

SYMPOSIUM ABSTRACTS

43rd ST ANDREW'S DAY FESTIVAL SYMPOSIUM: DIABETES AND ENDOCRINOLOGY

4 and 5 December 2003

4 December 2003

SESSION 1

OSTEOPOROSIS

Chair: Professor J Seckl, Professor of Molecular Medicine, Western General Hospital, Edinburgh

IS OSTEOPOROSIS SIMPLY A FUNCTION OF AGEING? SH Ralston, Professor of Medicine and Bone Metabolism, University of Aberdeen

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Abstract

Osteoporosis is a common disease characterised by reduced bone mineral density (BMD), architectural deterioration of bone tissue and an increased risk of fracture. Genetic factors play a major role in the pathogenesis of osteoporosis, reflected by the fact that a positive family history of osteoporosis is a strong risk factor for low BMD and fragility fracture. Osteoporosis affects both sexes, but the disease is about three times more common in women due to increased rates of bone loss after the menopause.

Family-based studies and cohort studies have been performed to try to dissect the relative contribution of genes and environment to osteoporosis susceptibility, focusing mainly on BMD as a surrogate marker.

Current evidence suggests that genetic factors account for up to 85% of the population variance in peak bone mass, and it is considered that several genetic variants of modest effect account for this contribution. Genome-wide scans have identified several quantitative trait loci for the regulation of BMD, but most of the causal genes within these loci remain to be identified. An exception is Bone Morphogenic Protein 2 (BMP-2), which was recently identified as an osteoporosis susceptibility gene by a positional cloning effort in the Icelandic population.¹ The collagen type I alpha 1 gene (COL1A1) is another susceptibility gene for osteoporotic fractures that was identified by the candidate gene approach. Polymorphisms of COL1A1 predict fractures by mechanisms that are independent of BMD, through effects on bone quality and mineralisation.²

Tremendous advances have been made in understanding

the genetic and environmental determinants of BMD over recent years, but more work needs to focus on the determinants of fragility fractures. This is particularly true in older people, who suffer an exponential rise in hip fracture rates from the age of 70 onwards by mechanisms that are largely independent of reductions in BMD. It is likely that these fractures are partly related to frailty and increased susceptibility to falling, but other factors such as reduced bone quality may also contribute. For the most part, these fractures cannot be prevented by current anti-osteoporosis treatments,³ emphasising that we still have a lot to learn about the pathophysiology of fractures and the most effective means of preventing them.

References

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- 2 Mann V, Hobson EE, Li B *et al.* A COL1A1 Sp1 binding site polymorphism predisposes to osteoporotic fracture by affecting bone density and quality. *J Clin Invest* 2001; **107**:899–907.
- 3 McClung MR, Geusens P, Miller PD *et al.* Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2002; **344**:333–40.

Key words: Bisphosphonates, collagen, genetics, osteoporosis.

Sponsors: None.

Declaration: Professor Ralston holds patents on the use of COL1A1 polymorphisms and other genetic markers to identify individuals at risk of osteoporotic fracture.

DIAGNOSIS AND MANAGEMENT – WHO NEEDS A DXA SCAN?

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Abstract

The UK has adopted the opportunistic case-finding approach to identify patients at risk for osteoporosis.

Thus, a prior history of fractures or the long-term use of glucocorticoids would prompt the referral for a dual-energy X-ray absorptiometry (DXA) scan. The diagnosis of osteoporosis would then be based on a result for hip BMD that falls more than 2.5 standard deviations below that found in young subjects.¹ The monitoring of treatment would then be carried out, with lumbar spine BMD measurements made annually until the result exceeded the least significant change.²

The following methods will be considered as alternative approaches to DXA of the spine and hip: BMD of the forearm or heel by DXA; quantitative ultrasound of the heel or fingers; and biochemical markers of bone turnover, e.g. C- and N-telopeptide of type I collagen and deoxypridinoline.

