

Metabolic Syndrome and Other Factors Associated with Increased Risk of Diabetes

Dan Streja, MD

Clinical Professor

David Geffen School of Medicine at UCLA

Co-Director of Cardiovascular Prevention Clinics for Division of Endocrinology

Division of Cardiology and Diabetes Clinic

Los Angeles Healthcare System

VA Medical Center of West Los Angeles

Los Angeles, California

The prevalence of diabetes has increased dramatically in the last 3 decades. Metabolic syndrome is a strong risk factor for incident diabetes. Among components of metabolic syndrome, obesity and abnormal carbohydrate metabolism are the most significant predictors. Primary care physicians should identify patients at risk and monitor their fasting glucose and/or postprandial glucose to enable timely diagnosis of diabetes and appropriate interventions. Lifestyle interventions that help reduce body weight and pharmacologic interventions that address insulin resistance and/or postprandial glycemia may help prevent diabetes. Intensive cardiovascular risk factor management should be an integral component of any diabetes prevention plan. (*Clinical Cornerstone*. 2004;6[Suppl 3]:S14–S29) Copyright © 2004 Excerpta Medica, Inc.

Diabetes mellitus has emerged as one of the most threatening epidemics of our time. In 1960, <1% of the US population reported having diabetes.¹ By the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), based on the same criteria used in 1960, the prevalence of diabetes had increased to 5.1%.² The rate of increase in diabetes cases in developing countries is even higher than in the United States and industrialized countries, and it is estimated that by 2030 there will be 366 million patients with diabetes worldwide.³ Increased longevity (leading to an increase in the aging population) and westernization of lifestyle are the main factors accounting for the increasing prevalence of diabetes. In addition, in the past 10 years, a rapid increase in the prevalence of type 2 diabetes mellitus (DM) has occurred among children and adolescents in the United States, especially among minority populations.^{4–6}

Type 2 DM is caused by the interplay of 2 pathophysiologic mechanisms: beta-cell dysfunction and insulin resistance. Beta-cell dysfunction is present in

nondiabetic relatives of patients with type 2 DM and is attributed to genetic factors,⁷ whereas insulin resistance is thought to be due to environmental factors. Since there is no reason to believe that the global genetic pool has changed over such a short period of time, the increase in the prevalence of type 2 DM can be attributed primarily to increased insulin resistance in the world population.

The socioeconomic consequences of the diabetes epidemic are far-reaching. The average cost of diabetes care in the United States was estimated at \$20 billion in 1987, \$90 billion in 1994, and \$132 billion in the most recent estimate.⁸ Diabetes is the main cause of end-stage renal disease, blindness in individuals of working age, and nontraumatic amputations.⁹ It also accounts for a 2- to 4-fold increase in coronary artery disease events, stroke, and congestive heart failure.¹⁰

Prevention of diabetes has become an extremely important task for primary care physicians in the United States. Prevention involves identifying individuals at risk, counseling patients to effect lifestyle changes,

implementing appropriate interventions in selected patients, and identifying patients where applicable who might be at higher risk due to a non-diabetes-related pharmacologic intervention.

IDENTIFYING RISK FACTORS FOR DEVELOPING DIABETES

Metabolic Syndrome

Metabolic syndrome was defined by the National Cholesterol Education Program (NCEP) in 2001 as a constellation of lipid and nonlipid risk factors indicative of insulin resistance and increasing the risk of cardiovascular disease and diabetes.¹¹ Metabolic syndrome predicts the development of type 2 DM, irrespective of ethnicity, family history, and preexisting disorder of carbohydrate metabolism.¹²

Metabolic syndrome comprises 5 factors: increased abdominal obesity, increased triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), blood pressure elevation, and impaired fasting glucose (IFG). The working definition of metabolic syndrome proposed by the NCEP is the presence of at least 3 of these factors and is discussed in detail elsewhere in this supplement.¹³ Each factor has been shown to be associated independently with insulin resistance^{14,15} and the development of diabetes.^{16–20} The risk of devel-

oping diabetes appears to increase logarithmically with the number of factors present (Figure 1).^{21,22}

Two components of metabolic syndrome, obesity and abnormal carbohydrate metabolism, have been shown to be the main predictors of diabetes. Abnormal carbohydrate metabolism includes IFG as well as impaired glucose tolerance (IGT), and the presence of either condition is referred to as “pre-diabetes.” Hypertension and dyslipidemia, 2 other components of metabolic syndrome, are primary predictors of cardiovascular risk but are less consistent predictors of disorders of carbohydrate metabolism. In a multiethnic cohort, IFG and large waist circumference were strongly associated with IGT, whereas the association of IGT with high triglycerides was weaker. The association of IGT with low HDL-C levels was inconsistent, and there was no apparent association between IGT and high blood pressure.²³ In another study of Pima Indians,²⁴ factor analysis showed a strong relationship between the incidence of diabetes and 2 factors: “insulinemia factor,” representing abnormal carbohydrate metabolism and insulin activity, and “body weight” factor, representing obesity. The “lipid factor” was a weaker predictor and the “blood pressure factor” was a poor predictor.

