Prevention of Type 2 Diabetes

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Diabetes is a major public health problem that is approaching epidemic proportions in our society and worldwide. Cardiovascular disease is the major cause of morbidity and mortality in people with diabetes. Control of cardiovascular disease risk factors is achieved only in a minority of patients. Given the magnitude of the problem and the seriousness of diabetes complications, prevention appears to be a logical approach to curb the rising prevalence of the disease. Interventions such as lifestyle modifications and the use of metformin and acarbose have been shown in randomized prospective trials to prevent diabetes in high-risk patients. Other interventions are currently being examined in large prospective studies. It is likely that one or a combination of these approaches will make diabetes prevention a reality in the near future.

Introduction

The rising prevalence and increasing incidence of type 2 diabetes are alarming in the United States and worldwide. It is estimated that by the year 2025 there will be over 300 million people diagnosed with diabetes around the world [1]. In the United States, as the population ages and with the rising prevalence of obesity and sedentary lifestyle, the prevalence of diabetes is on the rise [2]. Furthermore, the number of high-risk ethnic minorities is increasing, leading to a further increase in diabetes prevalence in our society. Other factors that contribute to the rising prevalence of diabetes include the reduction in mortality in diabetic patients, improved detection, and lowering the threshold for diagnosis of diabetes, from 140 mg/dL to 126 mg/dL in 1996 [3]. Furthermore, the prevalence of type 2 diabetes is rapidly increasing among children. Recent reports suggest an incidence of 8% to 45% of type 2 diabetes among children newly diagnosed with the disease, compared with 1% to 2% in previous reports [4,5].

Diabetes and Cardiovascular Disease

Cardiovascular disease (CVD), including stroke, is the major cause of morbidity and mortality in people with diabetes [6••,7]. Diabetic patients have a two- to fivefold increased risk of stroke compared to those without diabetes [7]. In the United Kingdom Prospective Diabetes Study, the major risk factors for CVD and stroke in type 2 diabetes were age, male sex, hypertension, atrial fibrillation, hyperglycemia, increased low-density lipoprotein (LDL) cholesterol, and low levels of high-density lipoprotein cholesterol [7–9]. Although there is evidence that both genetic and metabolic factors affect diabetes and cardiovascular risk, control of CVD risk factors has been shown to substantially reduce macro- and microvascular complications in people with diabetes [8–11]. However, only a minority of patients have their CVD risk factors controlled.

In a report by our group, among 1372 patients followed at two academic medical centers in 1999 to 2000, only 25.6% met the target goal blood pressure (BP) of 130/80 mm Hg, recommended by the American Diabetes Association (ADA), 35.5% met the goal LDL cholesterol of less than 100 mg/dL, and 26.7% had A_{1c} levels of less than 7% [12••]. The percentage of patients who met the combined ADA goal for BP, LDL cholesterol, and A_{1c} were only 3.2%. These figures did not improve significantly in a follow-up study [13], nor did they improve significantly from the NHANES III (Third National Health and Nutrition Examination Survey, 1988 to 1991). For example, less than one third of patients with diabetes had their BP controlled to less than 130/80 mm Hg [12••,13,14], the target BP goal recommended in the ADA guidelines. These data reflect the inherent difficulties in achieving these complex guidelines, leading to increased morbidity and mortality associated with diabetes.

Diabetes is the seventh leading cause of death (sixth leading cause of death by disease) in the United States. Each year, at least 190,000 people die as a result of diabetes and its complications [1,15]. Furthermore, diabetes is currently the major cause of blindness, nontraumatic leg amputation, and end-stage renal disease in the United States [15]. Given these facts, it is not surprising that studies have been done, and others are ongoing, to examine the feasibilities of the various approaches to diabetes prevention. In this review, we cover the major diabetes prevention studies, providing some mechanistic insights and pathophysiologic rationale for the various interventions used in these trials.