There may be some situations in which treatment is likely to be effective without a DXA measurement, such as vertebral fracture and high-dose glucocorticoids in a woman over the age of 65 years. Peripheral DXA (forearm and heel) and quantitative ultrasound may be useful when used in a triage approach; however, this approach still requires the use of hip DXA in about 50% of cases. These approaches cannot be used at present because we do not know the T-score threshold below which our treatments are effective. Bone turnover markers have proven to be useful for the monitoring of treatments for osteoporosis.³ The bone resorption markers, such as the N-telopeptide of type I collagen, decrease maximally by three months on treatment and exceed the least significant change in about two-thirds of patients with our commonly used treatments, and the change in bone turnover markers is related more closely to the reduction in vertebral fracture risk than to the change in BMD.

The DXA scan is required in most patients in order to characterise their fracture risk and to identify those patients most likely to benefit from treatment. Peripheral devices such as ultrasound may be used in conjunction with a DXA service using a triage approach. The response to treatment may be assessed using further measurements of spine BMD, but bone resorption markers are likely to prove more useful.

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Key words: Bone mineral density, bone turnover, osteoporosis.

Sponsors: None.

Declaration: No conflict of interest declared.

SESSION 2

DEBATE

Chair: Dr P Padfield, Consultant Physician, Western General Hospital, Edinburgh

IS ALDOSTERONE EXCESS REALLY A COMMON CAUSE OF HYPERTENSION? (AGAINST)

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Abstract

Aldosterone is a key cardiovascular hormone that can cause cardiovascular damage. Whether primary hyperaldosteronism is a common cause of hypertension is controversial. Autonomous production of excessive aldosterone from the adrenal gland is a recognised form of secondary hypertension, but has been considered to be rare in unselected cases. The advent of diagnosis based on the aldosterone/renin ratio (ARR) has led to the publication of several studies that suggest that the condition is much more prevalent than previously recognised. Management based on this test in unselected patients would be hugely expensive, and the ARR is as yet poorly validated. In most instances, a high ARR merely diagnoses low-renin essential hypertension, which responds well to treatment with conventional thiazide diuretics or spironolactone. Response to an aldosterone antagonist does not in itself equate to the presence of primary aldosteronism. It might be better to regard patients with hypertension and a raised ARR as one part of the spectrum of essential hypertension rather than as a specific diagnostic entity.

Key words: Aldosterone, aldosterone/renin ratio (ARR), cardiovascular damage, hyperaldosteronism, hypertension, spironolactone, thiazide diuretics.

Sponsors: None.

Declaration: No conflict of interest declared.

SYMPOSIUM ABSTRACTS

MARJORIE ROBERTSON LECTURE

Chair: Dr NDC Finlayson, President, Royal College of Physicians of Edinburgh

WHAT NOW WITH LUMPS IN THE THYROID? DOES SIZE MATTER?

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Abstract

Thyroid nodules are common in the general population.¹ Most are benign and of no clinical significance. Approximately 5% of palpable nodules are malignant.² Easy access to imaging of the neck with ultrasound and other modalities has led to an increased diagnosis of small thyroid nodules of epidemic proportions.

An understanding of the pathophysiology and natural history of thyroid nodules is paramount for appropriate and speedy management of these patients.

Fine needle aspiration biopsy is the investigation of choice for palpable thyroid nodules.³ Questions remain with regards to selection of patients for biopsy and follow-up.⁴

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Key words: Thyroid cancer, thyroid nodules

Declaration: No conflict of interest declared.

SESSION 3

ENDOCRINE EYE DISEASE

Chair: Professor S Lightman, Professor of Clinical Ophthalmology, Moorfields Eye Hospital, London

THYROID EYE DISEASE: WHO NEEDS TO SEE AN OPHTHALMOLOGIST?