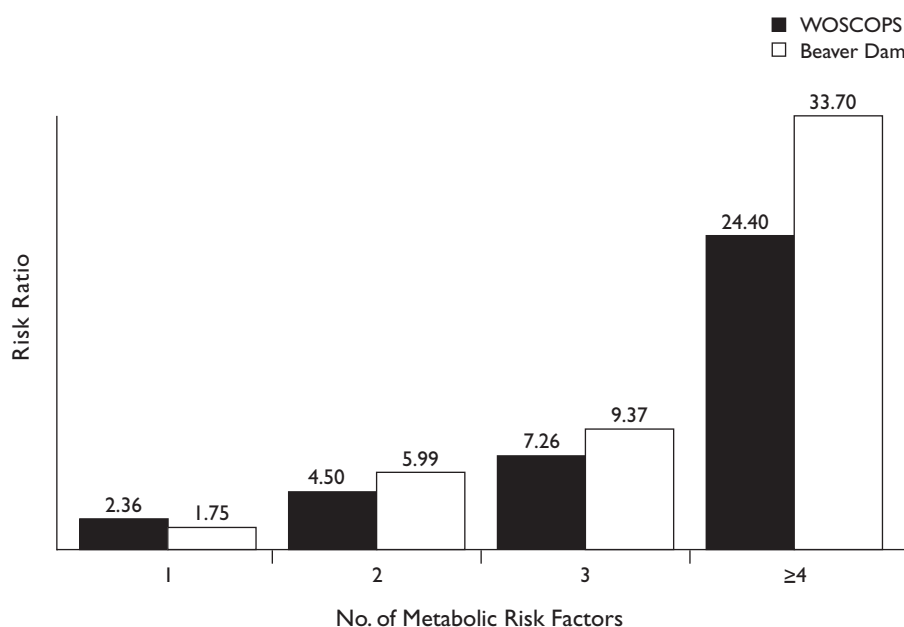


Figure 1. Risk ratio of incident diabetes as a function of number of factors of metabolic syndrome in the West of Scotland Coronary Prevention Study (WOSCOPS) and Beaver Dam Eye Study. Subjects with no feature of metabolic syndrome have a risk of 1.

Obesity in Metabolic Syndrome

Obesity is the central feature of metabolic syndrome, as defined by the NCEP.²⁵ The World Health Organization (WHO) definition of obesity in metabolic syndrome²⁶ is different from that of the NCEP. In the NCEP definition of metabolic syndrome, obesity is diagnosed based on waist circumference, whereas in the WHO definition it is diagnosed based on measurement of body weight and height and calculation of the body mass index (BMI), without taking into consideration the regional distribution of adiposity.

Insulin Resistance Syndrome

The American College of Endocrinology has recently introduced the term “insulin resistance syndrome” (IRS), a condition similar but not identical to metabolic syndrome.²⁷ BMI >30 kg/m² is a feature of WHO metabolic syndrome, whereas IRS is defined by a BMI >25 kg/m². Insulin resistance and obesity are closely associated, but not synonymous: 16% of patients with insulin resistance are of normal weight.¹⁵ Patients of normal weight who have features of metabolic syndrome or insulin resistance have been described as “metabolically obese, normal weight.”²⁸

The prevalence of metabolic syndrome increases with the degree of adiposity in men and women of all ethnic groups.²⁹ The value of evaluating regional distribution of adiposity in predicting incident diabetes is controversial. Intra-abdominal fat is better associated with documented insulin resistance than subcutaneous fat.³⁰ In the Hoorn study,³¹ a low amount of leg fat increased the risk of disorders of carbohydrate metabolism after adjustment for intra-abdominal fat. In other studies,^{32,33} both subcutaneous fat and intra-abdominal fat were related to insulin resistance, but only the latter was related to features of metabolic syndrome. In the Kuopio Ischemic Heart Disease Study,³⁴ waist circumference was not superior to BMI in predicting incident diabetes. In Pima Indians, BMI was found to be an excellent predictor of incident diabetes. Inclusion of other indicators of adiposity distribution did not provide any additional information about the risk of incident diabetes.³⁵

Impaired Fasting Glucose and Impaired Glucose Tolerance

In the NCEP definition of metabolic syndrome, IFG is defined by a fasting serum glucose >110 mg/dL.¹

