ABSTRACT

In patients with type 1 and type 2 diabetes, intensive therapy to lower blood glucose concentration reduces the incidence and the rate of progression of microvascular complications. Preventive measures are also important for patients with prediabetes (impaired glucose tolerance or impaired fasting glucose) or with metabolic syndrome. In addition to glycemic control, the use of medications to lower blood pressure and cholesterol also significantly reduces the risk of cardiovascular complications among patients with diabetes. Lifestyle modifications such as weight loss, exercise, and smoking cessation reduce the risk of complications for many patients. Although blood glucose control is clearly important for patients with diabetes, optimal risk reduction also requires consideration of a number of other significant risk factors.

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MICROVASCULAR COMPLICATIONS SUCH AS DIABETIC RETINOPATHY, DIABETIC PERIPHERAL NEUROPATHY, AND DIABETIC NEPHROPATHY ARE ASSOCIATED WITH CONSIDERABLE MEDICAL AND ECONOMIC IMPACT AMONG PERSONS WITH DIABETES. IN THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS), 37% OF PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES DEVELOPED AT LEAST ONE MICROVASCULAR COMPLICATION OVER A 10-YEAR PERIOD.1 IN THE UNITED STATES, IT HAS BEEN ESTIMATED THAT MEDICAL EXPENDITURES OF APPROXIMATELY $24.6 BILLION PER YEAR ARE ASSOCIATED WITH THE TREATMENT OF DIABETES COMPLICATIONS, ANOTHER $23.2 BILLION IN DIRECT DIABETES-RELATED MEDICAL COSTS, AND $44.1 BILLION ATTRIBUTABLE TO AN EXCESS OF OTHER MEDICAL CONDITIONS AMONG PERSONS WITH DIABETES.2

Although clinicians have long suspected that excellent control of diabetes can reduce the incidence of microvascular complications, only relatively recently has this been demonstrated in controlled clinical trials. In patients with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy to achieve near-normal blood glucose and glycosylated hemoglobin A1c (HbA1c) concentrations significantly reduced the risk of microvascular complications of diabetes, when compared with conventional therapy.3 Over a mean duration of follow-up of 6.5 years, intensive therapy was associated with a 76% reduction in the risk of developing diabetic retinopathy among patients who did not have retinopathy at baseline. Among patients with retinopathy at baseline, intensive treatment slowed the progression of retinopathy by 54%. Intensive treatment was also associated with a significantly reduced occurrence of microalbuminuria (by 39%) and of clinical neuropathy (by 60%). A follow-up study showed that these improvements with intensive glucose control persisted for several years. At the end of the original study, all patients were eligible to receive the more
intensive treatment regimen under the care of their own physicians. After 4 years, a lower incidence of diabetic microvascular complications was still evident in the intensive therapy group, including significant reductions in the proportion of patients with worsening diabetic retinopathy or with increased urinary albumin excretion.4

In patients with type 2 diabetes, the UKPDS compared diabetic complications among 3867 patients with newly diagnosed diabetes who were randomly assigned to either intensive treatment (with a sulfonylurea or insulin, with a target fasting plasma glucose of <6 mmol/L) or conventional treatment with diet, for up to 10 years.1 Compared with conventional therapy, assignment to the intensive treatment regimen was associated with a 12% reduction in the incidence of any diabetes-related endpoint (which included a number of clinical outcomes such as sudden death, fatal or nonfatal myocardial infarction, heart failure, stroke, limb amputation, and others; \( P = .029 \)). This decrease in diabetes-related events with more intensive therapy was due almost entirely to a 25% reduction in the incidence of microvascular complications, including the need for retinal photocoagulation \( (P = .0099) \).

**PREDIABETES AND THE METABOLIC SYNDROME**

The prevention of diabetes and the accompanying manifestations of cardiovascular disease (which are the major cause of death in diabetes) is a far better strategy than treating the complications of advanced diabetes after they occur. Two conditions in particular are associated with an increased risk of developing diabetes and cardiovascular disease complications if preventive steps are not instituted: prediabetes and the metabolic syndrome. The term prediabetes refers to patients who have either impaired glucose tolerance or impaired fasting glucose (IFG).1 IFG has traditionally been defined as a fasting glucose concentration of 110 to 125 mg/dL, although a recent expert consensus panel convened by the American Diabetes Association has recommended that the lower limit of this range be reduced to 100 mg/dL.4 Prediabetes is very common among overweight adults: in an analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III), using the older definition of IFG, 11.9% of overweight or obese adults between the ages of 45 and 74 years had IFG.7 The number of adults with IFG is expected to increase with the adoption of the new lower limit of 100 mg/dL for IFG.8

The term “metabolic syndrome” refers to a cluster of risk factors (including abnormal glucose and insulin metabolism, central obesity, dyslipidemia, and hypertension) that are associated with an increased risk of developing diabetes and cardiovascular disease.9 Several definitions of the metabolic syndrome have been suggested; in the United States, the most common definition is probably the one proposed by the National Cholesterol Education Program. According to this definition, metabolic syndrome is defined as the presence of 3 or more of the following: abdominal obesity, with a waist circumference of more than 40 inches in men or more than 35 inches in women; triglycerides above 150 mg/dL; high-density lipoprotein cholesterol below 40 mg/dL in men or below 50 mg/dL in women; blood pressure above 135/85 mm Hg; and fasting glucose above 100 mg/dL.10