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Abstract

Thyroid eye disease is a relatively rare condition, with approximately 5,000 new cases per annum in the UK.¹ Of these, 5% have severe, potentially sight-threatening, disease,^{2,3} but many patients with less severe forms of thyroid eye disease benefit from medical and surgical treatment. Identifying those patients who require referral is a challenge to all clinicians managing patients with thyroid diseases.

Effective medical and surgical treatments are available for patients with thyroid eye disease that can enhance quality of life. A brief clinical assessment of patients with thyroid eye disease can identify those who will benefit from referral to a specialist centre.⁴

References

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Key words: Thyroid eye disease.

Sponsors: None.

Declaration: No conflict of interest declared.

5 December 2003

SESSION 1

NEW ASPECTS OF DIABETES AND INSULIN RESISTANCE

Chair: Professor J Connell, Professor of Endocrinology, Western Infirmary, Glasgow

THE GENETIC SEQUENCER WILL SEE YOU NOW!

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Abstract

Access to a DNA sequencer is not traditionally part of diabetes care. However, it does offer the best way to confirm a diagnosis of monogenic diabetes that is found in about 2% of diabetic patients (40,000 people in the UK). Making a diagnosis is important if it is required for appropriate treatment. We need to ensure that monogenic diabetes is recognised by clinicians and provide an evidence base for the best treatment of the specific subgroups.

The different genetic subtypes of monogenic diabetes have discrete clinical phenotypes, and these need to be recognised by all diabetes clinicians. These clinical features include both the pancreatic phenotype (e.g. degree of hyperglycaemia, response to oral glucose tolerance test (OGTT)) and the extra-pancreatic phenotype (e.g. in the renal cysts and diabetes (RCAD) syndrome characterised by cystic renal disease, uterine abnormalities and gout in hepatocyte nuclear factor-1beta (HNF-1 β)).

Treatment decisions in patients with monogenic diabetes can be informed by the molecular genetic diagnosis. In HNF-1 α , maturity-onset diabetes in the young (MODY), there is clear randomised controlled trial evidence of pharmacogenetics with patients showing marked sensitivity to the hypoglycaemic effect of sulphonylurea therapy. The reduction in fasting glucose with gliclazide is four-fold greater than that seen in body mass index (BMI) and glycaemia matched Type 2 patients. This reflects both increased insulin secretion with sulphonylureas and increased insulin sensitivity. Patients with HNF-1 α mutations who have been on insulin since diagnosis (mean duration 25 years) frequently improve control on sulphonylureas.

The DNA sequencer can therefore inform both diagnostic and treatment decisions, and its appropriate use in the diabetic clinic is an important new skill for the diabetologist.

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Key words: Diabetes, DNA sequencer, extra-pancreatic phenotype, hepatocyte nuclear factor-1 alpha (HNF-1 α), increased insulin sensitivity, maturity-onset diabetes in the young (MODY), monogenic diabetes, pancreatic phenotype, sulphonylureas.

Sponsors: None.

Declaration: No conflict of interest declared.

A LINK BETWEEN DIABETES AND ENDOCRINOLOGY? THE POLYCYSTIC OVARY SYNDROME

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy to affect women of reproductive age. It is the major cause of both anovulatory infertility and hirsutism, but it is also associated with a characteristic metabolic abnormality, central to which is insulin resistance and hyperinsulinaemia. Women with PCOS are at increased risk of developing Type 2 diabetes in later life. This review explores the possibility of common aetiological factors, the impact of metabolic disturbance on reproductive function and long-term health and approaches to the management of the metabolic consequences of PCOS.

We have used a candidate gene approach to identify susceptibility loci for PCOS, particularly in genes affecting the secretion and action of insulin. In parallel, we have performed physiological studies of the effects of insulin or insulin resistance on ovarian and cardiovascular function. The effects of dietary intervention and insulin-sensitising agents on reproductive and metabolic function have been explored.