IFG is associated with insulin resistance³⁶ but appears to be an independent predictor of incident diabetes.³⁷ The NCEP Adult Treatment Panel recently noted the benefits of adding IGT to the definition of metabolic syndrome but stopped short of recommending routine IGT testing.³⁸ IGT is defined by a serum glucose between 140 and 200 mg/dL, 2 hours after oral administration of a 75-g glucose load. IGT represents a more severe abnormality than IFG. Patients with IGT have a higher degree of insulin resistance and more features of metabolic syndrome whether IGT occurs in association with IFG³⁹ or is isolated.⁴⁰ In addition, in some studies, patients with IGT have a more pronounced insulin secretory defect.^{36,41,42} IGT and IFG predict diabetes with the same specificity, but the IGT has a higher incidence⁴³ which gives the test more sensitivity.⁴⁴ On the other hand, IFG data are easier to obtain and more reproducible. Recently, the American Diabetes Association lowered the threshold for IGT to a serum glucose level of 100 mg/dL.⁴⁵ The result of this decision is an increased prevalence to match that of IGT and therefore an increase in sensitivity for prediction of incident diabetes¹² but, possibly, a decrease in its specificity.⁴⁶

All features of metabolic syndrome are also features of or risk factors for IRS. In addition, IRS comprises conditions that specifically increase the risk of incident diabetes: family history of diabetes, history of gestational diabetes, polycystic ovarian disease, acanthosis nigricans, nonalcoholic fatty liver disease, or ethnicity other than non-Hispanic white. Risk of incident diabetes in cohorts of women with gestational diabetes depends on the prevalence of beta-cell dysfunction and features of metabolic syndrome, which varies with ethnicity.⁴⁷ The degree of risk in individual patients increases with the degree of obesity and the number of abnormalities detected at the time of the diagnostic test (3 hours oral glucose tolerance test).^{48,49} Weight gain is a primary risk factor for gestational diabetes in individual patients⁵⁰ and accounts for the increasing prevalence of gestational diabetes in the last 25 years.⁵¹ Polycystic ovarian disease is associated with insulin resistance⁵² and predicts incident diabetes or IGT⁵³ independent of obesity. Increased level of androgens, a feature of most women with polycystic ovarian disease, is a risk factor for incident diabetes even in postmenopausal women.⁵⁴ Acanthosis nigricans is associated with features of metabolic syndrome and insulin resistance⁵⁵ and has a

high prevalence in patients with newly diagnosed type 2 DM.⁵⁶ Nonalcoholic fatty liver disease, defined by biopsy or noninvasive imaging, is associated with insulin resistance and features of metabolic syndrome^{57,58} but does not predict incident diabetes independent of fasting glucose.⁵⁹ Increased levels of gamma-glutamyl-transpeptidase⁶⁰ and ferritin,⁶¹ both associated with nonalcoholic hepatic liver disease, are predictors of diabetes.

The variation in diabetes prevalence across ethnic groups is well documented in epidemiologic studies.⁶² The prevalence of metabolic syndrome⁶³ and insulin resistance⁶⁴ is different at similar levels of adiposity across ethnic groups. The waist circumference threshold established by NCEP is inadequate for diagnosing insulin resistance in Asians⁶⁵ or predicting diabetes in European cohorts.³⁴

Recently, novel cardiovascular risk factors have been shown to predict the risk of incident diabetes. Increased C-reactive protein (CRP) level is a risk factor for diabetes in both men⁶⁶ and women.⁶⁷ CRP level predicts incident diabetes independent of metabolic syndrome in some studies^{19,21} but not in others.⁶⁸ Other studies have found that CRP predicts diabetes independent of insulin resistance,⁶⁷ disordered carbohydrate metabolism,⁶⁹ or lifestyle factors.⁷⁰ Tests for other inflammatory markers that are not yet commercially available (eg, interleukin-6 [IL-6]^{71,72} or tumor necrosis factor- α -receptor₂⁷¹) have been found to be useful for predicting incident diabetes. Adiponectin, an emerging primary marker of insulin sensitivity, has been shown to predict diabetes.⁷³⁻⁷⁵ Markers of endothelial function such as von Willebrand factor, E-selectin, and adhesion molecules are also associated with incident diabetes.^{76,77} The clinical value of these data needs to be confirmed through larger cohort studies and/or standardization of the laboratory methodology.

Lifestyle Factors Associated with Incident Diabetes

Weight Gain

Because adiposity is a main risk factor for disorders of carbohydrate metabolism, weight gain results in an increased risk of developing diabetes. Smoking, exercise, and dietary content might also be related to insulin resistance and incident diabetes, irrespective of changes in body weight.

KEY POINT

Obesity is the central feature of metabolic syndrome. The main predictors of diabetes are weight gain and prediabetes.

The magnitude of weight gain in adolescents as well as adults is directly related to the increase in risk of developing features of metabolic syndrome.⁷⁸ The increase in the indices of adiposity in the adult US population parallels the epidemic of diabetes.^{79,80} Just as BMI is associated with diabetes incidence without a specific threshold value, weight gain predicts diabetes independent of baseline degree of adiposity in both men and women (**Figure 2**).^{81,82} Weight loss was also shown to be negatively associated with the risk of diabetes. In the NHANES II, while each kilogram of body weight gained per year increased the risk of diabetes by 49%, each kilogram lost per year decreased the risk by 33%.⁸³ Thus, weight loss is an essential target for diabetes prevention programs.

