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Thwarting the progression to diabetes

By JAIME A. DAVIDSON, MD, OSAMA HAMDY, MD, PhD

Weight loss and increased physical activity can prevent or delay diabetes by overcoming insulin resistance. Diet and exercise are more effective in preventing diabetes than are glucose-lowering drugs.

CONSULTANTS

JAIME A. DAVIDSON, MD, Clinical Associate Professor of Medicine, University of Texas Southwestern Medical School, Dallas; Chair of the Managed Care Report Card, Texas Diabetes Council; and an endocrinologist in private practice, Dallas.

OSAMA HAMDY, MD, PhD, Director, Obesity Clinical Program, Joslin Diabetes Center, Harvard Medical School, Boston, Mass.

Prediabetes is defined by the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). While IFG has thus been redefined as a level between 100 and 125 mg/dL, the range for IGT remains between 140 and 199 mg/dL 2 hours after a 75-g oral glucose challenge.

IFG represents a metabolic state between normal glucose homeostasis and diabetes and may be secondary to increased hepatic gluconeogenesis and decreasing or impaired pancreatic beta-cell function. Many patients with IFG have normal or near-normal levels of glycosylated hemoglobin A1C, while others are at significant risk of diabetes and need to be identified early to prevent macrovascular complications that otherwise may be present 4 to 7 years before patients become diabetic.¹

FOLLOWING THE COURSE OF A PROGRESSIVE DISEASE

Frank diabetes develops in about a third of patients with IFG or IGT. It is estimated that nearly 60% of adult patients with type 2 diabetes (T2DM) had prediabetes 5 years before diagnosis. Diabetes develops sooner in patients with postprandial hyperglycemia than in those with IFG. IGT is associated with an increased risk for cardiovascular (CV) and all-cause mortality, whereas the link between IFG and CV complications is not as strong. Although factors such as age, family history of diabetes, waist-to-hip ratio, body mass index (BMI), BP, and lipid levels may be independently associated with the development of diabetes, abnormal glucose levels are the best single predictor of those in whom diabetes will occur.

Domino effect of obesity

Atherosclerosis accompanies and complicates the natural history of diabetes, causing much of its morbidity and mortality. Strengthening the case for diabetes prevention is evidence that people with

insulin resistance and prediabetes have 2 to 3 times the risk for coronary artery disease (CAD) as the normal population. Individuals who convert to T2DM have increased CV risk factors compared with nonconverters.

Seven-year follow-up data from the San Antonio Heart Study showed that insulin-secretory ability predicts the risk of developing T2DM, with a 3-fold increased risk in persons with isolated low insulin secretion, a 5-fold increased risk in persons with insulin resistance, and a 20-fold increased risk in those with both defects.² Atherogenic changes in the prediabetic state are mainly seen in insulin-resistant subjects.

Most overweight or obese people are insulin resistant, particularly when they are fat around the middle. Being just 10 to 20 lb overweight can trigger T2DM. Even more alarming is that the prevalence of excess weight and obesity in adolescents has nearly tripled in the past 2 decades. The prevalence of T2DM is increasing in obese children and adolescents, particularly in Native Americans, African Americans, and Hispanics/Latinos. The number of Americans with diabetes is expected to almost double from 18.2 million in 2003 to 30.3 million in 2030.³

Identifying who is at risk

Those who were underweight at birth and are overweight in middle age have the most severe insulin resistance and the greatest risk of T2DM, possibly because intrauterine growth restriction leads to inadequate pancreatic development.^{4,5} At all ages, the risk of IGT or T2DM rises with increasing body weight. Obesity induces resistance to insulin-mediated peripheral glucose intake.

Screening for prediabetes is strongly recommended for all overweight and obese individuals (BMI of 25 or greater) who are aged 45 and older, according to the American Diabetes Association (ADA) and the National Institute of Diabetes and Digestive and Kidney Diseases. Younger patients should also be considered for screening if they are significantly overweight or obese and have 1 or more of these risk factors: family history of diabetes, low HDL-cholesterol (HDL-C) and high triglyceride levels, elevated BP, history of gestational diabetes, or non-Caucasian ethnicity (see Table 1).

In all eligible patient groups, the panel advises screening for diabetes during office visits using either the fasting plasma glucose (FPG) test or the oral glucose tolerance test (OGTT).⁶ The FPG test involves no waiting, is better tolerated, has better reproducibility and reliability, and costs less. Neither test is considered superior. The A1C level is not recommended as an additional criterion for the diagnosis of prediabetes or diabetes or for following prediabetic patients because of lack of international standardization of reference ranges and the confounding effect of other conditions such as pregnancy, uremia, hemoglobinopathies, blood transfusions, and hemolytic anemia. Certain patients with an A1C value of 5.5% to 6.5% have prediabetes or diabetes, while others do not.

