Review

Prediction and prevention of type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus is one of the most costly and burdensome chronic diseases of our time and a condition that is increasing in epidemic proportions worldwide. Its complications are a significant cause of morbidity and mortality and a tremendous economic burden to the society. Effective prevention programs are therefore urgently needed. Some of the risk factors for the development of type 2 diabetes, such as obesity, physical inactivity and high-fat diet, can potentially be modified. Compelling evidence now exists from well designed randomized studies that the disease can be prevented or delayed in subjects at high risk for its development, i.e. subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The interventions studied include lifestyle modifications (with diet and exercise) and drug treatment. Weight loss with lifestyle modification seems to be the most effective way so far, given the fact that it addresses other cardiovascular disease risk factors as well. The big challenge we are facing now is to try to implement these findings in our society or among our high-risk patients, taking into consideration the great difficulties involved in changing lifestyle and in maintaining lifestyle modifications.

Key words: type 2 diabetes mellitus, prediction, prevention, lifestyle interventions

INTRODUCTION

The prevalence of type 2 diabetes mellitus (DM) is increasing and is reaching epidemic proportions worldwide, as the population becomes older and is less active and more obese. According to recent estimates in the United States, approximately 16 million Americans - one in every 14 individuals - have diabetes¹. Its future burden worldwide is expected to increase dra-

matically (from around 155 million people with DM in the year 2000 to around 300 million in the year 2025^{2,3}, more than 75% of whom will be in the developing countries).

DM is associated with increased long-term morbidity and an increased risk of mortality⁴. Microvascular complications, for example, lead to more than 50,000 lower extremity amputations each year, about 13,000 new cases of end-stage renal disease (ESRD) and about 15,000 to 39,000 new cases of blindness in the USA alone⁵. Cardiovascular disease is only one of the macrovascular complications and the leading cause of death in these people, especially women⁶. The economic burden of treating diabetes and its complications is likewise enormous^{7,8}. Effective primary prevention programs for type 2 DM are therefore urgently

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needed to reduce the clinical and economic health burden. It has been estimated, for example, that by delaying the manifestation of type 2 DM by 6 years with systematic treatment at its onset, the lifetime risk of severe diabetic retinopathy would be reduced by 65%⁹.

The microvascular complications of type 2 DM depend on the duration and intensity of hyperglycemia after the overt clinical manifestation of DM^{10,11}. On the other hand, the risk for macrovascular complications seems to start before the clinical appearance of DM, in the pre-diabetic phase (the ticking clock hypothesis)¹². Clinically manifested DM constitutes a cluster of cardiovascular risk factors¹³ and the actual number of people at risk for the detrimental effects of diabetes (especially on the cardiovascular system) is much higher than estimated.

Type 2 DM is characterized by hyperglycemia, insulin resistance and relative impairment in insulin secretion. Its pathogenesis is poorly understood, but both genetic factors affecting insulin secretion and responsiveness¹⁴ and environmental factors, such as obesity, physical inactivity and consumption of dietary fat, appear to contribute¹⁵. Some of these risk factors for the development of type 2 DM (obesity, physical inactivity, high-fat diet) can potentially be modified. In addition, some of the metabolic abnormalities that precede type 2 DM, such as insulin resistance or impaired glucose tolerance (IGT) can be improved by lifestyle changes and possibly drug treatment. Primary prevention of type 2 DM can be implemented either through a population strategy, i.e. changing the lifestyle and environmental determinants that are known to be risk factors for diabetes or through a high-risk strategy, i.e. targeting preventive measures only at those specific individuals or groups that are at high risk for the future development of type 2 diabetes. These include those who have close relatives with type 2 DM, have a history of gestational diabetes or are members of specific ethnic groups (e.g. Pima Indians, Polynesian and other Pacific Islanders, etc)¹⁶. Another important issue in prevention is distinguishing type 2 diabetes from type 1 diabetes. Although type 1 DM is more common in children and adolescents, approximately 30% of cases present after the age of 35¹⁷. A number of these patients sustain a slow autoimmune destruction of the pancreatic beta-cells and are characterized as suffering from LADA (Latent Autoim-

mune Diabetes in Adults). Prevention programs will obviously work differently in these individuals since the risk factors for developing overt DM are different.

PREDICTION OF TYPE 2 DIABETES

Our ability to predict type 2 DM in the general population is limited. Abnormal glucose metabolism can be documented years before the onset of overt diabetes¹⁸. In some groups, insulin resistance appears to be the best predictor of future type 2 diabetes¹⁹, but tests for insulin resistance are not practical in routine clinical practice. Other studies suggest that abnormalities in insulin secretion may precede the development of insulin resistance²⁰.