Diet

Epidemiologic studies have not shown a consistent relationship between total dietary fat content and incident diabetes independent of BMI and weight gain.⁸⁴ Polyunsaturated fat intake decreases the risk of diabetes, whereas intake of trans-fatty acids increases the risk.^{85,86} The role of N-3 fatty acids intake (fish oil) is controversial, but fish consumption has been shown to decrease the incidence of diabetes.^{85,87} In short, the data suggest a potential benefit from vegetable and fish fat and a potential deleterious effect of animal fat from sources other than fish.

The effect of food with high fiber content on the risk of incident diabetes has been studied in prospective cohorts. Total grain,⁸⁸ total dietary fiber,⁸⁸ cereal fiber,⁸⁸⁻⁹⁰ fruit and vegetable intake,⁹¹ and dietary magnesium⁹² have been shown to have a strong inverse relationship with the risk of diabetes. Weight gain is inversely associated with the intake of high-fiber, whole-grain foods and positively related to the intake of refined-grain foods.⁹³

Total amount of dietary carbohydrate, sugar content, and content of different monosaccharides and disaccharides in the diet have not consistently been shown to be associated with the risk of incident diabetes.^{88,94} The type of dietary carbohydrate in food products can be described by their glycemic index. Glycemic index is defined as the ratio of the serum glucose level in the first 2 hours after the ingestion of a specific carbohydrate to the level after the ingestion of a similar amount of carbohydrate as glucose. Examples of foods with high glycemic index are white and rye bread, cornflakes, puffed wheat, and pasta. In both the Physician Health Study⁹⁵ and Nurses' Health Study,⁸⁵ a diet with a high glycemic index was associated with an increased risk of diabetes. The data could not be reproduced in some cohorts^{88,96} but were recently confirmed in the Nurses' Health Study II using a more thorough methodology of classification of glycemic exposure and type of incident diabetes.⁹⁷

Although moderate alcohol intake has a beneficial effect in prevention of diabetes,^{98,99} binge drinking or high alcohol intake might increase the

risk of diabetes.¹⁰⁰ This relationship might be mediated by weight gain.¹⁰¹

Exercise

Reported level of physical activity is negatively associated with the risk of diabetes, independent of BMI, in both men¹⁰² and women.¹⁰³ In the Nurses' Health Study, a validated detailed questionnaire was used to quantitate the duration and the intensity of exercise.¹⁰⁴ After adjustment for age, BMI, hypertension, and dietary confounders, the risk of incident diabetes decreased with each quintile of metabolic equivalent task score.¹⁰⁵ Similar results were reported in middle-aged men and women in whom the data were also adjusted for the level of glucose tolerance.¹⁰⁶ Use of cardiorespiratory fitness data to evaluate the level of exercise objectively yielded similar results in European,¹⁰⁷ US,¹⁰⁸ and Asian¹⁰⁹ populations. In young adults, low cardiorespiratory fitness resulted in a 3- to 6-fold increase in the risk of new onset hypertension, metabolic syndrome, and diabetes. The association remained significant after adjustment for confounders such as BMI, weight change,

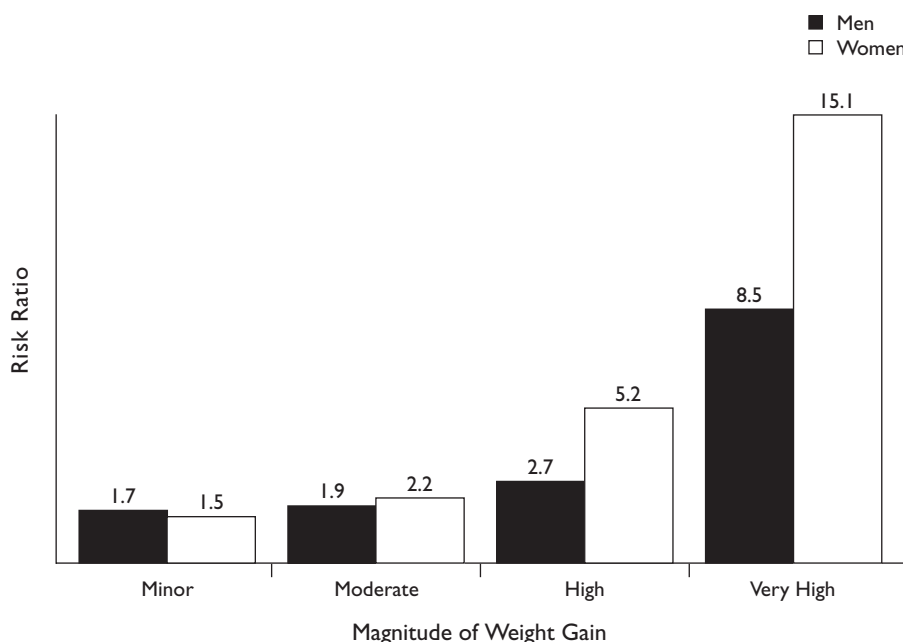


Figure 2. Risk ratio of long-term incident diabetes as a function of the magnitude of long-term weight gain. Subjects with stable weight have a risk of 1; data are adjusted for age. Minor weight gain: 3–6 kg for men, 5–8 kg for women; moderate weight gain: 7–11 kg for men, 8–11 kg for women; high weight gain: 12–18 kg for men, 11–20 kg for women; very high weight gain: >18 kg for men, >20 kg for women.