Table 1 Recommendations to prevent or delay diabetes
<p>Take a family history for type 2 diabetes, hypertension, and hyperlipidemia.</p> <p>If the patient is overweight or obese, estimate whether the excess adiposity is in the abdominal area (waist) about 35% weight.</p> <p>Measure BP, fasting plasma glucose, and other labs in individuals at high risk for developing diabetes (men and women >45 y and with a body mass index [BMI] >30, women younger persons with a BMI >35 who have additional risk factors).</p> <p>In individuals with hypertension, screen at 3-y intervals.</p> <p>Encourage patients with prediabetes (with impaired fasting glucose and/or impaired glucose tolerance) to stop smoking, exercise regularly, eat a low-calorie and healthy diet, lose weight, and then maintain a normal body weight by continuing to exercise.</p> <p>Pay attention to hypertension and dyslipidemia. Encourage follow-up screening to help the patient stay on track.</p> <p>Monitor annually for the development of diabetes.</p>

Table 1
Recommendations to prevent or delay diabetes

The US Preventive Services Task Force's updated recommendations for screening for T2DM concluded that evidence was insufficient to recommend for or against routinely screening asymptomatic adults for IGT, IFG, or diabetes. The task force recommends screening for T2DM in adults with hypertension or hyperlipidemia.

Positive FPG test results should be confirmed at a second office visit. Monitoring for the development of diabetes should be done annually. Other cardiovascular disease (CVD) risk factors, such as tobacco use, hypertension, and dyslipidemia, should also be addressed and treated. Counsel patients on the benefits

of modest weight loss of 5% to 10% and regular physical activity. Pharmacologic treatment generally is not recommended during the prediabetes phase because there is not enough information about its cost-effectiveness.

Metabolic syndrome

The cluster of risk factors known as the metabolic syndrome increases the risk for CVD and diabetes. Endocrinologists consider insulin resistance and compensatory hyperinsulinemia as the underlying pathophysiology of the syndrome and thus prefer the term *insulin resistance syndrome*. This constellation of risk factors affects 1 in 4 adults over age 20 and 1 in 2 over age 60 as a result of improper nutrition, inadequate physical activity, and increasing body weight. According to the National Cholesterol Education Program definition, 3 of the following abnormalities must be present for a diagnosis:

- Abdominal obesity (waist circumference of more than 40 in for men, more than 35 in for women)
- Triglyceride level of 150 mg/dL or more
- HDL cholesterol (HDL-C) level lower than 40 mg/dL in men, lower than 50 mg/dL in women
- BP of 130/85 mm Hg or higher
- FPG level of 100 mg/dL or higher.

The metabolic syndrome is more common in Latino/ Hispanic men and women and African American women than in the corresponding Caucasians of the same gender. Its rapid increase in prevalence parallels the increase in obesity in this country. Reductions in glucose tolerance and elevations in lipid constituents and BP, mediated through an increase in free fatty acids, culminate in diabetes and CVD. The degree of insulin resistance is significantly associated with CAD. Treating metabolic syndrome can prevent or arrest CVD and T2DM. By definition, prediabetic individuals have elevated FPG levels and usually have 1 or more of the other features of the metabolic syndrome. However, diabetes does not develop in everyone with the metabolic syndrome.

Fat distribution

Central adiposity is an important predictor of IGT. In obese persons, waist circumference is correlated with dyslipidemia and hypertension. Although the male waist circumference risk is set at greater than 40 in, the Adult Treatment Panel III noted that, in some male patients, multiple metabolic risk factors develop when the waist circumference is greater than 37 in. The degree of insulin resistance and the incidence of T2DM are highest in persons with abdominal obesity. This "male"-type obesity differs from the typical "female" type, which mainly affects the gluteal and femoral regions and is not as likely to be associated with glucose intolerance or CVD. Deleterious changes in lipid metabolism are more closely correlated with the amount of visceral fat than total body fat, and central adiposity is more related to metabolic risk factors than an elevated BMI. Even people with a normal BMI may have a high percentage of body fat, especially visceral fat.

In general, obesity leads to elevated fasting plasma total cholesterol and triglyceride levels and reduced HDL-C levels. Small, dense atherogenic LDL particles are especially increased in patients with insulin resistance associated with visceral adiposity. Central obesity and hyperinsulinemia may cause excess hepatic production of very low-density lipoprotein (VLDL), which is triglyceride rich.