In epidemiological studies, the development of type 2 diabetes has been associated with various risk factors, such as parental history of diabetes, baseline levels of body mass index (BMI), fasting glucose, plasma glucose levels one hour after a 75-g oral glucose load and black race²¹. Actual overweight or weight gain in lean subjects have also been shown to be associated with increased risk for the development of type 2 diabetes²², as has a history of gestational diabetes in women²³. Markers of inflammation²⁴, irregular menstrual cycles in women²⁵, low birth weight²⁶ and cigarette smoking²⁷ have also been implicated as risk factors. Subjects with impaired glucose tolerance (IGT) have the highest risk for progression to type 2 diabetes^{28,29} and have been the target for preventive strategies in most studies so far. Subjects with impaired fasting glucose (IFG), i.e. fasting plasma glucose 6.1-7.0 mmol/l (110-126 mg/dl), have also been found to be at increased risk for the future development of type 2 DM²⁹.

A brief review of the significance of the aforementioned risk factors for the development of type 2 diabetes follows.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG): IGT is defined as an intermediate state between overt diabetes and normal subjects during an oral glucose tolerance test (OGTT). Specifically, patients with IGT have a normal fasting blood sugar (<7.0 mmol/l or <126 mg/dl) and a value of 7.8-11.1 mmol/l (140-200 mg/dl) 2 hours after an oral glucose load of 75 g³⁰. The rate of progression from IGT to overt diabetes varies among different populations. In six prospective studies, for example,

the incidence rates of type 2 DM among patients with IGT ranged from 36 to 87 per 1000 person-years (or 18-43% in 5 years)³¹. The rates were higher among the Hispanic, Pima and Nauruan populations than among the whites. Estimates of obesity (BMI, waist/hip ratio and waist circumference), but not sex or family history of diabetes, were also related to the rate of progression in these studies. The problem with the OGTT is that it is a time-consuming test with a large within-subject coefficient of variation³². Furthermore, it is not sufficiently sensitive to detect early metabolic defects. As an example, first-degree relatives of patients with type 2 DM frequently have impairment in non-oxidative glucose metabolism (indicative of insulin resistance) despite a normal OGTT³³. For this reason, simpler prediction models have been investigated for identifying persons at increased risk for developing type 2 DM. In a recent study, a simple model that included BMI, fasting plasma glucose and fasting serum lipid profile was superior to the 2-hour plasma glucose value after oral glucose for identifying persons at high risk for developing type 2 DM³⁴. Specifically, for prediction of 7.5-year incidence of type 2 DM, the receiver-operating characteristic (ROC) curve for a multivariable model involving the above-mentioned variables was significantly greater ($p < 0.001$) than the area under the ROC curve for the 2-hour glucose value alone (84.3% vs 77.5%). IGT represented a single point on the latter curve. Adding the 2-hour glucose measurement to the multivariable model increased the area under its ROC, but only from 84.3% to 85.7%³⁴.

The addition of the measurement of hemoglobin A_{1c} (HbA_{1c}) to the OGTT seems to offer better prediction capabilities for identifying persons at increased risk for the development of type 2 DM. HbA_{1c} is an indirect measure of the average blood glucose concentration over the preceding 2 to 3 months³⁵ and has certain practical advantages over the OGTT: its measurement is not influenced by the time of the day, recent activity levels, metabolic stress or food intake; only minimal patient cooperation is required before and during the test and only a small blood sample is needed³⁶. In a prospective study of 381 non-diabetic high-risk Pima Indians, measurement of HbA_{1c} in addition to the OGTT predicted the development of type 2 DM more accurately than the OGTT alone. Specifically, of those subjects with IGT, a significantly greater percentage with elevated HbA_{1c} at baseline developed

DM within 6 years (68%), compared with those with normal HbA_{1c} at baseline (28%)³⁷. Despite the potential usefulness of HbA_{1c}, the International Expert Committee³⁰ does not recommend its use for diagnosing DM or for any screening purposes. The OGTT is still the preferred method in routine practice for identifying persons at high risk for type 2 DM (IGT subjects) and the one that has been used in most studies to predict its development.

The risk of conversion to diabetes is equivalent for IGT and IFG, but these two abnormalities overlap only 20-25%²⁹. In the Hoorn study, the risk of conversion to diabetes during a 6.5-year of follow-up period was more than 8 times higher in people with IGT (57.9/1000 person-years) or IFG (51.4/1000 person-years) than in people with normoglycemia (7/1000 person-years). The combination of IFG and IGT in a subject yielded an incidence density for the conversion to diabetes more than 16 times the normoglycemic rate (112.2/1000 person-years)²⁹. This is why the American Diabetes Association has defined "pre-diabetes" as either IGT or IFG, considering these subjects collectively at high risk for development of diabetes and its complications, and recommends efforts to prevent diabetes specifically in these groups³⁸.

Fasting plasma pro-insulin concentrations³⁹ or a low insulin response during the first 30 minutes of an OGTT²⁰ have also been found to predict the development of type 2 DM, but these tests are currently not widely used for screening.