and family history of diabetes.¹¹⁰ The number of hours per week spent watching television, as a measure of sedentary lifestyle, correlated with the risk of incident diabetes independently of BMI and exercise level in men¹¹¹ and women.¹¹² The authors estimated that 43% of cases of diabetes could be prevented by walking 30 minutes per day and reducing the time spent watching television to <10 hours per week.¹¹²

Smoking

Current cigarette smoking is an independent, modifiable risk factor for diabetes.^{113,114} The risk is higher in heavy smokers and lower in patients who are able to quit.¹¹⁵ In middle-aged men and women, smoking was an independent predictor of progression to hyperinsulinemia.¹¹⁶ The beneficial effects of smoking cessation on the risk of incident diabetes are low in the first 5 years after cessation because of the associated weight gain; however, after 5 years the risk of diabetes declines and reaches the level of nonsmokers after 20 years.¹¹⁷

In the Nurses' Health Study, the subgroup found to have a low risk of incident diabetes had a low BMI (<25 kg/m²); consumed a diet high in cereal fiber, high in polyunsaturated fat, low in trans-fatty acids, used food with low glycemic index; engaged in moderate to vigorous physical activity for at least half an hour a day; did not currently smoke; and consumed 5 g of alcohol or more.¹¹⁸ The epidemiologic data from the Nurses' Health Study suggest that physicians should counsel their patients on lifestyle interventions that may help reduce the risk of incident diabetes, with the exception of recommending daily alcohol intake to nondrinkers.

Pharmacologic Agents Associated with Increased Diabetes Risk

Recently, much attention has been focused on drugs that might contribute to an increased risk of diabetes. Four drug classes have been more extensively discussed: antihypertensive agents, antipsychotic agents, highly active antiretroviral therapy (HAART), and macrolide immunosuppressants. In these drug classes, agents with proven strong clinical benefit have also been suspected to be associated with increased risk of development of diabetes. Replacing these agents with drug regimens thought to be associated with lower risk of incident diabetes may depend on the perception by clinicians of their comparative efficacy.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the largest clinical trial of cardiovascular prevention through blood pressure control, has generated controversy concerning the choice of a first-line antihypertensive drug.¹¹⁹ The study showed that chlorthalidone (a diuretic), amlodipine (a dihydropyridine calcium channel blocker), and lisinopril (an angiotensin-converting enzyme [ACE] inhibitor) are equally effective in preventing the main combined end point of fatal and nonfatal myocardial infarction. Chlorthalidone was the most effective in controlling blood pressure, more effective than amlodipine in preventing congestive heart failure, and more effective than lisinopril in preventing congestive heart failure, stroke, and combined cardiovascular events. The drugs were also significantly different with respect to the risk of incident diabetes, with a rate of 11.6% for chlorthalidone, 9.8% for amlodipine, and 8.1% for lisinopril ($P < 0.001$). These data are also supported by other randomized trials (Table)¹²⁰⁻¹²⁶ that suggest that ACE inhibitors and angiotensin receptor blockers (ARBs) are associated with a lower risk of incident diabetes. Because some of these studies were placebo-controlled, the possibility arose of using ACE inhibitors and ARBs to prevent diabetes irrespective of a subject's blood pressure. This hypothesis is currently being explored in the DREAM¹²⁷ study (ramipril) and NAVIGATOR¹²⁸ (valsartan) study. The difference in risk of incident diabetes between diuretics and calcium channel blockers is supported by data from INSIGHT,¹²⁹ a clinical trial comparing the hydrochlorothiazide-containing diuretic, co-amiloride, with the calcium channel blocker nifedipine gastrointestinal therapeutic system (GITS). The incidence of diabetes with co-amiloride was 5.6% versus 4.3% with nifedipine GITS, a 23% risk reduction ($P = 0.02$). The fact that diuretics are not inferior to ACE inhibitors in terms of clinical outcomes suggests that incident diabetes that occurs during treatment of hypertension does not translate into an immediate increase in morbidity. This was not the case, however, in a recent report enrolling 797 patients undergoing treatment for hypertension, which showed that incident diabetes is associated with an almost 3-fold increased risk of cardiovascular events.¹³⁰ The increased risk remained significant ($P = 0.007$) after adjustment for all potential confounders, including ambulatory blood pressure monitoring data.¹³⁰ In clinical practice, it may be prudent to consider the

potential risk of inducing disorders of carbohydrate metabolism when choosing antihypertensive therapy for patients at risk for incident diabetes.