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Polycystic ovary syndrome has a major genetic basis. Polymorphism of the variable-number tandem repeat (VNTR) in the regulatory region of the insulin gene may confer susceptibility to PCOS, but nutritional factors also have a significant impact on reproductive and metabolic phenotype. Lifestyle changes and insulin-sensitising agents (such as metformin) improve reproductive function and are likely to reduce the risk of developing Type 2 diabetes and cardiovascular disease.

Polycystic ovary syndrome and Type 2 diabetes appear to share common aetiological factors: they are both complex traits characterised by important interactions between genetic and environmental (nutritional) factors. Lifestyle changes should be the main interventional aim in at-risk subjects in order to reduce the incidence of Type 2 diabetes and cardiovascular events.

References

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Key words: Insulin resistance, lifestyle changes, polycystic ovary syndrome, Type 2 diabetes.

Sponsors: Research sponsored by the Medical Research Council (MRC).

Declaration: No conflict of interest declared.

SESSION 2

OBESITY

Chair: Professor B Walker, BHF Senior Research Fellow and Professor of Endocrinology, University of Edinburgh

EVIDENCE-BASED THERAPY FOR OBESITY: CAN WE STEM THE TIDE?

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Abstract

In Scotland, 62% of men and 54% of women have an overweight/obesity problem and the numbers are rising. Already, 0.6% of men and 1.9% of women are morbidly

obese (body mass index (BMI) >40). Most worrying is that 8% of boys and 7% of girls are obese. The outcome of this rising tide of obesity is a rise of Type 2 diabetes, now increasingly diagnosed in obese children. The Scottish Intercollegiate Guidelines Network (SIGN) guideline *Obesity in Scotland: Integrating Prevention with Weight Management*¹ was published in November 1996 but there has been no systematic review since then. Health technology assessment (HTA) has funded a review of both conventional anti-obesity therapy and surgical (bariatric) treatment. This lecture concerns itself mainly with non-surgical therapy, but will discuss some aspects of the surgical review.

Thirteen electronic databases searched up to April 2001. Hand searching was undertaken in 20 obesity journals, with trialists and pharmaceutical companies contacted. The criteria included only RCTs in those over the age of 18 years where there was at least a one-year follow-up and patients were defined as obese. Reports of 2,163 RCTs were reviewed and eventually 84 were accepted.

Six hundred Kcal deficit diets reduce weight for at least 36 months, but this was not sustained for 60 months. Low-caloric diets (1,000–1,600 Kcal/day) had no added advantage to either 600 Kcal deficit or low-fat diets. Very low-calorie diets (<1,000 Kcal/day) were not beneficial as compared with low-calorie diets over 12 months. Protein-sparing modified fast, where carbohydrate content is <40g/day irrespective of calorie intake, offered no advantage to low-calorie or very low-calorie diets over 12 months. Exercise is beneficial if undertaken with a 600 Kcal deficit diet, especially after one year and if it is maintained longer than diet alone. Behavioural therapy is most beneficial in the first year, but benefit is lost by 36 months unless reinforced. Whereas family therapy is beneficial, group therapy has no added advantage. Orlistat and sibutramine, the two prescribable anti-obesity medicines in UK, are effective in enhancing weight loss in addition to diet, but with different effects on the lipid and blood pressure co-morbidity measurements. Surgery is most effective for weight loss long term in selected patients, with reduction in co-morbidity and the need for treatment of these especially in diabetes. The overall analysis will be discussed in relationship to co-morbidity improvements.

Six hundred Kcal deficit diets are effective for at least three years, with exercise having a prolonged beneficial effect. Anti-obesity medicines play a role in the management of the obese, as does bariatric surgery in selected patients.

References

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Key words: Bariatric surgery, behavioural therapy, BP, diet, exercise, lipids, obesity, orlistat, QUALY, sibutramine

Sponsors: Funded by NHS HTA.

Declaration: No conflict of interest declared.