In normoglycemic subjects, serum insulin-like growth factor I (IGF-I) concentrations are inversely correlated with the development of glucose intolerance (IGT or diabetes after 4.5 years of follow-up), suggesting that this hormone may play a role in glucose homeostasis, in particular protecting against the development of glucose intolerance⁴⁰. The usefulness of this test in predicting type 2 DM needs to be elucidated in prospective studies.

Obesity and Dietary Patterns: Obesity is generally defined as a body mass index (BMI) $> 30 \text{ kg/m}^2$. A BMI value of $25\text{-}30 \text{ kg/m}^2$ is defined as overweight, whereas values $18\text{-}25 \text{ kg/m}^2$ are considered to reflect normal body weight⁴¹. Obesity and overweight increase the risk of developing both IGT and type 2 diabetes at all ages⁴². They act, at least in part, by inducing resistance to insulin-mediated peripheral glucose up-

take, which is a significant component of type 2 DM⁴³.

In addition to the degree of obesity, the distribution of excess fat is another important determinant of the risk of insulin resistance and type 2 DM. The degree of insulin resistance and the incidence of type 2 DM are highest in those subjects with upper body or abdominal obesity, as manifested by a waist-to-hip circumference ratio >0.95 in men and >0.85 in women⁴⁴. Subcutaneous truncal fat rather than intraperitoneal fat appears to be of primary importance in this regard⁴⁵. This “male” type obesity is different from the typical “female” type, which primarily affects the gluteal and femoral regions and is not associated with glucose intolerance or cardiovascular diseases. The reason for this difference in risk between the two types of obesity is not known.

Dietary patterns have also been found to be associated with the risk of type 2 DM. In a study of over 42,000 male health professionals, a “western” diet (characterized by high consumption of red meat, processed meat, high fat dairy products, sweets and desserts) was associated with an increased risk of diabetes independent of BMI, physical activity, age or family history (RR: 1.6). In contrast, a “prudent” diet (characterized by higher consumption of vegetables, fruit, fish, poultry and whole grains) was associated with a reduced risk (RR: 0.8)⁴⁶. An inverse association between consumption of dairy products and the insulin resistance syndrome has recently been documented in the CARDIA study (Coronary Artery Risk Development in Young Adults)⁴⁷ in overweight but not lean individuals. In this study, overweight adults with the highest consumption of dairy products (≥ 35 times per week) had a significantly lower risk of insulin resistance syndrome when compared to those with the lowest dairy consumption (< 10 times per week) (adjusted OR: 0.28).

Birth weight: There is an inverse association between birth weight and risk for type 2 DM. Specifically, subjects who had low birth weights for gestational age have as adults reduced beta-cell function, insulin resistance⁴⁸ and an increased incidence of type 2 DM²⁶. The reason for this is unclear. One speculation is that intrauterine growth retardation leads to inadequate pancreatic development and impaired maturation of one or more components of the insulin action cascade. Another hypothesis is that fetal malnutrition may result in changes in the metabolic handling of nutrients

to provide for more efficient utilization, a process that can be imprinted and become permanent. The individual, when exposed to an abundance of calories in postnatal life, develops central obesity and insulin resistance. Phillips et al. presented evidence for this mechanism when they showed that adults who had intrauterine growth retardation have elevated plasma cortisol levels that are correlated with fasting and 2-h plasma glucose, systolic blood pressure, plasma triglycerides and insulin resistance. They suggested that fetal malnutrition alters intrauterine programming of the hypothalamic-pituitary-adrenal axis⁴⁹.

Markers of Inflammation: Inflammation may play a role in the pathogenesis of diabetes, suggesting that markers of inflammation may identify patients at increased risk for developing the disease. In a subset of 188 women from the Women’s Health Study, those women who developed type 2 diabetes during a 4-year follow-up period had significantly higher baseline serum concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) - two markers of inflammation - as compared to 362 age-matched normal control women, who did not develop diabetes²⁴. The multivariate relative risk was 2.3 for IL-6 and 4.2 for CRP. Similar findings were noted in the Mexico City Diabetes Study⁵⁰, where baseline CRP levels correlated with the development of DM and the metabolic syndrome in women, but not in men.

Irregular menstrual cycles: Women with long intermenstrual cycles appear to be at increased risk for type 2 DM. In the Nurses’ Health Study²⁵, the relative risk of developing type 2 DM in women with a menstrual cycle length greater than 40 days, as compared to women with a cycle length of 26-31 days, was 2.1. The risk was greater in obese (BMI $>30\text{kg/m}^2$, RR: 3.9) than in non-obese women - although the increased risk persisted in them as well (BMI $<25\text{kg/m}^2$, RR: 1.7). A possible explanation for this observation is that these women may have polycystic ovary syndrome, which is associated with increased risk for type 2 DM, independent of BMI.