Table 1. Risk factors for type 2 diabetes

Age > 45 years
Overweight (*eg*, BMI ≥ 25 kg/m^2)
Lifestyle (*eg*, habitual physical inactivity, high-caloric, high-fat intake)
Family history of type 2 diabetes (*eg*, parents or siblings)
Ethnicity (*eg*, African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
Gestational diabetes
Hypertension
Dyslipidemia (*eg*, low HDL cholesterol, high triglycerides)
Impaired fasting glucose (*eg*, ≥ 110 to ≤ 125 mg/dL)
Impaired glucose tolerance 2-hour plasma glucose ≥ 140 mg/dL

BMI—body mass index; HDL—high-density lipoprotein.
(*From* the American Diabetes Association [15].)

Risk Factors for Type 2 Diabetes

It is estimated that 90% to 95% of diabetic patients have type 2 diabetes [16]. The prevalence of diabetes increases with age. Under the age of 45, only 0.8% of the population have diabetes, whereas 11.7% of those aged 65 to 74, and 10.9% of those over the age of 75 are diagnosed with diabetes (Table 1) [1,16].

Marked racial and ethnic differences in the prevalence of diabetes exist. The risks for diabetes in African Americans, Hispanics, and Native Americans are approximately two, 2.5, and five times greater, respectively, than in Caucasians (Table 1). The highest prevalence of diabetes in the world is found in the Pima Indians of Arizona, where 65% of those 45 to 74 years of age have type 2 diabetes. Studies of the prevalence of type 2 diabetes in Mexican Americans and non-Hispanic whites in San Antonio, TX, showed that there is an inverse relationship between socioeconomic status and the prevalence of diabetes. It also appears that cultural effects lead to an increased incidence of obesity in these populations, which may lead to insulin resistance [17,18].

Family history is a very strong risk factor for the development of type 2 diabetes (Table 1). The high concordance rate of 58% to 75% of type 2 diabetes observed in identical twins strongly suggests a genetic component of the disease [17]. Lifestyle factors contributing to the development of type 2 diabetes include physical inactivity, diets that are highly caloric with high-fat content, and urbanization, after controlling for diet and exercise (Table 1) [17].

Hypertension and dyslipidemia are associated with type 2 diabetes, usually in the context of the metabolic syndrome, which also includes hyperinsulinemia, central obesity, and microalbuminuria [6••]. Patients with hypertension are 2.5 times more likely to have diabetes than are normotensive persons [19,20]. In the animal models, insulin resistance exists in genetic hypertensive rats [21]. Conversely, the association of hypertension and insulin resistance does not occur in secondary hypertension [22]. This suggests a common genetic predisposition for both hypertension and insulin resistance, a concept that is further supported by the finding of altered glucose metabolism in the offspring of patients with essential hypertension [20,23].

The incidence of type 2 diabetes is strongly related to the presence of dysglycemia, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), both of which are powerful predictors of future development of type 2 diabetes, particularly when combined [24]. However, IGT appears to have higher sensitivity than IFG for predicting the development of type 2 diabetes [25,26].

Screening Tests and Prediction of Diabetes

Screening for diabetes or IGT is controversial [27]. In 1997, the ADA recommended against community screening and against the routine use of the oral glucose tolerance test for identification of people with diabetes or IGT [28]. This has since generated a considerable amount of controversy regarding the importance of such testing and the predictive value of IFG and IGT in diabetes development [25,29–34]. However, most of the diabetes prevention trials required that participants have IGT (Table 2) [26]. The Diabetes Prevention Program (DPP) trial, however, required a fasting plasma glucose value less than 126 mg/dL and more than 95 mg/dL, as well as IGT [45]. Screening by the IFG criteria alone identifies fewer prediabetic patients than the oral glucose tolerance test [25,26].

Interventions to Prevent Type 2 Diabetes

Lifestyle changes

Exercise

In prediabetic subjects, exercise improves insulin sensitivity and peripheral glucose uptake. Long-term moderate exercise leads to more efficient energy use by increasing mitochondrial enzymes, the number of slow-switch muscle fibers, and the generation of new capillaries [46]. Furthermore, exercise promotes translocation of insulin-responsive glucose transporters (GLUT4) to the cell surface during exercise, enhancing glucose uptake and increasing insulin sensitivity [47].