Editor's note

Readers may be interested to note that a new SIGN guideline on childhood and adolescent obesity was published in May 2003. While this initially began as a review of SIGN 8, the subject area of the guideline was refined, so as to concentrate specifically on childhood and adolescent obesity rather than presenting an updated review on obesity in general.

LILLY LECTURE

OBESITY: IS IT IN THE BRAIN OR THE FAT CELL?

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Abstract

The current pandemic of obesity primarily reflects an imbalance between calorie intake and energy expenditure. The consequences are a rising incidence of the complications of obesity, including Type 2 diabetes, dyslipidaemia and hypertension, perhaps subsequently of ischaemic heart disease. Unfortunately, current treatments are either poorly taken up (diet, exercise), relatively ineffective (drugs) or impracticable for the large numbers of subjects involved (barostatic surgery). In this presentation, the scale of the problem and its consequences will be addressed. Potential future approaches to obesity will be discussed. This will include an examination of recent insights into appetite regulation by novel circulating hormones as well as increased knowledge of brain neuropeptides systems. The importance of the emerging biology of the adipocyte will be detailed. Parallels between the rare Cushing's syndromes of circulating glucocorticoid excess and the common insulin resistance or 'Metabolic Syndrome' will be considered and the emerging importance of tissue sensitivity to steroids discussed. In particular, the potential importance of 11beta-hydroxysteroid dehydrogenase type I as a tissue amplifier of glucocorticoid action in the adipocyte and hepatocyte will be addressed.

Key words: 11beta-hydroxysteroid dehydrogenase type I, calorie intake, Cushing's syndromes, diet, dyslipidaemia, energy expenditure, exercise, glucocorticoid excess, hypertension, 'Metabolic Syndrome', obesity, Type 2 diabetes.

Sponsors: None.

Declaration: No conflict of interest declared.

SESSION 3

THERAPEUTIC ASPECTS OF DIABETES MELLITUS

Chair: Professor B Frier, Consultant Physician and Honorary Professor of Diabetes, Royal Infirmary of Edinburgh

FUTURE THERAPEUTIC OPTIONS: MORE THAN INJECTING INSULIN?

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Abstract

For the past 80 years' subcutaneous (SC) injections have been the only route of delivery of insulin therapy to patients with diabetes. During this time, numerous attempts have been made to explore alternative routes for systemic insulin administration. However, thus far, no feasible other way of non-invasive insulin delivery has been developed. Dermal insulin application does not result in a reproducible and sufficient transfer of insulin across the highly efficient skin barrier. The dream of an 'insulin tablet' has also not become a reality, the main problem being digestion and a lack of a specific peptide carrier system in the gut.

Nasal insulin application was considered for a number of years as a potential method, because of the rapid absorption of insulin across the nasal mucosa. However, relative bioavailability was low and required use of absorption enhancers and, more importantly, the metabolic effect lasted too short to be of clinical usefulness. To date, the most promising alternative route of insulin administration is the pulmonary delivery of insulin by inhalation, which will probably lead to a practically usable system within the next few years. For maximal rate of absorption, insulin must be applied deep into the lung – i.e. into the alveoli. A considerable number of inhalers (in combination with appropriate insulin formulations), which are asked to generate insulin particles with an appropriate size for pulmonary delivery, are currently in the clinical phase of development. The pharmaco-dynamic effects of insulin formulations administered via the lung are comparable to, or even faster than, those of SC-injected regular insulin or rapid-acting insulin analogues. The relative biopotency of inhaled insulin in most cases is approximately 10%: the dose of insulin administered must be ten-fold higher than with SC application. The published results of clinical trials thus far indicate that metabolic control is comparable with that of SC insulin therapy. Side-effects like the development of insulin antibodies in many patients and the development of lung fibrosis in some patients have been reported from these human trials. However, the relevance of these observations is currently investigated in additional clinical trials.