Cigarette Smoking: Several large prospective studies have raised the possibility that cigarette smoking increases the risk of type 2 DM^{27,51-55}. The relative risk of developing diabetes for individuals who smoked more than 20-25 cigarettes per day in these reports ranged from 1.4 to 3.6, compared to non-smokers. The risk appears to be graded, with increasing risk as the

number of cigarettes smoked per day and pack-year history rises. Estimates from the Physicians' Health Study suggest that in the U.S.A., where approximately 25% of people smoke, about 10% of the incidence of type 2 diabetes may be attributable to smoking²⁷. While a definite causal association has not been established and the evidence linking cigarette smoking to diabetes is still considered preliminary⁵⁶, the relationship is biologically plausible: smoking increases blood glucose concentration after an oral and intravenous glucose challenge⁵⁷, impairs insulin sensitivity⁵⁸ and has been linked to increased abdominal fat distribution and increased waist-to-hip ratio⁵⁹, which increase glucose intolerance⁴⁴. A direct toxic effect on pancreatic tissue has also been suggested⁵¹.

Gestational diabetes: Gestational diabetes (GDM) is a predictor of diabetes (mainly type 2) later in life^{23,60}. Women with GDM have defects both in insulin secretion and insulin action⁶¹, the severity of which correlate with the future development of diabetes. Even one year after delivery, the frequency of glucose intolerance (diabetes and IGT) may be between 9-23%. Important risk factors for the early development of this glucose intolerance are significant weight gain after delivery, diabetes of a first-degree relative and diagnosis of GDM in the early pregnancy with considerably high fasting glucose values⁶². The cumulative incidence of type 2 DM is about 50% at 5 years after delivery²³. The risk is closely related to the results of an OGTT performed 4-16 weeks postpartum: specifically, diabetes developed in 12% of women with a normal OGTT compared to 84% of women with IGT postpartum²³.

Family history of diabetes: People with a family history of type 2 diabetes are likewise at increased risk of developing type 2 DM themselves. There is a strong genetic influence on the development of the disease. The lifetime risk for a first-degree relative of a patient with type 2 DM is 5 to 10 times higher than that of age- and weight-matched subjects without a family history of diabetes⁶³. Thirty nine percent of patients with type 2 DM have at least one parent with the disease⁶⁴. Direct evidence for a genetic factor comes from identification of mutations in specific genes that result in a type 2 diabetic phenotype. There are several monogenic forms of MODY (Maturity Onset Diabetes in the Young) that have been described, resulting from point mutations in the glucoki-

nase gene as well as in transcription factors involved primarily in beta-cell function⁶⁵. Rare syndromes involving diabetes with mitochondrial and somatic gene mutations have also been described⁶⁶. The vast majority of patients with type 2 diabetes, however, have a polygenic disorder with multiple genetic defects and considerable heterogeneity from a genetic perspective¹⁴. Mutations in a single gene account for only 5% of cases of type 2 diabetes⁶⁷. Studies of family and ethnic aggregation of the disease have also provided indirect evidence of a genetic cause of type 2 diabetes⁶⁸. The strongest evidence supporting genetic factors in type 2 DM comes from twin studies which have shown almost complete concordance for type 2 DM in monozygotic twins⁶⁹.

PREVENTION OF TYPE 2 DIABETES

Given the fact that type 2 diabetes is a widespread, devastating disease with significant morbidity and mortality and inflicting an enormous economic burden on society, it is not surprising that studies have been initiated in the last decade to determine the feasibility and benefit of various strategies to prevent or delay its onset. Although, as stated above, there is evidence that many risk factors are independently associated with the development of type 2 DM (such as age, family history, obesity, low birth weight, history of gestational diabetes, cigarette smoking), the majority of studies show that the incidence of type 2 DM is most strongly related to the hyperglycemic states of IGT and IFG. None of the other factors taken singly is as good in discriminating who will progress to diabetes as measuring glucose levels (fasting or postprandial). It should be noted, however, that when taken in the aggregate, these risk factors combined with glucose levels are more predictive of future diabetes than are glucose levels by themselves³⁴. Since these two pre-diabetic states (IFG and IGT) are relatively easily, reliably and safely identified (with a fasting blood glucose measurement and an OGTT), most studies investigating the issue of preventing type 2 DM have concentrated on them. The methods used to accomplish this goal of preventing type 2 diabetes have been either through lifestyle interventions (with diet and/or exercise) and/or medications.

Lifestyle Interventions: Since obesity and physical inactivity are risk factors for the development of the metabolic syndrome and DM, many studies have

investigated the role of weight loss through diet and/or physical activity in their prevention.

