Insulin resistance: *Current perspectives*

THE SECOND INSULIN RESISTANCE SYMPOSIUM TOOK PLACE IN LEEDS ON 5-6TH OF FEBRUARY 2004, AND WAS SUPPORTED BY AN EDUCATIONAL GRANT FROM TAKEDA UK.
A special report produced in association with Diabetes And Primary Care.

Contents

Introduction 99

The global epidemic of type 2 diabetes 99

Who is at risk of type 2 diabetes? 100

Preventing type 2 diabetes 100

The metabolic basis of insulin resistance and type 2 diabetes 101

Insulin resistance - an atherothrombotic syndrome 101

The view from primary care 102

The view from secondary care 102

Produced by SB Communications Group, publishers of Diabetes And Primary Care.

Supported by an educational grant from Takeda UK and printed by Pensord Press.

Introduction

The Second Insulin Resistance Symposium took place in Leeds early last February. Aiming to bring together knowledge and expertise on all areas of insulin resistance, speakers at the event included distinguised representatives from academia, primary and secondary care and the government. Professor Peter Grant thanked Takeda UK for their support of the event, which enabled the gathering of an eminent selection of healthcare professionals, and introduced the international faculty.

The meeting aimed to put insulin resistance into clinical perspective as well as examine its economic and social burden to society as a whole. Former health minister Frank Dobson gave a thought-provoking keynote speech highlighting the importance and role of the healthcare professional in preventing diabetes and cardiovascular disease and the translation of key health messages to the general public.

Professor Peter Grant, Academic Unit of Molecular Vascular Medicine, Leeds, UK

The global epidemic of type 2 diabetes

Professor Rhys Williams outlined the scale of the problem.

Setting the scene for the rest of the meeting, Rhys Williams, Professor of Clinical Epidemiology at the University of Wales, used the first presentation to emphasise the growing scale of the type 2 diabetes problem worldwide.

In particular, he cited the International Diabetes Federation's 2003 *Diabetes Atlas* as the most up-to-date source of information about the global situation. He quoted 194 million and 314 million people as currently suffering from diabetes (most of whom have type 2 diabetes) and impaired glucose tolerance (IGT) repectively, in the global population of 20–79 year olds.

Not taking into account likely increases in factors such as obesity, these figures are projected to rise to 333 and 472 million respectively – clearly, a global health problem on an immense scale.

Professor Rhys Williams, University of Wales

Professor Williams went on to explain that whilst Europe had the largest number of patients with diabetes out of the seven IDF world regions in 2003, by 2025, it is estimated that it will have been overtaken by the South East Asia and Western Pacific (China, Indonesia, Australasia) regions.

In conclusion, Professor Williams explained that the economic consequences could be severe if these projections are anywhere close to being realised, particularly for poorer countries, since they would necessitate an estimated 13% increase in global health care expenditure.

Who is at risk of type 2 diabetes?

Dr Jaakko Tuomilehto outlined the problems in diagnosing type 2 diabetes patients and suggested an alternative to blood testing approaches.

Dr Jaakko Tuomilehto
University of Helsinki and National Public Health Institute, Helsinki, Finland

Late diagnosis of diabetes (usually after the onset of symptoms) is one of the biggest barriers to the effective control of hyperglycaemia. Dr Jaako Tuomilehto, of the National Public Health Institute in Helsinki, Finland, explained that by the time symptoms occur in a patient, hyperglycaemia has already existed for longer than ten years.

Furthermore, he said, it has been shown in epidemiological studies that there are between eight and ten undiagnosed patients for every ten known patients with type 2 diabetes. Whilst some of these undiagnosed cases could be recognised with fasting glucose level testing, Dr Tuomilehto explained that most would remain unknown unless they were tested after eating, or with an oral glucose tolerance test (OGTT). Glucose levels recorded two hours after an OGTT are more effective in diagnosing hyperglycaemia than fasting levels, especially in older patents, since two hour levels increase with patient age but fasting glucose levels do not. To illustrate the point, Tuomilehto outlined the results of the DECODE study, which revealed an undiagnosed diabetes prevalence of more than one in ten in patients older than 70.

> ***'For every 10 known type 2 diabetes patients there are 8-10 undiagnosed patients in the population'***

Furthermore, he explained that, whilst IGT steadily increases as patients get older, the incidence of impaired fasting glycaemia (IFG) does not, and is not common in the elderly population.