The introduction of second-generation antipsychotics (SGAs) has improved the management of patients with schizophrenia. Compared with first-generation antipsychotics, they have fewer or no extrapyramidal side effects at clinically effective doses and some have been shown to be more effective in improving negative, affective, or cognitive symptoms. However, their use has been associated with reports of dramatic weight gain, diabetes onset, and atherogenic dyslipidemia. Patients with schizophrenia have a high prevalence of insulin resistance¹³¹ and diabetes,^{132,133} attributable to environmental and/or genetic factors. Exposure to drugs that induce metabolic syndrome is likely to increase this risk. The weight gain induced by different antipsychotic drugs seems to depend on their affinity for different neuroreceptors. The blockade of histamine-1, muscarinic, alpha₁-adrenergic, and 5-hydroxytryptamine (5HT) 2A, and 2C receptors has been shown to cause weight gain, and the blockade of 5HT_{1A}, dopamine-2, and alpha₂-adrenergic receptors has been shown to decrease appetite.¹³⁴ Since SGAs have different affinities for different receptors, the reported rates of weight gain can vary from one drug to another.¹³⁵ Other studies

have shown a high incidence of diabetes in patients treated with antipsychotic agents irrespective of the condition and the drug used.^{136,137} The US Food and Drug Administration (FDA) has mandated that the package inserts of SGAs carry a warning for potential metabolic complications. Recent consensus panels^{138,139} have established practice guidelines for the use of this class of drugs. They include comprehensive evaluation at the initiation of therapy and periodic monitoring throughout treatment for all features of metabolic syndrome. Both panels recommend considering switching drugs if weight gain occurs. The threshold for maximum acceptable weight gain is 1 BMI unit (3%–4% body weight)¹³⁸ or 5% body weight.¹³⁹

The clinical use of highly effective anti-HIV drugs has resulted in a dramatic reduction in AIDS-related mortality in industrialized countries. The prolongation of the life expectancy of these patients through long-term use of HAART has resulted in a markedly increased incidence of metabolic disturbances, including incident diabetes. The most common metabolic disturbance is AIDS-related dystrophy, characterized by trunkal obesity reminiscent of that of chronic glucocorticoid excess, as well as dyslipidemia and carbohydrate intolerance. Patients with this syndrome are insulin resistant and at high risk of developing type 2 DM.

TABLE. RANDOMIZED CLINICAL TRIALS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS SHOWING SIGNIFICANT BENEFIT IN LOWERING INCIDENCE OF NEW-ONSET DIABETES.

Study	No. of Patients	Drug	% of Patients with New-Onset Diabetes	Comparator	% of Patients with New-Onset Diabetes	% Reduction
ALLHAT ¹¹⁹	24,309	Lisinopril	8.1	Chlorthalidone	11.6	30
CAPP ¹²⁰	10,985	Captopril	6.1	Diuretics + beta-blockers	6.9	14
HOPE ¹²¹	5720	Ramipril	3.6	Placebo	5.4	34
INVEST ¹²²	22,576	Trandolapril	7.0	Diuretics + beta-blockers	8.2	15
ALPINE ¹²³	392	Candesartan	0.5	Hydrochlorothiazide	4.1	88
CHARM ¹²⁴	7601	Candesartan	6.0	Placebo	7.0	12
LIFE ¹²⁵	7998	Losartan	6.0	Atenolol	8.0	25
VALUE ¹²⁶	15,245	Valsartan	13.1	Amlodipine	16.4	23

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CAPP = Captopril Prevention Project; HOPE = Heart Outcomes Prevention Evaluation; INVEST = International Verapamil SR/Trandolapril Study; ALPINE = Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; CHARM = Candesartan in Heart Failure—Assessment of Mortality and Morbidity; LIFE = Losartan Intervention for Endpoint Reduction; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

The etiology of the syndrome is multifactorial, with infection, inflammatory response, and drug therapy all possibly contributing.¹⁴⁰ A retrospective review of the Veterans Affairs administrative database identified age, minority race, and HAART as main predictors of new-onset diabetes.¹⁴¹ Hepatitis C is also an important risk factor in the HAART era. Of the drugs used in HAART, protease inhibitors are the most likely to induce metabolic disorders. Dyslipidemia occurs in 3 of 4 patients treated with HAART.¹⁴² In Northern California Kaiser, the incidence of diabetes in HIV-positive patients has doubled during the HAART era to 1.88% per year.¹⁴³ The mechanism of action for inducing dyslipidemia is multifactorial and results in increased production of precursors of lipoproteins (free fatty acids, sterols, apolipoprotein B) and ultimately in increased production of very low-density lipoproteins.¹⁴² HAART may induce disorders of carbohydrate metabolism by increasing insulin resistance as well as by diminishing beta-cell function.¹⁴⁴ Protease inhibitor-sparing therapy regimens have been proposed but neither their metabolic benefit nor their safety has been proved.^{145,146}

KEY POINT

A program of diabetes prevention should consist of moderate reduction in caloric intake with a high content of fruits, vegetables, cereal fiber, and fish; regular moderate physical activity; and smoking cessation.