When performed on a regular basis, exercise may improve glycemic control and several diabetes-related cardiovascular risk factors, including hypertension and hypertriglyceridemia. The metabolic benefits appear to be partly related to the enhancement of insulin sensitivity⁷⁰. In addition, exercise may be a useful adjunct to diet in producing weight loss. In a prospective study of 5,990 male alumni of the University of Pennsylvania, followed for 14 years (from 1962 to 1976), leisure time physical activity (expressed in kilocalories [kcal] expended per week in walking, stair climbing and sports), was inversely related to the development of type 2 diabetes⁷¹. The incidence rates declined as energy expenditure increased from <500 kcal to >3500 kcal per week. For each 500-kcal increment in energy expenditure, the age-adjusted risk of type 2 DM was reduced by 6%. The protective effect of physical activity was strongest in persons at highest risk for type 2 DM, defined as those with a high BMI, a history of hypertension or parental history of diabetes.

The benefit of exercise has also been shown in persons with IGT. In a 6-year prospective non-randomized study from Sweden⁷², - the Malmo feasibility study - a program of diet plus regular exercise training was given to 161 men with IGT identified during screening of almost 7,000 men, aged 47-49 years. These 161 men were compared with 56 men with IGT who were not enrolled in the program for various reasons, but had similar baseline characteristics. The men in the intervention group were advised to reduce fat and sugar intake, to increase complex carbohydrate and fiber in the diet, to reduce body weight and to take part in a physical training program. The treated subjects produced a significant weight loss (2.3-3.7% vs 0.5-1.7% in controls), which in most cases was maintained for 5 years. At follow-up 5 years later, glucose tolerance had improved in 76% of the subjects in the intervention group but had deteriorated in 67% of those in the control group. Diabetes had developed in 11% of the subjects in the intervention group vs 29% of the controls (RR: 0.37, $p < 0.003$).

In the Chinese Da Qing IGT and Diabetes Study⁷³, a total of 577 subjects with IGT were randomized by clinic to either a control group or to one of three active treatment groups: diet only, exercise only, or diet

plus exercise. Follow-up evaluation examinations were conducted at 2-year intervals over a 6-year period to identify subjects who developed type 2 DM. The cumulative incidence of DM at 6 years was 67.7% in the control group compared to 43.8% in the diet group, 41.1% in the exercise group and 46.0% in the diet-plus-exercise group. These effects persisted after stratification for obesity ($\text{BMI} < \text{or} \geq 25 \text{ kg/m}^2$). In a proportional hazards analysis, adjusted for differences in baseline BMI and fasting glucose, the diet, exercise and diet-plus-exercise interventions were associated with 31% ($p < 0.03$), 46% ($p < 0.0005$) and 42% ($p < 0.005$) reductions in the risk of developing type 2 DM, respectively.

These two earlier reports (the Malmo feasibility study⁷² and the Chinese study⁷³), although suggesting that changes in lifestyle through diet and exercise could prevent type 2 diabetes, were criticized for weaknesses in study designs (non-randomization in the Swedish study, randomization by clinics instead of by subjects in the Chinese study), which limited their general relevance. Recently, however, two well-designed, randomized, controlled trials have been reported that strengthen the assumption that lifestyle interventions can effectively prevent type 2 diabetes^{74,75}.

In the Finnish study⁷⁴, 522 middle-aged (mean age 55 years), obese (mean BMI 31 kg/m^2) subjects with IGT were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instructions on weight reduction, food intake and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a relative reduction of 58% ($p < 0.001$) in the incidence of diabetes in the intervention group compared to the control subjects (Figure 1). The mean weight loss in the intervention group was 3.5 kg at the end of two years, compared to 0.8 kg in the control group. A strong correlation was also seen between the ability to stop the progression to diabetes and the degree to which subjects were able to achieve one or more of the following goals: lose weight (goal >5% weight reduction), reduce fat intake (goal of <30% of calories), reduce saturated fat intake (goal of <10% of calories), increase fiber intake (goal of $\geq 15 \text{ g/1000 kcal}$) and exercise (goal of >30 minutes/day). No untoward effects of the lifestyle intervention was observed.

In the Diabetes Prevention Program⁷⁵, a total of

Figure 1. Proportion of subjects without diabetes during the trial. The vertical bars show the 95% confidence intervals for the cumulative probability of remaining free of diabetes. The relative risk of diabetes for subjects in the intervention group, as compared with those in the control group, was 0.4 ($p < 0.001$ for the comparison between the groups).