The protective effects of physical activity have been demonstrated in two prospective cohort studies [48,49], where the development of type 2 diabetes was significantly lower in patients who exercised regularly, even after adjustment for obesity, hypertension, and family history of diabetes. In these two studies, diabetes reduction with physical activity was strongest in individuals at the highest risk for type 2 diabetes, and the incidence of diabetes declined as energy expenditure increased [48,49].

More recently, the Finnish Diabetes Prevention study [35••] evaluated the effects of diet and exercise on the progression from IGT to diabetes in 522 middle-aged overweight subjects followed for 3.2 years. Patients were randomly assigned to either an intervention or a control group. Each subject in the intervention group received individualized counseling aimed at reducing weight, total intake

Table 2. Various interventions in the diabetes prevention studies

Intervention	Study
Diet and exercise	The Finnish Diabetes Prevention Study [35••]
	The Diabetes Prevention Program (DPP) [36••]
	The Da Qing IGT and Diabetes Study [37]
Metformin	The DPP [36••]
Acarbose	The Study to Prevent non–insulin-dependent diabetes mellitus (STOP-NIDDM) trial [38]
Thiazolidinediones	Troglitazone in the Prevention of Diabetes (TRIPOD) [39]
Angiotensin-converting enzyme inhibitors	The Captopril Prevention Project (CAPPP) [40]
	The Heart Outcomes Prevention Evaluation (HOPE) [41••,42]
	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) [41••]
Angiotensin receptor blockers	Lorsatan Intervention for Endpoint reduction in hypertension (LIFE) [43••]
	The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study [44]
Natiglinide	NAVIGATOR [44]

of fat and intake of saturated fat, and increasing intake of fiber and physical activity. The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group, a 58% reduction in the risk of diabetes. Reduction in the incidence of diabetes was directly related to lifestyle changes [35••].

In the United States DPP [36••], a randomized controlled trial, 3234 individuals with IGT were enrolled (mean age 51, mean body mass index 34) and followed for an average of 3 years. Patients were randomized to one of three intervention groups, which included an intensive nutrition and exercise (lifestyle) program, or either one of two masked medication treatment groups—the metformin group or the placebo group. In this study, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group and a 31% relative risk reduction was observed in the metformin group, compared with placebo. Fifty percent of the subjects in the lifestyle group achieved the goal for weight reduction of 7%, and 74% maintained at least 150 min/wk of moderately intense physical activity. The risk reduction from lifestyle modification was similar to that seen in the Finnish study, 58%.

Weight loss

Increased body fat, particularly central obesity, is among the most modifiable risk factor for the development of diabetes [50]. The effect of weight loss on the progression of IGT to diabetes was examined in several studies [51,52]. In a prospective randomized controlled study involving 154 overweight individuals with family history of diabetes (one or both parents), modest weight loss of 4.5 kg reduced the risk of type 2 diabetes by approximately 30% compared with no weight loss [51]. In obesity, IGT results from impaired insulin action [53]. The abdominal adipocytes appear to have increased sensitivity to catecholamine-induced lipolysis and higher lipid turnover [50].

Dietary intervention

Several studies demonstrated the effect of high dietary fat on the development of type 2 diabetes [54–56]. The effect of long-term intake of fat or saturated fat appears to have an effect independent of weight gain. In the San Luis Valley Diabetes Study, fat consumption significantly predicted the risk of type 2 diabetes in subjects with IGT after controlling for obesity and markers of glucose metabolism [55]. Furthermore, reducing fat intake reduces or delays diabetes. The long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance showed improved glucose tolerance in patients on the reduced-fat diet, with a lower proportion having type 2 diabetes or IGT at 1 year [56]. One of the potential mechanisms of reducing the development of diabetes by diet is the reduction of nonesterified fatty acids. A very high ratio of saturated to unsaturated nonesterified fatty acids in the blood might promote hyperinsulinemia, dyslipidemia, and glucose intolerance [57].

