Primary Prevention of Type 2 Diabetes: How Do We Do It?

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Type II diabetes is the most common metabolic disease, affecting between 7% and 8% of adults in the Western hemisphere [1]. The number of diabetic patients is estimated to be 150 million worldwide and is expected to double within 20 years [2]. This rapid increase in the incidence of the disease positions it as a worldwide epidemic. The chronic nature of the disease and its resultant complications are the cause of significant morbidity and mortality. Since diabetes is one of the most costly and burdensome diseases in developed and developing countries, measures to prevent the disease or delay its development should be taken urgently.

Pathogenesis of type 2 diabetes

The exact mechanism for the development of type 2 diabetes is still not fully established. Recent findings, however, indicate that two defects exist in diabetic patients: the first is impairment in the secretion of insulin from pancreatic beta cells [3]; and the second, which is present in most diabetic patients, is impairment in insulin action, known as insulin resistance [4]. There is compelling evidence that improper diet and obesity, in particular central obesity, play a prominent role in the development of insulin resistance [5]; and further, reducing body weight and practicing regular exercise have a favorable effect on insulin resistance [6].

Longitudinal studies in high risk populations demonstrated that, in response to insulin resistance, beta cells increase their secretion rate of insulin to compensate for the relative insulin deficiency caused by insulin resistance [7]. However, further deterioration in either beta-cell function or insulin resistance interferes with the delicate balance between insulin secretion and insulin action and leads to the situation where beta cells become unable to compensate for the insulin resistance. Thus, deterioration in glucose metabolism occurs, first as impaired glucose tolerance and later on as overt diabetes [8].

Intervention trials

In view of the above – our increased understanding of the pathogenesis of type 2 diabetes, and the effect of losing weight on the distribution of body fat and insulin resistance – some investigators examined whether improving insulin resistance by reducing body weight in high risk populations can prevent or delay the appearance of diabetes. Two early studies [9,10] confirmed this hypothesis, suggesting that reducing body weight by a change in lifestyle can indeed prevent diabetes.

This question was recently addressed in four well-designed randomized and double-blind placebo-controlled studies. The first was conducted in Finland [11], and the larger one, the Diabetes Prevention Program (DPP), in the United States [12]. In both studies, a modest reduction in body weight (5–7%) combined with moderate physical activity (30 minutes daily) significantly reduced (by 58%) the incidence rate of type 2 diabetes among subjects with IGT compared to controls. Furthermore, in the DPP, a third group of IGT subjects who were given metformin also showed a lower incidence rate (31%) of diabetes than the controls.

Recent studies suggest that daily consumption of seven cups of coffee (compared to two cups) reduces the risk of type 2 diabetes by 50%. Although this observation is still in dispute and was not confirmed by other studies, it demonstrates that changing lifestyle, in particular food habits, substantially affects the incidence of type 2 diabetes [13].

Two other studies examined different pharmacologic interventions to stop the progression to diabetes in high risk patients. In the STOP-NIDDM trial [14], an alpha-glucosidase inhibitor, acarbose, reduced the incidence of diabetes by 25% among subjects with IGT. In the TRIPOD study, troglitazone reduced the incidence by 56% [15]. Two other interesting observations were made in this study: additional to the improvement in insulin sensitivity as assessed by the mini-model method, there was significant improvement in beta-cell function following treatment with troglitazone, suggesting that the drug affected both defects that underlie the disease. The second observation was that the benefit from the drug in reducing the progression to diabetes lasted for 8 months after drug cessation, suggesting that the drug probably "corrected" a defect in IGT patients.

Two other studies, designed to assess different drugs in preventing coronary events, observed a reduction in diabetes incidence, additional to the cardiovascular benefit. In the HOPE study [16], ramipril caused a 33% reduction in the incidence of type 2 diabetes, compared with placebo, after 3 years of treatment. In the West of Scotland Coronary Prevention Study [17], pravastatin reduced the incidence of type 2 diabetes by 30% compared with placebo. It is interesting to note that the patients selected for the West of Scotland and the HOPE studies were not high risk patients for diabetes (obese with impaired fasting glucose or IGT) but had

IGT = impaired glucose tolerance

high risk for coronary disease – i.e., otherwise healthy people with high cholesterol levels in the first study, and at least two cardiac risk factors in the second. The significant reduction of diabetes in this population by these drugs may suggest a common pathogenesis of both diseases: diabetes and atherosclerosis. Recent observations on the possible contribution of inflammatory factors such as C-reactive protein and cytokines to the pathogenesis of both diseases and the modification of these factors by insulin-sensitizing drugs such as rosiglitazone and lipid-lowering drugs such as pravastatin support this hypothesis [18].

The justification for diabetes prevention

There is enough evidence today to indicate that proper intervention among high risk patients can substantially reduce the incidence of type 2 diabetes. Before a comprehensive program for preventing diabetes in the community is initiated, two main questions should be addressed. The first, is it justified to prevent diabetes? And the second, does it do the job?