3,234 non-diabetic persons with elevated fasting and post-load glucose concentrations were randomly assigned to placebo, metformin (850 mg twice daily) or a lifestyle modification program with the goals of at least 7% weight loss and at least 150 minutes of physical activity per week. A 16-lesson curriculum covering diet, exercise and behavior modification was designed to help the participants of the latter group achieve these goals. The mean age of the participants was 51 years, the mean BMI 34 kg/m² and 45% were members of minority groups. The study was terminated early, after an average follow-up of 2.8 years (range 1.8 to 4.6 years) when it became clear that the results in the diet and exercise group were superior to those in the other groups. There was a 58% relative reduction in the progression to diabetes in the lifestyle intervention group and a 31% relative reduction in the progression to diabetes in the metformin group compared with control subjects (Figure 2). The lifestyle intervention was also significantly more effective than metformin (39% relative reduction) in preventing type 2 diabetes. On average, 50% of the lifestyle group achieved the goal of >7% weight reduction and 74% maintained at least 150 min/week of moderately intense activity. The average weight loss

Figure 2. Cumulative incidence of diabetes according to study group. The incidence of diabetes differed significantly among the three groups ($p < 0.001$ for each comparison).

was 0.1, 2.1 and 5.6 kg in the placebo, metformin and lifestyle intervention groups, respectively. Lifestyle intervention was effective in men and women, in all age groups and in all ethnic groups. No serious side effects were seen in any groups.

The combined effects of diet and healthy lifestyle were also important for the prevention of type 2 diabetes in women in the Nurses' Health Study, where 91% of the cases of diabetes could be attributed to obesity, lack of exercise, a poor diet, smoking and alcohol consumption⁷⁶. These findings suggested that many cases of diabetes could be prevented with a healthier lifestyle. A similar positive effect of diet and exercise has been reported in Japanese-American men and women⁷⁷. A beneficial effect of weight loss for the prevention of progression of IGT to overt DM through bariatric surgery has also been observed in 109 morbidly obese patients with IGT (>45 kg excess body weight, mean BMI 48 kg/m²), as compared to 27 similarly obese subjects with IGT (mean BMI 51 kg/m²) who did not undergo surgery. The risk of DM was reduced by more than 30-fold in the surgery group who lost about 50% of their excess weight over a period of 5.8 years⁷⁸.

Since many epidemiological studies have shown that cigarette smoking may be associated with increased risk for the development of type 2 diabetes^{27,51-55}, studies have been carried out to examine the impact of smoking cessation on preventing diabetes. In a recent prospective study of 7,735 men, aged 40-59 years, fol-

lowed for an average of 16.8 years, cigarette smoking was found to be associated with increased risk of diabetes, even after adjustment for age, BMI and other potential confounders⁷⁹. The benefit of giving up smoking was only apparent after 5 years of smoking cessation and risk reverted to that of never-smokers only after 20 years. Men who gave up smoking during the first 5 years of follow-up showed significant weight gain and subsequently higher risk of diabetes than continuing smokers, during these first 5 years. The risk of diabetes in those who switched from smoking cigarettes to pipes or cigars remained equal to the risk in continuing cigarette smokers.

Pharmacological Interventions: Due to ethical and socioeconomic considerations, any medicine regarded as a means of preventing type 2 diabetes must have a proven efficacy in influencing at least one of the metabolic abnormalities of pre-diabetes, and – most important – have an excellent safety profile. Various kinds of medications have been studied so far for the prevention of type 2 DM. Four of them have proven effective to date.

As stated earlier, metformin was found to reduce the incidence of type 2 diabetes by 31% compared to placebo, in the Diabetes Prevention Program⁷⁵. Metformin was about half as effective as diet and exercise in delaying the onset of diabetes overall (31% vs 58%), but it was virtually ineffective in older individuals (≥ 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 (44% risk reduction) or in those with a $\text{BMI} \geq 35 \text{ kg/m}^2$ (53% risk reduction). Thus, the population of people in whom treatment with metformin has equal benefit to that of a lifestyle intervention is only a small subset of those likely to have IGT or IFG. The way metformin exerts its beneficial effects is thought to be through normalization of impaired glucose tolerance in obese subjects⁸⁰, suppression of elevated rates of hepatic glucose production⁸¹ and probable delay or inhibition of glucose absorption from the gastrointestinal tract⁸². Metformin has also been shown to decrease food consumption and to induce weight loss in obese subjects with type 2 diabetes⁸³.

In the STOP-NIDDM trial⁸⁴, 1,429 participants with IGT were randomized in a double-blind fashion to receive either the α -glucosidase inhibitor acarbose (100 mg three times a day) or a placebo. The subjects

had a mean age of 54.5 years and a mean BMI of 31 kg/m^2 . After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose-treated group compared to the placebo. If the diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was observed in the acarbose-treated group compared to the placebo group. The effect of acarbose was consistent among all age groups, BMI values and both sexes. The mode of action of acarbose is thought to be through improvement of insulin sensitivity and decrease of post-prandial hyperglycemia, thereby decreasing the stress of hyperglycemia on the beta-cells⁸⁵.

