

## Prevention of Type 2 Diabetes

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### Abstract

The prevalence of diabetes is increasing worldwide. The World Health Organisation has estimated that there will be around 300 million diabetics by 2025. The largest increase will occur in Asia. The prevalence of type 2 diabetes is increasing due to a combination of factors: increasing lifespan, sedentary lifestyle, excessive intake of high energy foods, increasing prevalence of overweight/obese people. The Finnish Diabetes Prevention Study Group has clearly shown that changes in the lifestyle of both overweight men and women with impaired glucose tolerance can reduce the incidence of type 2 diabetes by 58%. This finding was confirmed by the Diabetes Prevention Programme which found that lifestyle intervention in individuals with impaired fasting glucose or impaired glucose tolerance reduced the risk of developing type 2 diabetes by 58%, whereas treatment with metformin reduced the risk of type 2 diabetes by only 31%. Both acarbose and troglitazone have also been shown to reduce the progression to diabetes in individuals who are at high risk of developing type 2 diabetes. Since the cure for diabetes remains some way off our concerted efforts should be directed at prevention of diabetes in order to curb the increasing prevalence of diabetes worldwide. Lifestyle changes are more beneficial than long term drug therapy in the prevention of diabetes and should be actively promoted.

*Key words:* type 2 diabetes, diabetes prevention, healthy lifestyle, acarbose, metformin, troglitazone

### INTRODUCTION

The prevalence of diabetes mellitus is increasing worldwide and diabetes is now a pandemic.' The World Health Organisation predicts that there will be 300 million diabetics by 2025, with the larger proportion of the increase occurring in Asia.

Around 4% of Europeans and 8% of the population of the USA have diabetes. In 1995, 7.7% of the population of Malaysia were diabetic. Although there are not any official figures for 2002, the prevalence of diabetes mellitus in Malaysia is now thought to be over 8%. This is predicted to rise to over 10% by 2020. In Singapore in 1998, 9.0% of the adults aged 19-69 years were diabetic. In certain populations, such as the Pima Indians in Arizona, USA, and the Nauruans (Pacific Island of Nauru), up to 50% of the population are diabetic. In Malaysia and Singapore, diabetes is most common in Indians, followed by the Malays, then the Chinese.

The increasing prevalence of type 2 diabetes worldwide is due to a combination of factors: increasing lifespan, sedentary lifestyle, a high fat diet, and an increasing number of people who

are overweight or obese, against a background of increased genetic predisposition to diabetes in some ethnic groups. Obesity-related type 2 diabetes in children, already common worldwide, has recently been reported in white children in the United Kingdom.<sup>2</sup>

### BODY MASS INDEX AND DIABETES

The most common definition of obesity is a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>, although for Asians it has been recommended that this should be lowered to  $\geq 25$  kg/m<sup>2</sup>. In the Nurses' Health Study, the relative risk of type 2 diabetes increased with BMI.<sup>3</sup> Even a BMI of 23-25 kg/m<sup>2</sup> increased the risk of diabetes threefold compared with a BMI of less than 21 kg/m<sup>2</sup>. The relative risk of type 2 diabetes in women with a BMI of 29-31 kg/m<sup>2</sup> was increased 28-fold and a BMI of greater than 35 kg/m<sup>2</sup> carried a 93-fold increased risk of type 2 diabetes.

In a study where gastrointestinal surgery was used to produce large weight losses in a group of 109 individuals with impaired glucose tolerance, the progression of impaired glucose tolerance to diabetes over 6 years was reduced thirty-fold.<sup>4</sup> More modest weight losses are also beneficial.

Weight losses of about 10% of initial weight have been shown to lower blood glucose levels and reduce insulin resistance in diabetics and those who are at risk of developing diabetes.