Enhanced lipolytic activity of visceral adipocytes increases free fatty acid flux to the liver and stimulates VLDL production. It also results in increased gluconeogenesis and decreased insulin sensitivity. Insulin resistance decreases the activity of lipoprotein lipase, the enzyme that transforms triglyceride-rich chylomicrons to HDL, and VLDL to LDL. Obesity-related insulin resistance may also impair clearance of LDL particles. Increased fatty acid and triglyceride levels are lipotoxic; in animals, lipotoxicity increases the apoptosis of beta cells, which in turn increases the risk of diabetes.

Whether the reversible insulin resistance of obesity is the same as the genetically determined insulin resistance of the metabolic syndrome, prediabetes, and diabetes is debated by endocrinologists. From a clinical view, whether a person is lean or obese, accumulation of intra-abdominal fat will result in insulin resistance and raise the risks of diabetes and CVD. In a recent study, the prevalence of the metabolic syndrome was high even in slightly overweight persons with a BMI between 25 and 27 kg/m².⁷ The amount and distribution of fat are genetically determined. People with a genetic susceptibility to increased visceral fat will gain weight when exposed to an environment that favors unhealthy eating habits and a sedentary lifestyle.

Adipose tissue metabolism

Alterations in adipose tissue metabolism in obese individuals may be the missing link between insulin resistance and CVD. Adipose tissue secretes resistin, leptin, tumor necrosis factor (TNF), and free fatty acids that dampen the effect of insulin, impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair insulin release by pancreatic beta cells. An increase in the number and size of fat cells, particularly intra-abdominal fat cells, leads to reduced secretion of a novel protein called adiponectin, which has anti-inflammatory and insulin-sensitizing properties. People with low adiponectin levels are more likely to be insulin resistant, obese, and at high risk of CAD. Weight loss through diet and exercise is the best approach to reduce visceral fat and improve insulin sensitivity.

Cytokines secreted from adipose tissue are thought to initiate a proinflammatory state that promotes the development of insulin resistance and endothelial dysfunction. Visceral and subcutaneous adipose tissues are major sources of cytokines, collectively called adipocytokines: TNF-alpha, interleukin-6 (IL-6), adiponectin, leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattracting protein-1 (MCP-1). Although leptin and adiponectin are exclusively produced by adipocytes, other cytokines are mainly produced by adipose-tissue resident macrophages in the stromal blood vessels. The number of these macrophages is increased in obesity.

TNF-alpha and IL-6 set the stage for chronic subclinical inflammation and interfere with signaling of insulin in the tissues. PAI-1 levels, higher in obese patients, are directly correlated with visceral fat. High levels of PAI-1 cause impaired fibrinolytic activity and increased risk of thrombosis. Overexpression of TNF-alpha, IL-6, and PAI-1 and underexpression of adiponectin have been observed in obese animals and humans. Reduction of adipose-tissue mass through exercise-driven weight loss decreases TNF-alpha, IL-6, and PAI-1, increases adiponectin, and is associated with improved insulin sensitivity and endothelial function.⁸

Decreasing adipose tissue mass alone will not improve metabolic abnormalities. When subcutaneous abdominal adipose tissue was removed by liposuction in obese women with normal glucose tolerance and women with diabetes, no significant changes in either group regarding insulin sensitivity of muscle, liver, or adipose tissue; plasma concentrations of C-reactive protein, IL-6, TNF-alpha, and adiponectin; and other risk factors, including BP and plasma glucose, insulin, and lipid concentrations, were noted.⁹

In a recent study, obese individuals with insulin resistance showed improvements in insulin sensitivity and endothelial function when they lost an average 7% of body weight after a 6-month program combining a hypocaloric diet and moderate physical activity. Weight reduction was associated with a significant decrease in leptin, IL-6, and PAI-1 and a tendency toward a decrease in circulating TNF-alpha. Adiponectin increased significantly only among patients with T2DM.^{10,11}

EVIDENCE FOR A HEALTHY LIFESTYLE

Well-designed randomized controlled trials show that more than half of new cases of diabetes could be

prevented through simple lifestyle changes. The most effective ways to prevent diabetes are to maintain a BMI under 25 kg/m² (optimal BMI, between 21 and 23 kg/m²) and to exercise at least moderately for 30 minutes a day.