Dr Tuomilehto explained that, whilst several screening approaches involving blood glucose measurement have been suggested, they are not effective at revealing patients at risk of type 2 diabetes early enough. He suggested instead that, if focused on high-risk groups (e.g. identified by questionnaire), screening for glucose intolerance could prove useful. As an example, he outlined the Finnish Diabetes Risk Score – an indicator compiled using non-blood testing type 2 diabetes risk factors in a prospective study. The risk score takes into account age, waist measurement, BMI, high blood glucose history, use of antihypertensive drugs, exercise, consumption of fruit and vegetables, and family history of diabetes. Dr Tuomilehto explained that the risk score successfully fulfills the criteria for a suitable screening test and that it predicts ten year onset of type 2 diabetes with 85% accuracy.

Preventing type 2 diabetes

Dr Melanie Davies highlighted the increasing prevalence of type 2 diabetes and outlined ongoing strategies to combat the problem.

Dr Melanie Davies
Leicester Royal Infirmary, UK

Over the period 1995–2010 it has been predicted that the incidence of type 2 diabetes will increase by nearly 50%, said Dr Melanie Davies, a Consultant Physician at Leicester Royal Infirmary. Furthermore, the increase in the number of people diagnosed closely correlates with the observed increase in obesity, and is of particular concern in children.

Dr Davies explained that strategies to prevent diabetes can be based around lifestyle modification (i.e. exercise, weight loss, better diet), pharmaceutical approaches, or a mixture of the two. Furthermore, strategies may be employed on different scales – targeting whole populations, particular risk groups or individuals.

Dr Davies focused on the latter, outlining a strategy that targeted adults with IGT. She presented results of lifestyle modification and pharmaceutical trials, along with recent results obtained using statins, ACE inhibitors and ARBs (angiotensin II receptor blockers).

The metabolic basis of insulin resistance and type 2 diabetes

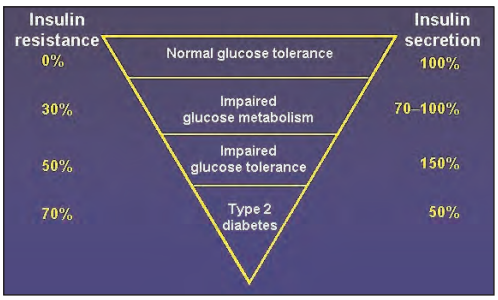
Professor John Nolan
St James Hospital,
Dublin, Ireland

Professor John Nolan discusses current knowledge and future issues surrounding the molecular basis of type 2 diabetes.

Lots of patients with type 2 diabetes are also obese and exhibit insulin resistance. Professor John Nolan, Consultant Endocrinologist at St James Hospital in Dublin, Ireland, explained that because of this, the condition is now being increasingly referred to as 'diabesity'.

Professor Nolan explained that type 2 diabetes is a continuum of several metabolic processes, evolving from normal glucose tolerance to IFG/IGT and through to diabetes itself (*Figure 1*), and that microvascular complications and endothelial dysfunction are present at blood glucose concentrations seen in the pre-diabetes phase.

Figure 1. Type 2 diabetes is a continuum of several metabolic processes (Adapted from Groop LC. Diabetes Obes Metab 1999;1 [Suppl 1]: S1–S7)



Furthermore, he explained that it is estimated that between two and three out of ten adults have been shown to exhibit 'disglycaemia'.

Insulin resistance and loss of insulin secretion are the causes of disease progression, with insulin resistance being the main early abnormality. Impaired insulin secretion begins in the IGT phase, but becomes more pronounced with the onset of diabetes – heralding fasting insulinemia and a loss of the first phase insulin response to glucose, and a diminished response to meals.

Professor Nolan explained how the cellular and molecular basis of insulin resistance and loss of secretion are not yet fully understood – although it is known that insulin resistance involves the disruption of cell signalling pathways downstream of the receptor.

'Combination treatments that provide additional insulin as well as treating resistance offer the best results'

Turning his attention to treatment approaches, Professor Nolan went on to explain that at all stages, but especially in the pre-diabetes phase, interventions focused on improving insulin sensitivity can be beneficial. However, during IGT and later stages, approaches that provide additional insulin and also combat insulin resistance offer the best way forward.

Insulin resistance: an athero-thrombotic syndrome

Professor Peter Grant explains the links between diabetes, cardiovascular disease and inflammatory pathways.