Approximately 45% of persons over the age of 50 in the United States have metabolic syndrome.11 Most physicians do not routinely measure abdominal circumference, and some definitions of metabolic syndrome replace waist circumference with body mass index (BMI). However, some studies have found that waist circumference or the waist-hip ratio are better predictors of subsequent disease than BMI.12,13 Although it has long been known that diabetes is an important risk factor for cardiovascular disease morbidity and mortality, recent studies have demonstrated that the metabolic syndrome even in the absence of diabetes is also associated with increased risk. Lakka and colleagues examined the incidence of cardiovascular disease in middle-aged men with metabolic syndrome who did not have cardiovascular disease at baseline.9 Individuals who had metabolic syndrome were at a significantly elevated risk of cardiovascular disease mortality over a mean duration of follow-up of 11 years (Figure 1).

Several measures may help to reduce the risk of progression to diabetes in patients with metabolic syndrome or prediabetes. In patients with prediabetes, the Diabetes Prevention Program examined the effects of a lifestyle modification intervention or metformin treatment on the development of type 2 diabetes in individuals with elevated fasting and post-load glucose, but not diabetes, at baseline.14 A total of 3234 patients were randomized to placebo, metformin (850 mg twice daily), or to a lifestyle intervention intended to produce a 7% weight loss and 150 minutes per week of physical activity. Over an average follow-up period
of 2.8 years, the incidence of diabetes was 11.0%, 7.8%, and 4.8% for the placebo, metformin, and lifestyle intervention groups, respectively. Compared with placebo, lifestyle modification produced a 58% reduction in the incidence of diabetes, and metformin produced a 31% decrease. The lifestyle modification was associated with an incidence of diabetes that was 39% lower than that with metformin treatment.

Medications such as metformin may be considered for preventing the development of diabetes. Glucose control is clearly very important in preventing the microvascular complications of diabetes, but it is less well established that glucose control is important in the prevention of cardiovascular disease in patients with metabolic syndrome or prediabetes. Medical treatment to address the individual components of the metabolic syndrome can also reduce the incidence of cardiovascular disease and the progression to type 2 diabetes. Aspirin is also appropriate to reduce the risk of cardiovascular events for selected patients.

**PREVENTING DIABETES COMPLICATIONS**

In addition to blood glucose control, a number of pharmacologic and behavioral strategies have been shown to reduce the risk of diabetic microvascular complications and cardiovascular disease among patients with diabetes. Smoking cessation clearly lowers the risk of cardiovascular disease, and may reduce diabetic microvascular complications as well. Exercise is also very important for decreasing the risk of diabetes complications and cardiovascular disease; 30 minutes of exercise per day improves HbA1c in patients with type 2 diabetes and prevents the progression of diabetes and cardiovascular disease. In the UKPDS, pharmacologic treatment that produced a relatively modest lowering in blood pressure resulted in a significant fall in the risk of cardiovascular disease among patients with diabetes, as well as a 37% relative reduction in the risk of microvascular endpoints.

The benefits of lipid lowering in diabetes were demonstrated in the Collaborative Atorvastatin Diabetes Study (CARDS). In the CARDS clinical trial of patients with type 2 diabetes, treatment with atorvastatin significantly reduced the occurrence of acute major cardiovascular events (the study primary endpoint) during a median follow-up of 3.9 years. CARDS = Collaborative Atorvastatin Diabetes Study; CI = confidence interval. Reprinted with permission from Colhoun et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-696.
Patients with type 2 diabetes, who were between 40 and 75 years of age, were randomized to treatment with either placebo (n = 1410) or atorvastatin 10 mg (n = 1428) for a median duration of 3.9 years. Statin treatment produced a significant 37% reduction in the incidence of the primary endpoint, the appearance of an acute cardiovascular event (myocardial infarction, coronary revascularization, or stroke), from 9.0% with placebo to 5.8% with atorvastatin (hazard ratio, 0.63; P = .001; Figure 2). Treatment was also associated with significantly lower rates of several separately assessed endpoints, including acute coronary events (5.5% vs 3.6% for the placebo and atorvastatin groups, respectively); coronary revascularization (2.4% vs 1.7%); stroke (2.8% vs 1.5%); and all-cause mortality (5.8% vs 4.3%; all P values ≤.001). Although this is the largest study to date that has examined the use of statins in patients with diabetes, smaller studies have also shown similar benefits with other statins. These results demonstrate that treating hyperlipidemia and hypertension in patients with diabetes is critically important.

SUMMARY AND CONCLUSIONS

Although tight control of blood glucose is critical for the prevention of diabetic microvascular complications, attention to other modifiable risk factors, including blood pressure, lipids, and cigarette smoking, can all significantly affect the development of cardiovascular complications among patients with diabetes. Too often, physicians focus doggedly on the control of blood glucose and do not aggressively manage the other risk factors for cardiovascular disease in their patients with diabetes.

REFERENCES