In the Troglitazone In Prevention Of Diabetes (TRIPOD) study⁸⁶, 236 Hispanic women with previous gestational diabetes were randomized to receive either placebo or troglitazone (a thiazolidinedione withdrawn from the market since 1998 because of significant liver toxicity). After a median follow-up of 30 months, the annual incidence of type 2 diabetes in the two groups was 12.1 % and 5.4%, respectively ($p < 0.01$). Thus, troglitazone was associated with a 56% relative reduction in progression to diabetes. Of note is the fact that, after a washout period of > 8 months, the preventive effects of the drug were still observed. The protective effect was associated with the preservation of pancreatic beta-cell function and appeared to be mediated through a reduction in the secretory demands placed on beta-cells by chronic insulin resistance. Thus, it is possible that troglitazone, acting through the nuclear receptors $\text{PPAR}\gamma$, may affect the natural history of glucose intolerance and may actually prevent diabetes in some people rather than just delay its onset. Future studies with the other two thiazolidinediones currently on the market (rosiglitazone and pioglitazone) will show if these effects are really class-effects and if these medicines, by improving insulin sensitivity, prove helpful in preventing type 2 diabetes.

In the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study⁸⁷, 3,304 obese subjects (mean BMI 37.3 kg/m^2) – 21% with IGT at baseline – mean age 43.3 years, were randomly assigned to treatment with the weight loss agent orlistat (120 mg three times daily) plus lifestyle changes (800 kcal/day deficit and moderate physical exercise) or placebo and lifestyle changes. People were monitored over

a period of 4 years for the prevention of type 2 diabetes. Mean weight loss was significantly greater in orlistat than in placebo patients at 1 year and at the end of the 4 years. The hazard ratio analysis showed that at 4 years, orlistat had decreased the risk of type 2 diabetes by 37.3% compared to placebo. Orlistat treated patients also achieved a significantly greater mean reduction in waist circumference and LDL-cholesterol and greater improvement in systolic and diastolic blood pressures than placebo treated patients.

A surprising finding in the Heart Outcomes Prevention Evaluation (HOPE) trial of patients with cardiovascular disease was that angiotensin-converting-enzyme (ACE) inhibitors may delay or prevent the onset of type 2 diabetes⁸⁸. Among the 5,720 patients in the study who were non-diabetic at randomization, 257 developed diabetes during the 4.5 years of follow-up. There were significantly fewer cases in the ramipril (the ACE-inhibitor) group than the placebo group (3.6 % vs 5.4%; RR: 0.66, $p < 0.001$). A similar benefit was noted with the angiotensin II receptor blocker losartan in hypertensive patients⁸⁹. How inhibition of angiotensin II activity may prevent type 2 diabetes is still unclear. Possible mechanisms include increased insulin sensitivity and increased blood flow to the pancreas⁹⁰.

The use of sulfonylureas in prevention studies of type 2 diabetes is somewhat ambiguous. In two previous randomized studies performed in Bedford⁹¹ and Malmohus⁹² County in Sweden, there was no discernible effect of tolbutamide therapy on the incidence of type 2 diabetes over a 10-year period. In the latter study⁹², tolbutamide treatment showed a reduction in the incidence of diabetes, but only on 23 subjects with IGT, thus yielding inadequate statistical power and consequently equivocal results. Similarly negative results had been reported earlier with chlorpropamide⁹³. Thus, together with the considerable risk for hypoglycemia, sulfonylureas are not considered very good candidates for prevention studies.

CONCLUSIONS

Type 2 diabetes is a major public health problem and the resultant enormous personal and social costs in terms of complications, patient quality of life and health care system resources are now widely recognised⁴⁻⁸. The current system of reactive, acute episode

focused disease care, practiced in most (if not all) countries, does not adequately address this public health problem. Without an adequate approach to the prevention of type 2 diabetes, the current type of curative medicine, by simply reducing or delaying mortality without preventing morbidity, is creating the predicted "global burden of type 2 diabetes"². Type 2 diabetes is projected to become an even bigger problem in the developing countries, affecting more middle-aged people in the future. These predictions should lead to prevention strategies aiming at the reduction of risk factors which requires urgent action from national and international public health services. Ideally, this should be part of an integrated program that addresses lifestyle-related disorders. This appears to be the most promising way to prevent some of the consequences of the so-called "coca-colonization", one of them being the emerging global epidemic of type 2 diabetes in the next decades⁹⁴. In addition, in populations at high risk, pharmacological measures to prevent or delay the development of type 2 diabetes may also be useful.

