

Abstracts: diabetes and endocrinology symposium 2007: genes, environment and emerging therapies

ABBREVIATIONS dipeptidylpeptidase-4 (DPP-4), glucagon-like peptide-1 (GLP-1), medullary thyroid cancer (MTC), multiple endocrine neoplasia type 2 (MEN 2), neurofibromatosis type 1 (NF1), somatostatin analogue (SA), succinate dehydrogenase (SDH), von Hippel-Lindau (VHL), growth hormone (GH), Type 2 diabetes (T2D), randomised controlled trial (RCT), computerised tomography (CT), Magnetic resonance imaging (MRI)

SESSION 1 MODIFYING ENVIRONMENTAL FACTORS IN DIABETES AND CARDIOVASCULAR DISEASE

Chairman: Dr R Reynolds, Clinical Senior Lecturer in Endocrinology and Diabetes, Queen's Medical Research Institute, Edinburgh, Scotland

Promoting and maintaining physical activity in people with Type 2 diabetes

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Abstract The evidence that physical activity is an effective therapeutic tool in the management of Type 2 diabetes is well documented. Unfortunately, the majority (approximately 80%) of people with Type 2 diabetes do not achieve the current physical activity recommendations for health of accumulating 30 minutes of moderate-intensity physical activity most days of the week. In comparison to the general population, people with Type 2 diabetes report higher levels of relapse from a physically active lifestyle. Compared to other self-care behaviours they have the lowest self-efficacy for physical activity, and the lowest belief in its effectiveness. Limited research has addressed how best to promote and maintain physical activity in these individuals. Motivational tools such as pedometers and point of choice prompts appear to be effective at stimulating short-term substantial increases in physical activity, but further strategies to maintain physical activity behaviour change are required. Physical activity consultation has demonstrated effective physical activity promotion over periods of up to two years in people with Type 2 diabetes. Future research should identify the longer term effects of this intervention, and the effectiveness of different methods of delivery. Overall, there needs to be a lot more focus on this area of research. Without this, the abundance of research investigating the effects of physical activity on people with Type 2 diabetes is essentially redundant.

Key words Type 2 diabetes, physical activity, relapse from a physically active lifestyle, motivational tools.

Sponsors None.

Declaration No conflict of interest declared.

Macro and micro-nutrients: can diet reduce risk of cardiovascular disease?

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Abstract

Background A very large body of literature deals with the relationship between diet and cardiovascular risk. There is considerable variation in the strength and consistency of the evidence for different dietary factors.

Methods or Theme Cohort studies show associations between diet and disease incidence, but the effects of confounding variables are difficult to eliminate. Randomized controlled trials with health outcomes supply the best evidence, although compliance may be inadequate. Indirect evidence of benefit comes from trials with physiological variables as endpoints.

Modifying fat intake reduces cardiovascular disease incidence, as shown by a systematic review of RCTs.¹ Cohort studies suggest that fruit, vegetables, wholegrain foods, nuts and moderate alcohol intake are protective. Most RCTs of fish and fish oil show benefit, though one study showed an adverse effect.² Supplementary antioxidants and folic acid appear to be ineffective.^{3,4} Salt reduction reduces blood pressure and the incidence of cardiovascular events.⁵

Conclusions Cardiovascular risk can be reduced by diet, though the evidence is not equally strong for all relevant factors. Supplements do not necessarily have the same effects as the foods in which they occur naturally.

References

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Key words Diet, heart disease, cardiovascular disease.

Sponsors None.

Declaration Grants for my research were obtained from The Flora Project, Seven Seas Ltd, Novex Pharma Ltd, and The Fish Foundation.

MARJORY ROBERTSON LECTURE

Chairman: Professor N Douglas, President, Royal College of Physicians of Edinburgh, Edinburgh, Scotland

Finnish diabetes prevention study: translating lifestyle advice into clinical practice

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Abstract Not available at the time of going to press.