Regarding the first question, there is no doubt that diabetes fulfills all the criteria for preventable disease. Firstly, it imposes a significant burden on the public health. Second, a great deal of progress has been achieved in recent years in terms of the natural history of the development of diabetes and the parameters that influence progression to the diabetic state; this progress had led to the definition of the pre-diabetic state (impaired fasting glucose and impaired tolerance or IGT), a situation in which the individual is still healthy but at high risk of developing the disease [19]. Third, this pre-diabetic state can be identified easily and safely with the oral glucose tolerance test. Finally, the intervention studies mentioned earlier prove that there is a safe, effective and reliable method that prevents or at least delays the progression from IGT to diabetes, namely, a change in lifestyle. The efficacy of such a change was proven by the number of subjects still requiring treatment – 22 after 1 year in the Finnish study and 7 in the American DPP after 3 years.

With regard to the second question, i.e., the cost-effectiveness of preventing diabetes, there are no studies to date that prove beyond any doubt that preventing diabetes is cost-effective. However, the recent DPP study that also analyzed the cost of preventing diabetes concluded that the cost of intervention to the healthcare system appears reasonable [20]. When this cost is compared to the direct and indirect medical and non-medical cost of diabetes [21], the unequivocal conclusion is that primary prevention of diabetes is highly cost-effective. Furthermore, people with IGT are also at high risk for developing other diseases such as cardiovascular disease and hypertension [22]. As mentioned earlier, a substantial body of evidence suggests that changing lifestyle and reducing weight has a beneficial effect on the progression not only to diabetes but to other diseases as well. It follows, therefore, that efforts to prevent diabetes are worthwhile.

The target population for prevention

Most of the diabetes prevention studies were performed in IGT patients. Different studies demonstrated that this population is at high risk for progression to diabetes, and that one-third of this population will progress to diabetes within 5 years [19]. Other subjects also at high risk for developing diabetes are those with IFG, who have a similar cumulative incidence of diabetes as those with IGT. Accordingly, people with combined IGT and IFG are at the highest risk for progression to diabetes, having a cumulative incidence of diabetes in 5 years of about 65% [19]. Thus people with IGT, IFG, or both, should be targeted for prevention of diabetes.

On the other hand, people with normal glucose tolerance should not be targeted since they are at low risk for developing diabetes, with an annual incidence rate of about 1%, and they will convert to either IGT or IFG before they develop diabetes. Thus, by identifying individuals with IGT or IFG, one can reach most of the population at high risk for type 2 diabetes.

Screening methods

The main task in designing a national program for primary prevention of type 2 diabetes is identification of the population with impaired glucose homeostasis. The best means of achieving this goal is to perform OGTT in the entire adult population. Although this method is ideal, it is not comfortable and there is no reliable alternative. Neither fasting glucose alone, nor in combination with glycosylated hemoglobin, has sensitivity and specificity comparable to OGTT [23]. Recently, models based on simple clinical parameters were shown to predict individuals at high risk for diabetes in certain populations; however, although these models seem promising they have yet to be confirmed in other populations [24].

Based on the age-dependent risk for diabetes, the American Diabetes Association issued a statement in which it recommended screening for IGT using OGTT in individuals above 45 years of age and with a body mass index higher than 25. Screening people below this age is recommended in overweight individuals if they have additional risk factors, such as a positive family history or previous gestational diabetes, hypertension dyslipidemia, or belonging to a high risk ethnic group such as African-American or Hispanic. The ADA also recommended that the screening test be repeated every 3 years [25].

The recommended intervention method

Two strategies were shown to be effective in preventing diabetes: lifestyle modification and pharmacologic intervention with glucose-lowering drugs. Although lifestyle change is effective and safe in preventing diabetes, it is not easy to achieve. In both studies that examined change in lifestyle [11,12], intensive efforts by well-trained staff were needed to yield a modest reduction in body weight. Nonetheless, that modest change was sufficient to achieve a substantial reduction in the incidence of diabetes

Although pharmacologic interventions were also effective in preventing diabetes, their efficacy was more modest than that achieved by lifestyle change [12]. Various factors – the huge benefit of weight loss in preventing diabetes and its superior efficacy over

IFG = impaired fasting glucose
OGTT = oral glucose tolerance test
ADA = American Diabetes Association

drug intervention (at least when compared with metformin), together with the lack of adverse side effects, the fact that monitoring is no longer necessary, as well as its role in preventing other diseases such as cardiovascular disease and hypertension – led the American Diabetes Association to issue a statement [25] in which they recommend that modest weight loss (5–10%) and modest physical activity (30 minutes daily) be the first choice for preventing or delaying the onset of type 2 diabetes among high risk populations.

It should be mentioned, however, that in the intervention group with lifestyle change, 3–5% of individuals will nonetheless progress to diabetes. Thus, in people with IGT or IFG, even when lifestyle changes are instituted, continuous monitoring for the development to diabetes is still warranted, preferably every 2–3 years.

Conclusions

There is convincing evidence that type 2 diabetes can be prevented or at least its onset delayed. The target population for a prevention program is individuals with IGT or IFG since they can be identified easily. There is an urgent need for a preventive policy that focuses on lifestyle change, mainly moderate weight loss and modest physical activity. This policy should be formulated into programs of action that should involve primary care providers. Such a program will not only contribute to primary prevention of diabetes, but will also have additional benefits in preventing cardiovascular disease hypertension and improving the well-being of our population.

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Men who are weak never give in when they should

Cardinal de Retz (1613-79), French churchman and leader of the "Fronde" rebellion