Diabetes Prevention Program

When overweight people in the Diabetes Prevention Program (DPP) study lost 7% to 10% of their body weight and began taking half-hour walks 5 days a week, they decreased their risk of developing diabetes by 58%.¹²

In the DPP, 3234 enrolled subjects (mean BMI 34; average age 51) with IGT were randomized to 1 of 3 intervention groups: intensive nutritional and exercise counseling (lifestyle) group, or either of 2 masked medication treatment groups—the biguanide metformin group or the placebo group. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group and a 31% relative reduction was seen in the metformin group compared with control subjects. On average, 50% of the lifestyle group achieved the goal of a 7% or greater weight reduction in the first year and sustained a 5% total loss for the study's duration; 74% maintained at least 150 minutes per week of moderately intense activity.

Forty-five percent of the participants were from minority groups that suffer disproportionately from T2DM: African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and Native Americans. The trial also recruited other groups at higher risk: those older than 60, women with a history of gestational diabetes, and people with a first-degree relative with T2DM. Lifestyle intervention worked equally well in men and women and in all ethnic groups. It was also successful in people aged 60 and older, who have a nearly 20% prevalence of diabetes, reducing their development of diabetes by 71%.

Metformin was also effective in men and women and in all the ethnic groups but relatively ineffective in the older volunteers and in those who were less overweight. It was almost as effective as lifestyle changes in subjects younger than 45. In a follow-up study of 1247 subjects in the DPP metformin group in whom diabetes had not developed, OGTTs after stopping metformin (on average 11 days) showed that about 75% of the metformin benefit persisted. A fourth arm of the study, treatment with troglitazone combined with usual diet and exercise, was discontinued in June 1998, when the drug was recalled because of the potential for liver toxicity.

It remains unknown whether diabetes can be delayed beyond the 3-year period that was studied. The DPP population will be followed to determine whether the interventions reduce CVD occurrence.

The DPP research group recently assessed the cost-effectiveness of intensive lifestyle modifications and the use of metformin compared with the control group.¹³ In each case, intensive lifestyle modifications cost less than metformin therapy. Altering the interventions to include group settings instead of individual sessions and the use of generic metformin would further reduce costs.

STOP-NIDDM

In this double-blind trial (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus), 1429 participants with IGT were randomized to receive either acarbose or placebo.¹⁴ The subjects had a mean age of 55 years and a mean BMI of 31. After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on 1 OGTT, was observed in the acarbose-treated group compared with the placebo group. If this diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was seen in the acarbose group. The effect of acarbose was consistent among all age-groups and BMI values

and for both sexes.

A secondary analysis of the STOP-NIDDM data was performed to assess reductions in CV outcomes. After adjusting for major CV risk factors, there was a 53% relative risk reduction in CV events in the acarbose-treated patients.¹⁵ This trial points up the importance of improving postprandial hyperglycemia, which is a marker of derangements in lipid metabolism. By lowering postprandial hyperglycemia, CV events can be reduced and diabetes prevented.

Finnish Diabetes Prevention Study

In the first large-scale study in lifestyle intervention, 522 middle-aged (mean age 55 years) obese (mean BMI 31) subjects with IGT were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group).¹⁶ After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects. 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: lose weight (goal of 5% weight reduction), reduce fat intake (goal of fewer than 30% of calories), reduce saturated fat intake (goal of fewer than 10% of calories), increase fiber intake (goal of 15 g/1000 kcal or more), and exercise (goal of more than 150 min/wk).

In a more recent Finnish study, increasing physical activity protected against diabetes in obese subjects with both normal and impaired blood glucose regulation and in those with a normal BMI during a mean follow-up of 9.4 years.¹⁷ Diet and healthy lifestyle also were found to be important in preventing T2DM in women in the Nurses' Health Study, in which 91% of the cases of diabetes could be attributed to obesity, lack of exercise, poor diet, smoking, and abstinence from alcohol.¹⁸

The follow-up of the Finnish study showed that lifestyle intervention in people at high risk for T2DM resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counseling was stopped.¹⁹ Lifestyle interventions can prevent the deterioration of IGT to manifest T2DM, at least as long as the intervention continues. After a median period of 4 years of active intervention, participants who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. Risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat and increased intake of dietary fiber, and increased physical activity.

TRIPOD

The efficacy of thiazolidinediones for the prevention of T2DM was shown in the Troglitazone in Prevention of Diabetes (TRIPOD) study, in which 235 Hispanic women with previous gestational diabetes were randomized to receive placebo or 400 mg/d of troglitazone (a drug that was subsequently withdrawn in the United States, although 2 related drugs are still available).²⁰ After a median follow-up of 30 months, the annual incidence of T2DM was 5.4% and 12.1% in the troglitazone and placebo groups respectively ($P<.01$). This translated to a 56% relative reduction in progression to diabetes.

