-menopausal osteoporosis. Recognising the recent concerns over the risk of cardiovascular disease and breast cancer, he stressed that in the Women's Health Initiative study,[24] which investigated the effects of HRT in women with a mean age of 64 years (i.e. around 10 years older than most women treated with HRT in the UK), the absolute risk of complications was low (cardiovascular disease <8/10,000 women years, breast cancer <7/10,000 women years). There is a therapeutic window within 10 years of the menopause when treatment seems safe from the cardio-vascular and breast cancer perspectives, although there is still an increase in stroke. These issues are particularly topical given the recent evidence from the oestrogen-only arm of the Women's Health Initiative study,[25] suggesting that women aged 50–59 treated with oestrogen alone had a lower coronary artery calcified-plaque burden compared to women on placebo. An advantage of HRT is the reduction of fractures irrespective of BMD, while bisphosphonates only prevent fractures in those with low BMD.

Prof Stuart Ralston countered these arguments by pointing out that fragility fractures increase with age and bisphosphonates, unlike HRT, can be used safely in older age. Bisphosphonates won the final vote by a narrow margin, although fewer people voted for bisphosphonates at the end of the debate than at the beginning, suggesting that Prof Purdie had reassured a proportion of the audience about the safety and efficacy of HRT.

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