The prevention studies mentioned above, and especially the recent Finnish Diabetes Prevention Study⁷⁴ and the USA Diabetes Prevention Program (DPP)⁷⁵, showed rather conclusively that the natural history of the development of type 2 diabetes can be altered. The most heartening news is that this delay or prevention of type 2 diabetes can be accomplished with a safe, inexpensive therapy, namely lifestyle modification (with the reservation, of course, that exercise-related injuries are not uncommon). The appeal of lifestyle interventions is that, apart from being inexpensive and generally safe, they also reverse the proximal factors associated with diabetes – i.e. overweight, central obesity, physical inactivity, high-fat and high-energy diets. In the process, they also promote health in general (by reducing blood pressure and lipids), empower people, make them less reliant on medicine and improve quality of life. Thus, focusing on lifestyle interventions truly shifts the paradigm from preventing disease to promoting health and well-being⁹⁵.

The flip side to our optimism is that we currently live in a society that is becoming ever more sedentary and obese. Indeed, this is the main reason we have seen such an increase in the incidence of type 2 diabetes. The increased availability of "fast foods", the lack of physical activity in our daily lives, the increase

in our dependence on the automobile and other unhealthy social developments are taking their toll. Although these recent studies indicate that, if we reverse our current lifestyle trends, we will reduce the burden of diabetes, the truth is that lifestyle changes are for most of us, a difficult challenge. Although both intervention studies mentioned above^{74,75} showed that diabetes could be prevented or delayed with only modest changes in weight and physical activity, considerable effort from well-trained staff was required to achieve these behavioral changes. In the Finnish study⁷⁴, the intervention group had 7 sessions with a nutritionist during the first year and 1 session every three months thereafter. They also received individualized guidance on increasing physical activity. Free membership to an exercise club was also offered. In the DPP⁷⁵, participants in the lifestyle arm met with a case manager 16 times over the first 6 months and monthly thereafter. They made telephone contact at least monthly. Group courses on exercise and weight loss, lasting 4-6 weeks, were offered every 3 months. Two supervised exercise sessions were offered each week. Moreover, anyone having difficulty achieving or maintaining the study's goals on weight loss or exercise were offered incentives, such as exercise tapes or equipment, free enrollment in exercise facilities, free low-calorie foods, more structured eating plans and home visits for encouragement and counseling. Keeping all this in mind and considering the generally modest goals of weight loss (5% and 7% in the two studies, respectively), it is certainly discouraging that the substantial levels of effort described above were only partially successful in achieving the desired objectives. In the Finnish study, only 43% of subjects achieved the weight reduction goal and 36% increased their physical activity. In the DPP, only 50% reached the weight loss goal and 74% reached the exercise goal. In both studies, some weight was regained despite the continuation of intensive strategies. Similar difficulties in maintaining weight loss and physical activity levels have been described in other studies of lifestyle intervention⁹⁶. The real challenge therefore now is not only to change the lifestyle of individuals at risk of developing type 2 diabetes but of the entire society.

Apart from lifestyle modifications, medications were shown in the above mentioned studies to be effective in the prevention of type 2 diabetes. With the exception of troglitazone though in the TRIPOD

Study⁸⁶ (which showed a 56% risk reduction compared to placebo), the other medicines studied (metformin, acarbose and orlistat) were half as effective as the lifestyle interventions. We do not yet know if the newer thiazolidinediones (pioglitazone and rosiglitazone) will be equally effective as troglitazone, which has been discontinued due to serious hepatic side-effects.

In response to this impressive evidence, the American Diabetes Association's Position Statement on prevention of diabetes³⁸ has recommended screening to detect people with IGT or IFG during routine healthcare office visits by people over age 45 years – particularly those with a BMI >25 kg/m². These people, collectively referred to as “pre-diabetes”, will be given counseling on weight loss as well as instruction on increasing their physical activity. Since all people who develop diabetes go through pre-diabetes (although the length of this phase may vary)⁹⁷, effectively delivering preventive methods to people with pre-diabetes will ensure that most, if not all, future cases of diabetes are targeted⁹⁸. Using medications to prevent diabetes is not yet recommended in the Position Statement, given the cost, side effects and relative ineffectiveness compared with lifestyle modifications.

Hopefully, newer medications currently in ongoing clinical trials will prove more effective than those studied so far. The combination of nateglinide (a new insulin secretagogue that restores the reduced first phase of insulin release in people with IGT and early diabetes) together with valsartan (an angiotensin II, type 1, receptor inhibitor) are currently being studied in a large multi-center study of 7,500 people with IGT - the NAVIGATOR study (Nateglinide And Valsartan In impaired Glucose Tolerance Outpatient Research). Also, the combination of ramipril (an ACE inhibitor) and rosiglitazone (a thiazolidinedione) are being investigated in a 3-year study involving 6,000 subjects with IGT, regarding the prevention of type 2 diabetes (the DREAM Study: Diabetes Reduction Approaches with ramipril and rosiglitazone Medications).

Another important issue to be addressed in future studies is whether intervention at the stage of IGT or IFG is a cost-effective way to prevent or delay the complications of diabetes, an issue of greater importance to the patient, family and society than simply the diagnosis and prevention of diabetes itself.

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