New-onset diabetes is a frequent complication of solid organ transplant. It affects graft and patient survival and adds cardiovascular risk to a patient already at high risk due to previous exposure to end-stage renal disease and its comorbidity. The incidence of diabetes after renal transplant in the Medicare population at 3 years' follow-up is 24%.¹⁴⁷ Risk factors for incident diabetes after a transplant include age, African American or Hispanic ethnicity, male gender, number of human leukocyte antigen mismatches, hepatitis C infection, obesity, and type of immunosuppression. BMI is a risk factor for diabetes even at levels below the threshold of 30 kg/m², which defines

obesity.¹⁴⁸ The effect of immunosuppressants on glucose metabolism varies with the regimen used. The risk of diabetes increases with the dose of steroids and becomes extremely high in cases of acute graft failure when large doses are part of the management plan. The introduction of calcineurins (cyclosporin and tacrolimus) has dramatically improved survival and comorbidity after transplantation and has allowed reduction in the dose of steroids required, thus reducing the risk of incident diabetes. Calcineurins differ in their association with metabolic effects. Cyclosporin is associated with a higher incidence of lipoprotein abnormalities¹⁴⁹ but a lower incidence of diabetes.¹⁵⁰ Both calcineurins decrease insulin sensitivity, but tacrolimus has more dose-dependent inhibitory effects on insulin release,¹⁵¹ possibly due to its different mode of transport into the beta cell.¹⁵⁰ Studies of switching calcineurins have not been adequately powered to allow a clear conclusion to be drawn.¹⁵² Recent treatment algorithms using mycophenolate mofetil and decreasing the dose of tacrolimus have been reported to result in a lower incidence of diabetes.¹⁵³ Low-dose tacrolimus is part of the Edmonton protocol for islet-cell transplant,¹⁵⁴ where it is essential to avoid deleterious effects on beta cells. A recent consensus on management of diabetes after transplant did not make any recommendations concerning graft survival management but emphasized the need for pretransplant management, metabolic monitoring, cardiovascular risk management, and intensive glycemic control.¹⁵⁵

RANDOMIZED TRIALS OF DIABETES PREVENTION

Lifestyle Interventions

The Da Qing IGT and Diabetes Study¹⁵⁶ enrolled 577 subjects with IGT in a randomized clinical trial of lifestyle intervention versus "usual care," with diabetes as an end point. Patients were randomly assigned to 1 of 4 groups: control, diet intervention, exercise intervention, and diet and exercise interventions. After 6 years the incidence of diabetes per 100 patient-years was 15.2% in the control group, 10.1% in the diet group, 10.5% in the exercise group, and 8.0% in the diet and exercise group. After adjustment 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% ($P < 0.005$) reduction in risk of developing diabetes, respectively. The decrease in diabetes risk remained significant after adjustment for baseline insulin resistance, insulin secretion, BMI, and postchallenge glucose level.

The Finnish Diabetes Prevention Study¹⁵⁷ enrolled 523 subjects in a randomized clinical trial of moderate weight reduction and exercise versus “usual care.” The study used individualized dietary and exercise counseling with multiple visits per year. At 4 years’ follow-up, the incidence of diabetes was reduced from 23% to 11% ($P < 0.001$), a 58% risk reduction. The weight loss was modest: 3.5 kg (4.0%) in the intervention group and 0.9 kg (1.1%) in the control group.¹⁵⁸ The reduction in the incidence of diabetes was directly associated with the magnitude of lifestyle changes achieved.¹⁵⁹ In both arms of the study, changes in insulin sensitivity correlated with the magnitude of weight changes.¹⁶⁰ The data suggest that weight loss was a marker for changes in energy intake balance and constituted the core of the program.

The Diabetes Prevention Program^{161,162} randomized 3234 subjects with IGT to 1 of 3 arms: “usual care,” lifestyle changes, or metformin therapy (850 mg BID). The average follow-up period was 2.8 years. The incidence of diabetes was 11.0% in the control arm and 4.8% in the lifestyle intervention arm, with a difference of 58% (95% CI, 48%–66%). Patients in the lifestyle intervention arm were followed up intensely with group and individualized counseling. A cost analysis of the program determined that a similar program in routine clinical practice would cost ~\$750 per patient per year and the cost would be \$13,200 per case of diabetes prevented and \$27,100 per quality-added life-year.^{163,164}

Pharmacologic Intervention

Pharmacologic intervention to address insulin sensitivity is currently being explored as an approach to diabetes prevention.