Cardiovascular disease is highly prevalent in patients with type 2 diabetes, and it is believed that common genetic and environmental factors play a role in the development of both diseases.

Professor Peter J Grant at the Academic Unit of Molecular Vascular Medicine in Leeds, UK, explained that whilst it is currently not known how environmental factors influence diabetes and cardiovascular disease, there are indications that inflammatory response pathways are involved.

As an example, Professor Grant pointed to trials which have shown increased levels of C-reactive protein (CRP; a constituent of inflammatory pathways) predating the onset of both conditions. Analagous results have also been obtained for other factors, such as complement factor 3 (C3). CRP measurements seem to offer further insight into vascular outcomes over traditional risk factors.

Furthermore, said Professor Grant, there is evidence that, in addition to vascular conditions, inflammatory processes play a role in the development of non-alcoholic steato-hepatitis and respiratory abnormalities in patients with type 2 diabetes.

Professor Grant then outlined the related therapeutic issues – such as the observation that certain cardiovascular drugs may have a useful role in attenuating type 2 diabetes (i.e. ACE inhibitors, metformin, TZDs and statins).

Prevention of diabetes and cardiovascular disease: The view from primary care

According to GP Mark Davis, the primary care sector has an important role to play in the campaign against diabetes and cardiovascular diease in the UK population as a whole. Importantly, though, the approach taken will continue to be based upon tending to those patients at highest risk until capacity restraints are overcome – focusing on those who have already had cardiovascular problems; those with conditions such as diabetes and hypertension; and patients who smoke or who are obese. A focused national initiative is needed to promote exercise and a healthy diet in the population as a whole, he said.

Dr Davis then outlined the importance of integrated care pathways (ICP) – ensuring patient care is seemless between different healthcare providers, and that the correct care is provided by at the correct time by appropriate professionals. In Dr Davis' opinion, the care of diabetes patients is an ideal model for ICP development.

'Primary care will have an increasing role in the management of most type 2 diabetes patients'

The role of primary care in treating diabetes will increase. Dr Davis outlined a series of clinical guidelines developed in Leeds which are being used to treat microvascular and macro-vascular complications in patients with diabetes. The implementation of these directives in primary care will be the responsibility of primary care trusts, he said.

Drivers for change

Dr Davis went on to outline the two main drivers for improving care. Firstly, the diabetes National Service Framework (NSF), which offers guidance on service models and setting targets, and states cinical interventions. Secondly, the new General Medical Services (GMS) and Personal Medical Services (PMS) contracts, which offer financial incentives to achieving targets.

Dr Mark Davis
Moorfield House Surgery, Leeds, UK

In conclusion, Dr Davis said that he expects to see a marked improvement in the quality of care given the establishment of clear targets and incentives and a new enthusiasm for primary and secondary care to work together.

The view from secondary care

Dr Michael Mansfield
Diabetes Centre, St James's Hospital, Leeds, UK

Cardiovascular disease is on the increase amongst the UK Asian population, and whilst rates are falling in the white population, they are still high in general. Furthermore, said Consultant Physician Dr Michael Mansfield, the increasing incidence of type 2 diabetes and obesity are a major problem for the UK. However, he said, the potential to ease the problem exists in the form of the new GP contract and National Service Frameworks for cardiovascular disease and diabetes.

Dr Mansfield explained that these initiatives focus on the detection of those at highest risk with targeted drug and behaviour change approaches. In those patients where symptoms are yet to present, risk of disease can be estimated using mathematical models, although the approach is limited by the reluctance of patients to adhere to advice and the accuracy of the algorithms.

'Developments in secondary care will enhance the effectiveness of public health programmes'

Dr Mansfield explained that the discovery of new drugs and conditions associated with insulin resistance have increased our under-standing of diabetes and cardiovascular disease. He explained that insulin resistance was a phenomenon common to patients suffering from a number of different conditions (e.g. HIV), and that as more is learnt about the mechanisms that underlie insulin resistance, the more we can refine risk models. He pointed to the possible role of chronic inflammation as an example, since the measurement of C-reactive protein is an effective risk marker.

In conclusion, Dr Mansfield said that public health programmes will be made more effective by developments in secondary care, which are in turn lead by advances in clinical research, such that they are more likely to be adopted by patients of diabetes and cardiovascular disease.