Diet plus exercise

In 1986, 110,660 men and women from 33 health care clinics in the city of Da Qing, China, were screened for IGT and diabetes [37]. Of these individuals, 577 were classified (using World Health Organization criteria) as having IGT. Subjects were randomized by clinic into a clinical trial, either to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. Follow-up evaluations were conducted at 2-year intervals over a 6-year period to identify subjects who developed type 2 diabetes. Risk reductions in diabetes were 31% with diet, 46% with exercise, and 42% with diet plus exercise [37].

Pharmacologic interventions

Several drugs have been shown to reduce the development of diabetes (Table 2).

Biguanides (metformin)
In the DPP trial [36••], metformin reduced the progression of prediabetes to diabetes by 31%, compared with placebo, a risk reduction somewhat less than that seen in the lifestyle-intervention group (58%). Furthermore, the number needed to treat with metformin to prevent one case of diabetes in 3 years was 13.9, compared with 6.9 in the lifestyle-intervention group.

Metformin is a potent insulin-sensitizing agent that acts primarily by suppressing hepatic glucose production [58]. Metformin inhibits free fatty acid (FFA) production and oxidation, thereby reducing FFA-induced insulin resistance and hepatic glucose production [58]. Metformin also has favorable effects in patients with the metabolic syndrome, as demonstrated in the BIGPRO (Biguanides and Prevention of Risks in Obesity) study [59].

Thiazolidinediones
In the TRIPOD (Troglitazone in the Prevention of Diabetes) study [39], the thiazolidinedione, troglitazone, has been shown to delay or prevent the onset of type 2 diabetes, compared with placebo, in a group of 133 high-risk Hispanic women with a history of gestational diabetes followed for 30 months. Troglitazone prevention of diabetes was proportional to the reduction in plasma insulin level after 3 months of treatment [39]. These results are consistent with the notion that thiazolidinediones prevent diabetes by ameliorating insulin resistance.

The mechanism of action of thiazolidinediones involves binding to the peroxisome proliferator-activated receptor γ, a transcription factor that regulates the expression of specific genes, especially in fat cells, but also in other tissues. It is likely that thiazolidinediones primarily act in adipose tissue, where peroxisome proliferator-activated γ is predominantly expressed. Thiazolidinediones have been shown to interfere with the expression and release of mediators of insulin resistance originating in adipose tissue (*eg,* FFAs, adipocytokines, such as tumor necrosis factor α, resistin, adiponectin) in a way that results in net improvement of insulin sensitivity in muscle and liver [60]. The thiazolidinedione, rosiglitazone, is currently being investigated in a large multicenter trial involving the use of the angiotensin-converting enzyme (ACE) inhibitor, ramipril, in a 2×2 design, with the primary end point being the development of diabetes in patients with IGT [41••].

α-Glucosidase inhibitors
A multicenter, randomized, placebo-controlled study, the STOP-NIDDM (Study to Prevent non–insulin-dependent diabetes mellitus) trial [38] examined the ability of acarbose to prevent type 2 diabetes in patients with IGT. Seven hundred and fourteen patients were randomized to acarbose and 715 to placebo and were followed for 3 years. Thirty-two percent of patients randomized to acarbose, and 42% of those randomized to placebo, developed diabetes, a relative risk reduction of 25%. Furthermore, acarbose also significantly increased reversion of IGT to normal glucose tolerance [38]. By decreasing postprandial blood glucose, acarbose improves both insulin secretion and sensitivity [61].

ACE inhibitors and ARBs
Medications that interrupt the renin-angiotensin system have been shown in randomized controlled trials to reduce the incidence of type 2 diabetes as a secondary outcome measurement [40,42,43••]. In the CAPPP (Captopril Prevention Project) randomized trial, the ACE inhibitor captopril reduced the development of diabetes by 14%, compared with the β blocker or thiazide diuretic treatment arm [40]. The possibility that an ACE inhibitor (ramipril) may prevent diabetes was also explored in the HOPE (Heart Outcomes Prevention Evaluation) study [42], in which patients with high risk for CVD were randomized to receive either ramipril or placebo. This study included 5720 individuals without prior history of diabetes followed for 4.5 years. Ramipril was shown to decrease the development of type 2 diabetes by 34% compared with placebo. The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications) trial is a randomized controlled trial, testing the hypothesis generated in the HOPE study, in which ramipril or rosiglitazone are being evaluated for diabetes prevention [41••].