SESSION 2 HOW GENETICS ALTER CLINICAL PRACTICE

Chairman: Dr R Lindsay, Clinical Senior Lecturer in Diabetes and Endocrinology, University of Glasgow, Glasgow, Scotland

Genetics of pheochromocytoma

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Abstract

Background Traditionally, pheochromocytoma has been reported to be inherited in ~10% of cases, but molecular genetic testing has revealed a significantly higher frequency of genetic susceptibility e.g., 15–25%, of apparently sporadic cases. The major genetic causes of pheochromocytoma are VHL disease, MEN 2, NF1 and SDH subunit mutations. Von Hippel-Lindau disease is

characterised by the development of retinal and central nervous system haemangioblastomas, renal cell carcinoma, pheochromocytoma and pancreatic islet cell pancreatic cancers. However, germline VHL tumour suppressor gene mutations may also cause familial and sporadic non-syndromic pheochromocytoma. Pheochromocytoma in MEN 2 tends to present after MTC. Pheochromocytoma occurs in only a small minority of patients with NF1 and a clinical diagnosis of NF1 can be made in such cases. Both pheochromocytoma and head and neck paragangliomas (glomus tumours) may be associated with germline mutations in succinate dehydrogenase (mitochondrial complex II) subunits (SDHB, SDHC and SDHD). Germline mutations in SDHB or SDHD may present at familial or sporadic pheochromocytoma. Succinate dehydrogenase mutations are more commonly associated with extra-adrenal pheochromocytomas and there is an increased frequency of malignant tumours in SDHB mutation carriers. Molecular genetic studies should be instigated in all cases of familial, early onset or multicentric pheochromocytoma. Although there is not general consensus on the criteria for testing apparently sporadic non-syndromic cases, testing should be prioritised in those with malignant or extra-adrenal tumours and younger onset cases of adrenal pheochromocytoma. Indications for testing include a younger age at onset (e.g. <40 years) and extra-adrenal or malignant pheochromocytomas. In addition, a detailed personal and family history may uncover evidence of VHL disease or MEN 2 and so provide an indication for specific gene testing. A family history of head and neck paraganglioma will highlight a likely SDHB or SDHD mutation (particularly if there are the parent-of-origin effects suggestive of an SDHD mutation).

Conclusions Families in whom a germline mutation is identified should be offered appropriate further investigation and management. However, protocols for the long-term surveillance of SDHB and SDHD mutation carriers are still 'a work in progress'.

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Key words Pheochromocytoma inherited syndrome genetics.

Sponsors Cancer Research UK.

Declaration No conflict of interest declared.

Genetics of Type 2 diabetes

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Abstract Existing approaches to T2D prevention and/or treatment have limited impact, due to our poor understanding of the aetiological mechanisms. The identification of genetic variants that increase T2D risk is a powerful way to improve aetiological understanding. Well-powered genome-wide association studies now offer a unique chance to identify type 2 diabetes genes and increase our understanding of this disease. Results from the first wave of genome-wide association scans for T2D are now emerging, and mean that there are now nine genes with a confirmed role in T2D risk.¹⁻⁶ These include newly identified variants at FTO, CDKALI, CDKN2A/B, IGF2BP2, HHEX/IDE, and SLC30A8. The rapid identification of these six loci contrasts sharply with the limited progress achieved with all previous efforts in the field (three robustly-identified loci – PPARG, KCNJ11 and TCF7L2). Risks conferred by these loci range from odds ratios of 1.12 to 1.4 for each risk allele inherited. The T2D-association at FTO is driven entirely by an effect on body mass index, a result confirmed in a total of 39,441 participants ($p=4 \times 10^{-35}$). For the FTO variant, 16% of the population carrying two minor alleles are 2.8 kg heavier than the 35% of common allele homozygous carriers and DEXA scans in 6,000 children show that this effect is entirely due to altered fat mass.

The challenge now is to find more genes that alter diabetes and obesity risk, and to translate these findings into clinical practice. This is most likely to come from our improved understanding of the aetiology, but as more genes are found, it may be possible to tailor treatments to people with different sets of risk genotypes.

