Commentary

The prevention of type 2 diabetes mellitus: recent advances

N. YOUNIS¹, H. SORAN² and S. FAROOK¹

From ¹Department of Diabetes & Endocrinology, University Hospital Aintree, Liverpool, and ²Department of Diabetes & Endocrinology, Stepping Hill Hospital, Stockport, UK

Summary

Diabetes is a major public health problem that is approaching epidemic proportions globally. There is an urgent need for strategies to curb the rising prevalence of this disease, and prevention appears a logical approach. Lifestyle modifications with weight loss and moderate exercise can reduce the incidence of diabetes by >50% in patients with impaired glucose tolerance (IGT). The use of metformin, acarbose and other agents have been shown in randomized prospective trials to prevent type 2 diabetes in high-risk subjects with IGT. Other pharmacological interventions are currently being examined in large prospective studies. It is likely that one or a combination of these approaches could make diabetes prevention a reality in the near future.

Introduction

Type 2 diabetes mellitus (DM) is a major health issue associated with excess mortality and morbidity. The condition is increasing in epidemic proportions in both developed and developing nations, with the global population predicted to rise from 118 million in 1995 to 220 million in 2010.¹⁻³ Individuals with type 2 DM are at a significantly higher risk for coronary heart disease, peripheral vascular disease and stroke, as well as microvascular complications affecting various organs such as eyes, kidneys and nerves. The economic impact of diabetes is substantial: in developed countries, it accounts for 10% or more of the total health care budget on its management or that of its associated complications.⁴ The epidemic is thought to be in part related to the rising levels of obesity and fat accumulation as a result of a positive calorific balance.¹

Pathogenesis and natural history of type 2 diabetes mellitus

Individuals who have develop type 2 DM are thought to proceed through a phase of impaired glucose tolerance,⁵ with defects in the action or secretion of insulin thought to be the two major abnormalities leading to the development of glucose intolerance and DM. As tissue resistance to insulin progressively increases, insulin secretion by pancreatic beta cells progressively rises as it attempts to compensate for this resistance. Glucose tolerance remains normal as long as the beta cells can compensate for insulin resistance.

Eventually, beta cell failure tends to be slowly progressive over time and leads to a progressively rising glucose levels. Initially, impaired glucose tolerance (IGT) develops, resulting in postprandial hyperglycaemia and subsequently type 2 DM, when glucose levels reach a critical point at which the risk of microvascular complications ensues.
The risk of progressing from IGT to type 2 DM is variable, depending on the type of population studied, ethnicity, obesity and other cardiovascular risk factors present. IGT is associated with a 6–10-fold increase in overall risk of progression to type 2 DM compared to individuals without IGT, averaging around 6% per annum. Individuals with IGT also have a significantly increased risk of cardiovascular disease and death. Although these individuals do have a greater frequency of cardiovascular risk factors, including hypertension, dyslipidaemia and obesity, this does not entirely explain the increased risk.

The need for diabetes prevention

The high economic and social costs of type 2 DM and its rising prevalence makes a compelling case for its prevention. In patients with established type 2 DM, intervention trials have demonstrated clear benefits of good glycaemic control in preventing or retarding the progression of microvascular complications, and have also reported non-significant reductions in cardiovascular disease with tight glycaemic control in subjects with type 2 DM. However, in clinical practice, long-term tight glycaemic control is difficult to achieve in patients with type 2 DM, as demonstrated in the UK Prospective Diabetes Study (UKPDS), which showed an inexorable decline in glucose control over time, and complications still occur in individuals who attain good glycaemic control. Furthermore, in newly diagnosed patients, microvascular disease is already present in up to one-third due to asymptomatic hyperglycaemia prior to diagnosis. Intervention prior to the onset of type 2 DM may be the only way of preventing the complications of DM. Thus in individuals with IGT, preventing or delaying the progression to type 2 DM is a potential mechanism to reduce the burden and complications of diabetes.

How do we prevent type 2 diabetes?

Various studies have assessed strategies to prevent or delay the onset of type 2 DM. We will review the evidence in the more recent trials for lifestyle changes and pharmacological agents in the prevention of type 2 DM.

Life style, weight loss and exercise

Reduction in weight has been an important measure in preventing type 2 DM. In overweight subjects with IGT undergoing gastric bypass surgery, the rate of conversion to type 2 DM after an average weight loss of 22.5 kg over 4–6 years was 0.15% per year, compared to an average rate of 4.72% in a control group without the operation. A number of small early uncontrolled studies have shown benefits of health and lifestyle changes in preventing progression from IGT to type 2 DM. More recently, two large well-designed randomized control studies have compared the impact of lifestyle measures in individuals with IGT and progression to DM.

The Finnish Diabetes Prevention Study (FDPS) enrolled 522 middle-aged men with mean age of 55 years and a mean Body Mass Index (BMI) of 31 kg/m² (normal BMI 20–25 kg/m²). Subjects with IGT according to the WHO criteria were randomized to receive either brief diet and exercise counselling (control arm) or intensive individual instructions on weight reduction (>5%), reduction of food intake (<30% of calorific intake) and increased moderate physical exercise (>150 min/week), (intervention arm). Subjects in the intervention arm received sessions with a dietician seven times during the first year. The proportion of patients progressing to type 2 DM per year was 3.2% in the intervention group vs. 7.8% in the control group. Mean weight loss was 3.5 kg in the intervention vs. 0.8 kg in the control group. After 3.2 years, there was a 58% relative risk reduction in incidence of DM in the intervention compared to control group.