### DIETARY FAT AND DIABETES

The Nurses' Health Study found no relationship between the incidence of type 2 diabetes and intake of total dietary fat, saturated fat or monounsaturated fat.<sup>3</sup> However, polyunsaturated fat was protective while *trans* fatty acids were harmful. Replacing 2% of the energy from *trans* fatty acids with polyunsaturated fat reduced the incidence of type 2 diabetes by 40%. The San Luis Valley Diabetes Study, however, found a relationship between total fat intake and incidence of diabetes<sup>4</sup> while other studies have found a relationship between saturated fat intake and fasting glucose levels,<sup>6</sup> fasting and postload insulin levels<sup>7</sup> or levels of HbA1c.<sup>8</sup> Fat intake may be related to the development and maintenance of obesity. Body weight is far more important in the risk of developing diabetes than a saturated fat intake.

### EXERCISE AND DIABETES

Increased physical activity decreases the risk of developing type 2 diabetes directly through improvements in insulin sensitivity and, indirectly, through promoting weight loss, which also increases insulin sensitivity. Modest increases in leisure-time physical activity were found to be inversely related to the risk of developing type 2 diabetes<sup>9</sup> Incidence rates of diabetes declined as energy expenditure increased from less than 500 kcal/week to 3500 kcal/week. For each 500 kcal increment in energy expenditure per week the age-adjusted risk of type 2 diabetes was reduced by 6%. The protective effect of physical activity was greatest in persons at highest risk of developing diabetes, defined as a high BMI, a history of hypertension, or a parental history of diabetes. The protective effect of strenuous exercise is greater than that of moderate exercise, but both are effective.

### PREVENTION OF TYPE 2 DIABETES

The 6-year Finnish Diabetes Prevention Study was the first properly randomised study to be published which assessed the effect of lifestyle intervention on progression to type 2 diabetes.<sup>10</sup> The subjects in the study were overweight (BMI > 25 kg/m<sup>2</sup>), had impaired glucose tolerance and, hence, were at high risk of developing type

2 diabetes. The targets for the lifestyle changes were a reduction in weight of  $\geq 5\%$ , reduction in total fat intake to < 30% of energy consumed, reduction in intake of saturated fat to less than 10% of energy consumed, increase in fibre intake to  $\geq 15$  g/100 kcal and moderate exercise for  $\geq 30$  minutes per day. Lifestyle intervention was found to reduce the overall incidence of type 2 diabetes by 58%.

There were earlier studies which showed that lifestyle changes reduced the risk of type 2 diabetes but there were faults with the study design. A 6-year Swedish study conducted in Malmo found that type 2 diabetes could be prevented by diet and physical exercise.<sup>11</sup> This was, however, not a randomised study. The Da Qing Impaired Glucose Tolerance and Diabetes Study in China also found that diabetes could be prevented in people with impaired glucose tolerance by diet and exercise.<sup>12</sup> This study was randomised only by clinic and not by individual.

Following the publication of the Finnish Diabetes Prevention Study, the results of the Diabetes Prevention Program Research Group in the United States were awaited with great interest.<sup>13</sup> This was a clinical trial comparing diet and exercise with metformin treatment, 850 mg twice a day, in preventing type 2 diabetes in individuals with impaired fasting glucose (fasting venous plasma glucose levels  $\geq 6.1$  mmol/L but less than 7.0 mmol/L) or impaired glucose tolerance. This trial was supposed to end in 2002. On the advice of the diabetes prevention programme's external data monitoring board, the trial ended a year early because the data had clearly answered the main research questions. In this study, participants were randomly assigned to one of three groups: intensive lifestyle modification with the aim of reducing weight by 7% through a low fat diet and exercising for 150 minutes a week, treatment with 850 mg of metformin twice daily, and subjects in the third group were given a placebo. The average follow-up period was 2.8 years. The risk of developing type 2 diabetes was reduced by 58% in the group which had undergone intensive lifestyle modification but only by 31% in the group treated with metformin. Hence, intensive lifestyle modification was better at preventing the development of type 2 diabetes than drug treatment with metformin.

The Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) found that acarbose (an  $\alpha$ -glucosidase inhibitor), 100 mg three times a day, reduced the progression to diabetes in individuals with impaired glucose

tolerance by 25% over 3.3 years.<sup>14</sup> Furthermore, acarbose also significantly increased reversion of impaired glucose tolerance to normal glucose tolerance.