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Key words Type 2 diabetes, risk alleles, genome wide associations FTO, CDKALI, CDKN2A/B, IGF2BP2, HHEX/IDE, SLC30A8 PPARG, KCNJ11, TCF7L2 .

Sponsors None.

Declaration No conflict of interest declared.

Recent developments in the therapy of acromegaly

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Abstract The acromegaly treatment algorithm has changed dramatically in the last ten years with the introduction of new pharmaceutical agents, improvements in surgical outcomes and a move away from radiotherapy. While transsphenoidal surgery remains first line treatment for most patients, the choice of surgeon is crucial with cure rates being two-fold better and complications fewer with experienced surgeons. When used as primary therapy SAs have been shown to be effective at both achieving biochemical control and inducing tumour shrinkage in a significant minority of patients. Primary therapy with SAs is expensive as it implies life-long treatment and recent data suggested that lowering GH levels with non-curative, debulking surgery improves the prospects of subsequent SA treatment achieving the desired therapeutic goals. Pegvisomant is a GH receptor antagonist that is capable of achieving biochemical disease control in virtually every patient. Unlike all other modes of therapy this agent does not attempt to inhibit GH secretion but rather blocks GH action. A concern at the beginning of clinical trials in 1997 was that it would, in a manner akin to Nelson's syndrome, induce pituitary tumour growth but the data to date are reassuring. Pegvisomant is licensed for patients in whom the disease remains active despite conventional therapy including SAs and data are emerging that it is effective in such patients whether used as sole therapy or in combination with SA.

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resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. *EJE* 2005; **152**:61–6.

Key words Acromegaly, pegvisomant, octreotide, lanreotide, GH, IGF-I.

Sponsors None.

Management of neuroendocrine tumours

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Abstract

Background The term 'neuroendocrine tumour' covers a broad spectrum ranging from indolent, non-secreting tumours to aggressive malignancies. The variable presentation and long natural history of neuroendocrine disease pose significant diagnostic and management difficulties.

Diagnosis Diagnostic imaging advances including endoscopic ultrasound have improved the sensitivity of pre-operative localisation of solitary tumours. Functional imaging using radiolabelled tumour specific molecules is increasingly used to compliment conventional anatomical imaging such as CT and MRI in initial staging and monitoring treatment response in advanced disease. Useful prognostic indicators include the biochemical markers chromogranin A and B, specific patterns of hormone hypersecretion and histopathological assessment of proliferative index (Ki-67).

Management Surgery remains the only curative option for patients with solitary tumours. The majority of patients present relatively late, however, and management options in advanced disease range from watchful waiting to combination chemotherapy. Somatostatin analogue therapy delivers durable symptom palliation for patients with functionally active tumours. This may be combined with loco-regional treatment such as hepatic artery embolisation or radiofrequency ablation in patients with symptomatic hepatic metastases.

Targeted radionuclide therapy using high activity radiolabelled peptides is a well tolerated systemic approach for patients with disseminated disease. Indications for treatment include symptom breakthrough despite maximal somatostatin analogue therapy and/or evidence of tumour progression.

Clinical trials using anti-angiogenesis drugs, which exploit the vascularity of neuroendocrine tumours, and growth factor inhibitors are in preparation.

Conclusions The rarity and clinical complexity of metastatic neuroendocrine tumours demand close multidisciplinary collaboration in specialist centres. The optimal timing and potential side effects of treatment in relatively indolent disease should be considered on an individual patient basis.

References

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Key words Neuroendocrine tumour, somatostatin analogue, targeted radionuclide therapy.

Sponsors None.

Declaration I am a member of the UK Neuroendocrine Tumour Network which is supported by educational grants from Novartis Oncology and Ipsen Limited.