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A number of novel therapeutic agents have been developed or are under development for the treatment of patients with diabetes, including amylin, insulin sensitisers (e.g. dual agonists of peroxisome proliferator-activated receptor (PPAR) α and PPAR γ), glucagon-like peptide-1 (GLP-1) analogues and derivatives (e.g. exendin-4), beta-3 receptor agonists and potassium channel openers). Currently available therapeutic agents have a number of substantial limitations, the most important of which is their inability to prevent disease progression owing to declining beta-cell function and their subsequent lack of long-term efficacy. For example, Amylin, a second beta-cell hormone that is co-secreted with insulin in response to nutrient stimuli, acts as a neuroendocrine hormone that complements the effects of insulin in postprandial glucose regulation through several centrally mediated effects. These include regulation of gastric emptying and suppression of postprandial glucagon secretion. Prandial SC injections of pramlintide, a synthetic analogue of Amylin, resulted in clinical studies in which it was injected in addition to the current insulin regimen, in reduced postprandial glucose excursions and decline of HbA1c in Type 1 and Type 2 diabetic patients and in conjunction with weight loss rather than weight gain. The intestinal peptide hormone GLP-1 has received much interest because of its potential to treat patients with Type 2 diabetes. Subcutaneous injection of GLP-1 increases insulin secretion, decreases glucagon secretion and delays gastric emptying – all of which contribute to lower blood glucose levels. However, GLP-1 has proven difficult to use therapeutically because it is rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV). This may be overcome by inhibiting DPP-IV or using GLP-1 analogues that are resistant to DPP-IV degradation. In clinical trials, SC administration of GLP-1 analogues decreased blood glucose to near-normal levels in most patients with Type 2 diabetes. Thus, agents that utilise the insulinotropic properties of GLP-1 may be viable treatment options for patients with Type 2 diabetes in the future.

It appears that after several decades of research a feasible alternative route for insulin administration is within reach, for the first time. In addition, novel antidiabetic agents will become available soon.

Key words: Amylin, beta-3 receptor agonists, diabetes, dipeptidyl peptidase IV (DPP-IV), exendin-4, glucagon-like peptide-1 (GLP-1), inhaled insulin, insulin sensitizers, nasal insulin, peroxisome proliferator-activated receptor (PPAR α and PPAR γ), potassium channel openers, pramlintide, pulmonary delivery, subcutaneous injections of insulin.

Sponsors: None.

Declaration: The author has cooperated with a large number of companies active in the areas of research mentioned.

BLUE-SKY THINKING: WHAT'S NEXT?

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Abstract

Type 1 diabetes is mostly a consequence of autoimmune beta-cell loss, while Type 2 diabetes reflects the accumulated deficits of insulin resistance, beta-cell dysfunction and eventually reduced beta-cell mass. Interplay of genetic and environmental factors underpins each condition, and several of the recognised environmental factors are modifiable. Therapies to interrupt the early pathogenesis of these conditions would require early diagnosis and preferably intervention during the prodromal period, necessitating a more proactive vision of screening and risk factor assessment.

For Type 1 diabetes, aetiological blue-sky research has yet to identify the vital rays of sunlight to enable prevention. However, treatment is advancing apace with new insulins, more physiological and convenient insulin administration, transplants and surrogate beta-cells.

For Type 2 diabetes, the feasibility of early intervention has been demonstrated with lifestyle measures and current agents that reduce insulin resistance (metformin and thiazolidinediones) or slow carbohydrate digestion (alpha-glucosidase inhibitors). Reducing insulin resistance is consistent with an anti-diabetic strategy to simultaneously address the multiple cardiovascular risk factors of 'Metabolic Syndrome'.