In the Troglitazone in Prevention of Diabetes (TRIPOD) Study, 235 Hispanic women with previous gestational diabetes and who are, therefore, at high risk of developing type 2 diabetes, were randomised to receive either placebo or the thiazolidinedione, troglitazone.<sup>15</sup> After a median follow up of 30 months, the annual incidence of type 2 diabetes in the 2 groups was 12.3 and 5.4%, respectively. Troglitazone treatment resulted in a 56% relative reduction in progression to type 2 diabetes. Treatment with troglitazone in this study had to be stopped since the drug was withdrawn due to problems of hepatotoxicity. After a washout period of more than 8 months the preventive effects of troglitazone were still observed.

### SHOULD WE ATTEMPT TO PREVENT TYPE 2 DIABETES?

Diabetes mellitus is one of the most costly and burdensome chronic diseases that is increasing in epidemic proportions throughout the world. The complications resulting from the disease are a significant cause of morbidity and mortality. The microvascular complications of the disease are retinopathy, peripheral and autonomic neuropathy and nephropathy while the macrovascular complications are coronary heart disease, peripheral vascular disease and cerebrovascular disease. Tight glycaemic control has been shown to delay the onset and slow the progression of microvascular complications in type 1 diabetics.<sup>16</sup> The United Kingdom Prospective Diabetes Study (UKPDS) found that intensive blood glucose control with either sulphonylureas or insulin in type 2 diabetics reduced the risk of microvascular complications but the reduction in the risk of myocardial infarction was of borderline significance.<sup>17</sup> Metformin, which increases peripheral insulin sensitivity, gave significant risk reduction of diabetes-related end points, including myocardial infarction, in overweight patients with type 2 diabetes.<sup>18</sup> In an updated study, each 1% reduction in mean HbA1c in patients treated with insulin or sulphonylureas was associated with a reduction of 21% for any end point related to diabetes ( $P < 0.0001$ ), 21% for deaths related to diabetes ( $P < 0.0001$ ), 14% for myocardial infarction ( $P < 0.0001$ ) and 37% for microvascular complications ( $P < 0.0001$ ).<sup>19</sup> No

threshold of risk was observed for any end point. The reduction in risk of microvascular complications with tight glycaemic control was greater than that for myocardial infarction. In view of the fact that tight glycaemic control in a diabetic may not prevent, but merely delays, the development of complications, and the reduction in risk of macrovascular complications is less than that of microvascular complications, it is better to prevent the development of diabetes.

In order to justify initiating a programme to prevent a disease there should be at least five conditions that should be met:

- 1) The disease should be an important health problem that imposes a significant burden on the affected population. Diabetes mellitus certainly satisfies this criterion.
- 2) The early development and natural history of the disease should be understood sufficiently well to identify parameters that measure its progression to disease. Existing data show that the incidence of diabetes is strongly related to impaired fasting glucose and impaired glucose tolerance.<sup>20-23</sup> There is evidence that other factors are independently associated with the development of diabetes, such as age, family history of diabetes, BMI, waist-to-hip ratio, serum lipid levels and blood pressure. However, none of these factors taken singly is as good at discriminating who will progress to diabetes as glucose levels. When these risk factors are considered together, including plasma glucose levels, they are more predictive of future diabetes than glucose levels on their own.<sup>24</sup>
- 3) There should be a safe, reliable and predictive test to detect the pre-disease state. Impaired fasting glucose or impaired glucose tolerance are both associated with a high risk of developing diabetes and are, thus, good predictive tests for the development of diabetes.
- 4) There should be safe, effective and reliable method(s) to prevent or delay the disease from developing. The results of the Finnish study,<sup>10</sup> Diabetes Prevention Programme,<sup>13</sup> STOP-NIDDM trial<sup>14</sup> and the TRIPOD study<sup>15</sup> indicate that there are now interventions capable of preventing or at least delaying the onset of type 2 diabetes. It is also important to consider whether there are benefits to an intervention, in addition to preventing the disease in question. In nearly all the trials mentioned above the average participant was overweight and likely to be sedentary. Both of these characteristics are risk factors for

cardiovascular disease.<sup>25,26</sup> Impaired glucose tolerance and impaired fasting glucose are also independent risk factors for cardiovascular disease. In addition to prevention of diabetes, lifestyle modification has a beneficial effect on health.