Angiotensin receptor blockers (ARBs) may also prevent diabetes. In the LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial [43••], there was a 25% lower incidence of new-onset diabetes in the losartan group, an ARB, than in the atenolol group. The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) [44] is an ongoing trial that examines, as a primary end point, the development of new-onset diabetes, in a 2×2 factorial design, with the use of an ARB (valsartan) and an insulinotropic agent (nateglinide). Nateglinide is a D-phenylalanine derivative that improves early insulin secretion and controls postprandial glucose excursions in prediabetic patients [62].

The mechanism by which ACE inhibition and, perhaps, ARB therapy reduce the development of type 2 diabetes in patients at risk is not clear. Several hypotheses have been proposed [6••,19,63]. However, there appears to be postreceptor insulin-signaling abnormalities associated with insulin resistance [6••,19]. These signaling abnormalities are accentuated by angiotensin II, and include alterations in phosphatidylinositol 3-kinase (PI3-K) and protein kinase B (Akt) signaling abnormalities [6••,19]. Thus, interruption of the renin-angiotensin system may be one mechanism for improving insulin sensitivity, and thereby preventing or delaying the onset of diabetes.

Statins and diabetes prevention
The development of new diabetes was examined in men aged 45 to 64 years in the subanalysis of the West of Scotland Coronary Prevention Study [64]. Subjects who self-reported diabetes at baseline, or had a fasting glucose level of less than 126 mg/dL, were excluded from the analyses.

In this study, pravastatin therapy reduced the risk of developing diabetes by 30%. This prevention in the onset of diabetes was associated with significant reduction in triglyceride levels. However, upon further analysis, this reduction did not account for the effect of statins on the development of diabetes. These findings, however, have not been shown in other studies, and the evidence to date for diabetes prevention with statins is inconclusive.

Statins may affect substrate delivery to insulin-sensitive tissues or modulate insulin-activated signaling cascades that mediate glucose uptake. Statins also increase nitric oxide synthase expression, which may result in increased capillary recruitment and glucose disposal [65••]. Insulin activates a series of kinase cascades that include PI3-K and Akt, resulting in the translocation of glucose transporters to cell membrane and enhanced glucose uptake [6••]. This cascade is inhibited by circulating cytokines. Statins, like insulin, in addition to decreasing cytokine levels, also inhibit the cellular cascade, such as Rho-kinase, that inactivates the insulin receptor and signaling [6••,63]. These mechanisms might explain, in part, the reduction in the risk of developing diabetes observed with statins [64].

Conclusions

Diabetes is a major public health problem that is potentially preventable. Interventions involving lifestyle changes, such as exercise, diet, and weight loss, have substantial role in diabetes prevention. With the results of the major ongoing studies, further opportunities for intervention will be identified. Additional research is necessary to clarify the role of statins alone and in combination with other interventions in the prevention of diabetes. Finally, examination of the cost-effectiveness of the various interventions needs to be done to determine the optimal public health policy for the control of the growing epidemic of diabetes.

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65.•• McFarlane SI, Muniyappa R, Francisco R, Sowers JR: **Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond.** *J Clin Endocrinol Metab* 2002, **87:**1451–1458.
Rated one of the most frequently read articles by the *Journal of Clinical Endocrinology and Metabolism*, this clinical review bridges the basic and clinical science on the effects of statins and their roles beyond traditional thinking of the lipid-lowering effect. The effect of statins on inflammation and nitric oxide in the vasculature, kidney, and bone were also discussed. Potential beneficial pleiotropic effects of statins were comprehensively reviewed in this article.