Troglitazone also caused a substantial improvement in insulin sensitivity with an associated improvement of pancreatic beta-cell function. After a washout period of more than 8 months, the preventive effects of the drug were still present. The findings suggest that this class of drugs may prevent diabetes rather than delay its onset. Similar trials are under way with rosiglitazone and pioglitazone.

DREAM

Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study was to assess prospectively the drug's ability to prevent T2DM in individuals at high risk of developing the condition.²¹ For this study, 5269 adults aged 30 years or more with IFG or IGT, or both, and no previous CVD were randomly assigned to receive rosiglitazone (8 mg/d) or placebo. The participants were followed for a median of 3 years. The trial showed that rosiglitazone at 8 mg/d for 3 years substantially reduces incident T2DM and increases the likelihood of regression to normoglycemia in adults with IFG or IGT, or both.

Diabetes Detection Initiative

The program entitled The Diabetes Detection Initiative: Finding the Undiagnosed is being piloted in 10 urban and rural communities with the goal of increasing the number of individuals identified as having prediabetes, diabetes, or high risk for diabetes. People in these communities will undergo a risk assessment and, if indicated, receive glucose testing. They will also receive a tool kit from the National Diabetes Education Program called "Small Steps, Big Rewards. Your GAME PLAN for Preventing Type 2 Diabetes." Patients can go to <http://www.ndep.nih.gov/diabetes/prev/prevention.htm> for information and tips on diabetes prevention.

CONTAINING THE DIABETES EPIDEMIC

Three strategies are known to be effective for preventing T2DM: exercise, weight loss, and pharmacotherapy. Although glucose-lowering drugs and ACE inhibitors can lower the risk of developing diabetes by improving insulin sensitivity, more studies are needed before these drugs can be advised for the prediabetic population.^{22,23} Reasons cited by the ADA are the limited efficacy of treatment with oral agents versus lifestyle modifications, the potential for adverse drug reactions, lack of data showing a reduction in microvascular or macrovascular complications, and insufficient evidence of cost-effectiveness of drug treatment. The DPP found that weight loss and regular physical activity were superior to drug therapy. People who are prediabetic should be encouraged to lose 5% to 10% of body weight to prevent or delay diabetes.

Benefits of exercise

Physical activity seems to confer a protective effect against diabetes independent of obesity or body fat percentage. This effect can be seen among the Old Order Amish, whose typical diet and rate of obesity do not differ from those of typical Americans but whose rate of diabetes is about 50% less.²⁴ Although the percentage of Amish with prediabetes is about the same as other Caucasians in the United States, not as many Amish go on to develop diabetes, presumably because they lead a more active life.

The benefits of exercise include increased energy expenditure, which, when combined with dietary restriction, leads to decreased body fat, increased insulin sensitivity, improved long-term glycemic control, improved lipid profiles, lower BP, and increased CV fitness. Moderate exercise alone without changes in diet can reduce total and abdominal fat.²⁵ *The Surgeon General's Report on Physical Activity and Health* recommends that people of all ages strive for a minimum of 30 minutes of physical activity of moderate intensity on most, if not all, days of the week (30 minutes of brisk walking at 3 mph or more) plus resistance training 3 times a week.²⁶

Exercise must be continued to maintain weight loss. In a study among Boston police, those who dieted and exercised lost slightly more weight than those who only dieted. When participants went off the diet

and kept exercising, they maintained weight loss for up to 18 months. At any time during the study, when they stopped exercising, they started gaining weight.²⁷

Small, simple steps

Offer structured, practical advice to patients, such as writing this prescription—with unlimited refills:

1. Cut 500 calories a day with portion control.
2. Increase physical activity by 10 to 20 minutes a day; aim for more than 150 minutes a week.
3. Keep records of your food intake and activities.

Set an example by achieving and maintaining a normal weight yourself. Also consider a referral to a dietitian who can discuss the merits of consuming foods low on the glycemic index, ensuring adequate calcium and fiber intake, avoiding trans fats in favor of more monounsaturated fats, controlling portion size, and eliminating sugar-containing drinks.^{28,29} Consumption of nuts and peanut butter was inversely associated with risk of T2DM independent of age, family history of diabetes, physical activity, smoking, and other dietary factors among women in the Nurses' Health Study. This relationship was seen even in women who were obese.³⁰

Speak plainly with prediabetic patients to the effect that their lifestyle is slowly killing them and point out that they might be disabled or dead within a few years if they do not take action soon. That may be the wake-up call they need.

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