The larger and ethnically more diverse population of the Diabetes Prevention programme (DPP) in the USA, consisting of Caucasian, African American, Hispanic, American Indian and Asian Americans, also confirmed the findings of the Finish Diabetes Prevention Study. Compared with the FDPS, participants were slightly younger (mean age 51 years) and were more obese (mean BMI 34 kg/m²). Subjects with IGT were randomized to intensive nutrition and exercise counselling (lifestyle group) or either one of two masked groups: metformin or placebo. After a period of two years, a 58% reduction in the progression to type 2 DM was observed in the lifestyle group compared with controls. These changes were observed in all of the various ethnic and racial subgroups, and at least 50% of the lifestyle group had achieved the goal of >7% weight reduction.

These two studies have clearly demonstrated the effects of lifestyle changes, with at least a 50% reduction in the progression from IGT to type 2 DM. However whether these lifestyle measures can be sustained in the longer-term, is unknown, as is whether the benefits in the intervention studies described can be replicated in clinical practice.
rather than a research setting. A number of well-described large community based studies in Finland (North Karelia) and the US (Stanford, Pawtucket and Minnesota) have determined the long-term benefits of health promotion. These studies were aimed at the primary prevention of cardiovascular disease by the delivery of an integrated health education programme that included behavioural modifications such as regular exercise, improvements in diet and achieving ideal body weight. Unfortunately the long-term results of these programmes have been disappointing. Only modest reductions in cardiovascular disease risk factors were observed, and there was no change in overall mortality.

**Pharmacological intervention**

Another approach to the prevention of type 2 DM has been by the use of pharmacological agents. There have been a handful of early intervention studies using oral hypoglycaemic agents published over a decade ago. These early studies were difficult to interpret, as they did not clearly define the diagnosis of diabetes using standard criteria and/or were underpowered, with fewer than 200 subjects in each intervention groups. We will examine the use of pharmacological agents in subjects with IGT in the more recent larger randomized control studies that have been completed. Although certain drug interventions have shown potential benefit, economic studies to assess the cost effectiveness are lacking, and are urgently required to consider this approach in preventing type 2 DM.

**Metformin**

The American Diabetes Prevention Programme (DPP), in addition to lifestyle measures, also randomized patients to metformin or troglitazone, a thiazolidinedione agent. The troglitazone arm was discontinued after 2 years because of case reports of hepatotoxicity and case fatalities. The study found that metformin reduced the risk of progression of IGT to type 2 DM by 31%, compared to patients in the placebo arm. The benefit was not seen in patients aged >60 years or those with a BMI < 30 kg/m². The TRIPOD study was an intervention study in 236 Hispanic women with previous gestational DM, a targeted group at considerable high risk of progressing to type 2 DM. Patients were randomized to receive the thiazolidinedione troglitazone or placebo. After a follow-up of 2.5 years, the incidence of DM was 12.1% in the placebo compared to 5.4% in the troglitazone group. Even after a treatment washout of 8 months, the preventative effect of the drug was still observed.

**Acarbose**

The STOP-NIDDM study was an international double-blind placebo-controlled study designed to evaluate the effects of acarbose in delaying the progression of IGT to type 2 DM. The primary endpoint was the development of type 2 DM, based on an oral glucose tolerance test. There were 1429 patients, who were randomized to the alpha-glucosidase inhibitor acarbose or placebo. Mean age was 55 years, mean BMI 31/kgm² and mean duration of follow-up was 3.3 years. There was a 25% relative risk reduction of progression to type 2 DM in the acarbose compared to the placebo arm. The effect of acarbose was seen in all age groups and BMI values, but the acarbose group had a 25% discontinuation rate.

**Thiazolidinedione**

The TRIPOD study was an intervention study in 236 Hispanic women with previous gestational DM, a targeted group at considerable high risk of progressing to type 2 DM. Patients were randomized to receive the thiazolidinedione troglitazone or placebo. After a follow-up of 2.5 years, the incidence of DM was 12.1% in the placebo compared to 5.4% in the troglitazone group. Even after a treatment washout of 8 months, the preventative effect of the drug was still observed.

**Other drugs**

The results of secondary endpoints from several other cardiovascular drugs trials have hinted that angiotensin-converting enzyme inhibitors (ACE) or angiotensin II receptor antagonists may play a role in the prevention of type 2 DM. For example, in the HOPE study (Heart Outcome Protection Evaluation), a 34% significant reduction in incidence in newly diagnosed DM was observed in patients using ramipril compared to placebo. Similarly, the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) reported a lower incidence of type 2 DM in the losartan compared to the beta-blocker group. In both these studies, however, the diagnosis of diabetes was not a primary end point and the method of ascertainment of type 2 DM was based on self-reported diabetes or a fasting blood glucose concentration ≥ 7.0 mmol/l. Current studies are underway to investigate the efficacy of ACE inhibitors and angiotensin II antagonists in the prevention of type 2 DM.

**Conclusion**

The prevention of type 2 DM is an urgent priority in most countries, in order to halt this rising epidemic. Recent trails have shown that a >50%
reduction in progression of IGT to type 2 DM can be achieved by lifestyle measures with moderate exercise and diet.\textsuperscript{21,22} The real challenge is to support such an intervention outside the framework of a clinical trial to large-scale populations with an increasing epidemic of obesity, and to maintain these benefits long term. The use of pharmacological intervention with use of drugs such as metformin and acarbose can prevent progression of IGT to Type 2 DM.\textsuperscript{22,23} However their cost-effectiveness and long-term safety are largely unknown.

References