SESSION 3 EMERGING THERAPIES IN ENDOCRINOLOGY

Chairman: Dr M Strachan, Consultant Physician, Western General Hospital, Edinburgh, Scotland

Incretin hormones as targets in the management of Type 2 diabetes

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Abstract

Background Type 2 diabetes is a progressive disease with dual defects of insulin resistance and islet cell dysfunction, the latter involving both the pancreatic beta cell (producing insulin) and alpha cell (producing glucagon). The incretins are gut-derived hormones secreted in response to nutrient ingestion. They potentiate insulin secretion from pancreatic beta cells and reduce glucagon production from the alpha cells. The main hormone of interest is GLP-1 which also has additional effects on slowing gastric emptying and appetite reduction. GLP-1 is reduced in T2D. The incretins are rapidly degraded by the enzyme DPP-4.

Conclusions Incretin based therapies include the incretin-mimetics which are GLP-1-like and DPP-IV resistant (exenatide and liraglutide) and DPP-4 inhibitors which inhibit degradation of DPP-4 (e.g. vildagliptin, sitagliptin). Exenatide has recently been licensed and is given by twice daily subcutaneous injection. It is associated with improvement in glycaemic control, reduced risks of hypoglycaemia compared with insulin, and reduced body weight. Nausea is a common side-effect.

The first DPP-4 inhibitor (sitagliptin) has recently been licensed. These agents are taken orally, providing reductions in HbA_{1c} which appear to be sustained over at least one year are weight neutral and with reduced risks of hypoglycaemia compared with sulphonylureas and insulin. Sitagliptin is licensed for combination therapy with metformin or a glitazone and has a good tolerability profile. The place in therapy of these agents will be discussed.

Key words Type 2 diabetes, insulin resistance, islet cell dysfunction, insulin, incretins, GLP-1, DPP-4 inhibitors, exenatide, liraglutide, vildagliptin, sitagliptin.

Sponsors None.

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BOOKS YOU SHOULD READ

The silent takeover. Global capitalism and the death of democracy

Noreena Hertz
ISBN 0099410591
Arrow Books; 2000 £8.99

The corporation. The pathological pursuit of power

Joel Bakan
ISBN 139781845291747
Constable; 2004 £6.99

Few can be unaware of what is called the global economy, but how many are aware of the main players in this economy, their interaction, and the way in which they influence all our lives? These two books, each well worth reading, give an interesting and alarming insight into this global economy, and the extent to which it has reduced our control over our lives. The authors are well qualified to give us their views. Noreena Hertz was Associate Director of the Centre of International Business and Management at the Judge Institute of the University of Cambridge, and Joel Bakan was professor of law at the University of British Columbia with a distinguished legal career behind him.

Hertz describes the main components of the global economy, the structure within which capitalism operates, and the ways in which they interact. This includes national governments, the World Trade Organisation (WTO) and other international organisations,

the money markets and large international corporations, with the powerful Western economies having a dominant influence. National governments theoretically control the rules of international trade through the WTO, but corporations have become so powerful that they can coerce national governments and exercise considerable influence on the WTO. National governments often appear unwilling or unable to defend their electorates against the corporations, and to this Hertz attributes current disenchantment with politics and particularly politicians. Consumers and shareholders are the Achilles heels of the corporations, and opposition to corporations comes increasingly from them. These groups are themselves alliances of the better off, and how far they will be an influence for good remains to be seen.

Bakan turns his attention specifically to the corporations, and he does not like what he sees. He points out that they have no other function, in law or in practice, beyond maximising the

profits of their shareholders. Indeed, he points out that a corporation can only act legally for social benefit when that is commensurate with its duty to pursue profit. This has given rise to organisations devoid of loyalty, lacking any sense of obligation, and intent on observing the letter rather than the spirit of regulations designed to protect communities. The result is that corporations feel no obligation to the countries in which they originated, in which they operate, or to those they employ. Bakan points out, however, that just as corporations exist by virtue of law, they can also be changed by law, and he produces a cogent case for effecting such change.

Health and the provision of medical services depend greatly on economic factors, and doctors will want to understand what determines the welfare of their patients and the help they can be given. These two books can contribute to that understanding.

Niall Finlayson
Director of Communications, RCPE