- 5) The effort to find individuals who are at high risk of getting the disease and the cost of intervention should not be burdensome and should be cost-effective. Opportunistic screening (i.e. screening during routine encounters with the health care system) is probably the most cost-effective way of detecting individuals at risk of developing diabetes."

### HOW SHOULD DIABETES PREVENTION BE PERFORMED?

The strategies shown to be effective in preventing diabetes were lifestyle modification and the use of oral hypoglycaemic agents. The Diabetes Prevention Programme is the only study in which a comparison of lifestyle modification and the use of an oral hypoglycaemic agent was made.

Weight loss strategies are difficult to accomplish and maintain. The lifestyle goals of the Finnish study and the Diabetes Prevention Programme were modest and the participants were motivated to join a clinical trial. Substantial efforts were made to help participants who were randomised to the lifestyle modification arm of both studies to achieve the desired goals. It is, therefore, discouraging to observe that the desired objectives were only partially achieved.

There is strong epidemiological evidence that physical activity and weight loss are of medical benefit, not just for preventing diabetes but also for improving various aspects of health, including cardiovascular health.<sup>28,29</sup> Health care policymakers and health care systems should aggressively explore low cost ways of promoting physical activity and weight loss. Cost-effective patient education and counselling should continue to be developed and tested.

The three diabetes intervention trials which used pharmacological therapy have all reported a significant lowering of the incidence of diabetes. Although all the three drugs concerned, metformin, acarbose and troglitazone, delayed the onset of diabetes, the TRIPOD study suggests that troglitazone may have a true preventive action as well.

In the Diabetes Prevention Programme, metformin was about half as effective as diet

and exercise in delaying the onset of diabetes. It was, however, nearly ineffective in older individuals ( $\geq 60$  years of age) or in those who were less overweight ( $\text{BMI} < 30 \text{ kg/m}^2$ ). Conversely, metformin was as effective as lifestyle modification in individuals aged 24-44 years or those with a  $\text{BMI} \geq 35 \text{ kg/m}^2$ . This indicates that the population in whom treatment with metformin has equal benefit to that of lifestyle modification is only a small subset of those who are at high risk of developing diabetes.

Regular monitoring is required if an oral hypoglycaemic agent is used for diabetes prevention. The above drugs have also been linked to undesirable side effects that preclude their use in some patients and troglitazone has been withdrawn from commercial sale. These side effects must be taken into consideration, especially when the drugs are used to prevent or delay diabetes rather than to treat it.

It is unknown whether other oral hypoglycaemic agents will delay or prevent diabetes or even whether other agents in the  $\alpha$ -glucosidase inhibitor or thiazolidinedione classes will be as effective as those already tested.

The greater benefit of weight loss and physical activity, not just in diabetes prevention but also in improving cardiovascular health and overall well-being, suggests that lifestyle modification should be the first choice to prevent or delay diabetes. Drug therapy with acarbose or metformin is less efficacious, has adverse effects and may even be contraindicated in some individuals. Furthermore, none of the glucose-lowering agents tested or commercially available have been studied with regard to protection from cardiovascular disease or have any other clinical benefit to non-diabetic individuals.

### SUMMARY

The recent success of major intervention trials clearly indicate that type 2 diabetes can be delayed, if not prevented, in individuals at high risk of developing diabetes. The cost-effectiveness of intervention strategies is not clear, but the huge burden resulting from the complications of diabetes and the potential benefits of some of the interventions suggest that an effort to prevent diabetes is more than worthwhile. A healthy lifestyle should be actively promoted, not only to high risk individuals, but to everyone in order to curb the increasing prevalence of diabetes worldwide.

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