Dual agonists of peroxisome proliferator-activated receptor alpha and gamma (PPAR α/γ) are being developed to enhance control of hyperglycaemia (γ -mediated) and hypertriglyceridaemia (α -mediated). Partitioning between lipid and glucose metabolism and directly stimulating glucose utilisation continue to be explored as possible anti-diabetic avenues. Novel activators of insulin receptor phosphorylation and inhibitors of dephosphorylation are offering encouraging leads for partial insulin substitutes. Agents that selectively suppress glucagon secretion, antagonise glucagon action, stimulate adenosine monophosphate (AMP)-activated protein kinase or inhibit glycogen phosphorylase or glucose-6-phosphatase could provide further therapeutic templates. Blocking the cellular activation of glucocorticoids within particular target tissues and stimulating the renal elimination of glucose also offer new therapeutic opportunities.

Analogues of glucagon-like peptide-1 (GLP1) and related peptides with more stability than native GLP1 are progressing in development to increase nutrient-induced insulin secretion and increase beta-cell neogenesis. A similar effect is envisaged by enhancing the effects of

GLP1 using inhibitors of dipeptidyl peptidase IV (the main enzyme that degrades GLP1). Targeting progenitor cells to differentiate into beta-cells and anti-apoptotic agents to reduce beta-cell death remain preliminary but enticing.

The epidemic of Type 2 diabetes urgently requires new interventions to obviate insulin resistance and beta-cell dysfunction. As the pathogenic processes become better appreciated, new therapeutic targets are being identified and a diversity of potential new agents is emerging.

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Key words: Diabetes, glucose homeostasis, insulin resistance, insulin secretion, pancreatic beta-cells.

Sponsors: None.

Declaration: No conflict of interest.

SESSION 4 THERAPEUTIC CHOICES IN DIABETES MELLITUS - WHAT ELSE?

Chair: Dr J McKnight, Consultant Physician, Western General Hospital, Edinburgh

DEBATE: SAVING LIFE IN DIABETES – DON'T WORRY ABOUT ANGIOTENSIN II, IT'S THE BLOOD PRESSURE, STUPID! (FOR)

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Abstract

In these days of evidence-based medicine we should expect to be able to turn to placebo-controlled, randomised, trials to inform us as to how we might reduce the excess morbidity and mortality from cardiovascular disease seen in patients with diabetes. We know that any level of blood pressure (BP) conveys greater cardiovascular risk in the presence of diabetes,^{1,2} but it is somewhat salutary to note that our knowledge that benefit accrues from reducing BP comes either from sub-group analysis of larger treatment trials of hypertension, or from comparisons of different drug-

based interventions in a population of patients with diabetes. There are no placebo-controlled trials!

As treatment trials in hypertension have included more older people the prevalence of diabetes amongst participants has increased and in such trials the benefits observed in the whole group have been realised to at least the same extent in the diabetic sub-groups.^{3,4} By the time the United Kingdom Prospective Diabetes Study (UKPDS) was designed it was considered unethical to include a placebo group and thus a comparison of tight versus loose control of BP became the compromise solution. In both in UKPDS⁵ and Hypertension Optimal Treatment (HOT) randomised trial⁶ the benefits of tight BP control were unequivocal in patients with diabetes, but both of these studies documented the need to use two or more drugs to have any chance of reaching target BP.

The intervention trials described above have used diuretics, beta blockers, calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors, and it has been suggested that ACE inhibitors have a peculiar benefit that is over and above their ability to lower BP.⁷ There can be little doubt that the Heart Outcomes Prevention Evaluation (HOPE) study has had a major impact on clinical practice⁸ but it should be emphasised that the ramipril group in this study had a lower BP by 3/2 mm Hg and in a sub-set of patients undergoing ambulatory BP monitoring⁹ the difference in nocturnal BP was a striking 15/7 mm Hg in favour of the ramipril group. In treatment trials that have suggested a specific effect of ACE inhibitors on mortality rates it has been the case that BP levels have been lower in the ACE inhibitors group.

The most recent publication of the largest intervention trial ever¹⁰ together with a meta-analysis of 29 randomised trials in more than 150,000 patients¹¹ all indicate that BP lowering is the critically important issue, how BP is lowered is of secondary concern.

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