Metformin is a drug that decreases hepatic glucose output, rendering insulin more effective in maintaining glycemic control. In the metformin treatment arm of the Diabetes Prevention Program study discussed earlier, the incidence of diabetes was 7.8%, with a 31% statistically significant reduction compared with the control group. The benefit was higher in younger (44%) and heavier (53%) patients.¹⁶² A cost analysis

of the program determined that a similar program in routine clinical practice would cost \$14,300 per case of diabetes prevented and \$35,000 per quality-added life-year.¹⁶³

The TRIPOD Study was a single-center, randomized clinical trial that enrolled 236 Hispanic women with gestational diabetes.¹⁶⁵ The subjects were randomized to receive placebo or troglitazone 400 mg/d. Troglitazone is a true insulin sensitizer and increases insulin-mediated glucose disposal. Women who did not develop diabetes during the trial were tested 8 months after having discontinued the medication. After a median follow-up of 30 months, the incidence of diabetes was 12.1% in the control arm and 5.4% in the troglitazone arm for a 56% reduction in risk. The effect of troglitazone persisted 8 months after its discontinuation and was associated with preservation of beta-cell function in addition to the expected improvement in insulin sensitivity. Because troglitazone was withdrawn from the market as a result of safety concerns, a large-scale international study is currently exploring the effect of another drug from the same class, rosiglitazone, in the prevention of diabetes. The DREAM study has enrolled 5269 subjects with IFG or IGT and has a 90% power to detect a 22% reduction in incident diabetes.¹²⁷

Another approach to preventing insulin resistance is to add a pharmacologic agent aimed at enhancing the results of a weight reduction program. The XENDOS study randomized 3305 patients to a lifestyle intervention plus either orlistat 120 mg or placebo taken 3 times daily.¹⁶⁶ The study had a high dropout rate. After 4 years, the incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, a reduction of 37% ($P = 0.003$). Patients with IGT accounted for most of the difference, with a risk reduction of 53% ($P = 0.017$). The difference in weight loss between the arms was modest (5.8 vs 3.0 kg).

IGT is a powerful predictor of incident diabetes as is the ingestion of food with high glycemic index. In addition, the magnitude of postchallenge glycemia has emerged as an important predictor of cardiovascular risk¹⁶⁷ and atherosclerosis.¹⁶⁸ Postchallenge glucose levels have been associated with high levels of oxidative stress, which contribute to the pathogenesis

*Metformin has not yet received approval from the FDA for prevention of diabetes.

of both atherosclerosis and diabetes.¹⁶⁹ In light of these data, randomized clinical trials have attempted to reduce the incidence of diabetes and cardiovascular disease by targeting postprandial glucose.

The STOP-NIDDM trial randomized 1429 patients with IFG and IGT to treatment with acarbose 100 mg or placebo 3 times daily.¹⁷⁰ Acarbose is an α -glucosidase inhibitor that specifically targets postprandial glycemia. The study drug was poorly tolerated at the recommended dose, and 31% of subjects withdrew early. Despite the high dropout rate, there was a 25% reduction in incident diabetes ($P = 0.002$),¹⁷⁰ a 49% reduction in cardiovascular events ($P = 0.03$), and a 34% reduction in incident hypertension ($P = 0.02$).^{171,172} Cardiovascular benefit remained significant after adjustment for major risk factors. The reduction in cardiovascular events was primarily due to a reduction in the incidence of myocardial infarction.¹⁷² A subgroup of the study population underwent measurements of carotid intima media thickness (IMT). Acarbose reduced the progression of this index of vascular remodeling by 50% ($P = 0.027$).¹⁷³ These data are supported by a recent meta-analysis showing a 34% reduction in cardiovascular events and a 64% reduction in myocardial infarction in patients with diabetes treated with acarbose.¹⁷⁴

Meglitinides are a class of oral hypoglycemic agents designed to target postprandial hyperglycemia by enhancing glucose-mediated insulin release. The ability of nateglinide to reduce incident diabetes and cardiovascular events is currently being tested in a long-term randomized international clinical trial (NAVIGATOR).¹²⁸ The Campanian Postprandial Hyperglycemia Study was conducted to assess the relationship between postprandial glycemia, carotid IMT, and inflammatory markers in patients with type 2 DM.¹⁷⁵ It randomized 175 drug-naïve patients with type 2 DM to treatment with either glyburide or repaglinide for 12 months. At the end of the trial there was no difference in glycemic control between the arms, but postprandial glucose peak was reduced further in the repaglinide arm. Regression of carotid IMT was seen in 52% of patients treated with repaglinide and 18% of patients treated with glyburide ($P < 0.01$). IL-6 and CRP were reduced significantly by repaglinide ($P = 0.04$ and $P = 0.02$, respectively). This study is pertinent to incident cardiovascular disease and confirms the value of specifically targeting postprandial glycemia.

KEY POINT

Metabolic syndrome is a strong risk factor for incident diabetes. Among components of metabolic syndrome, obesity and prediabetes are the most significant predictors.

CONCLUSIONS

Metabolic syndrome is a strong risk factor for incident diabetes. Among components of metabolic syndrome, obesity and prediabetes are the most significant predictors. At the time of diagnosis, a large proportion of patients with diabetes are affected by its microvascular complications. Primary care physicians should identify the patients at risk and monitor their fasting glucose and/or postprandial glucose to enable timely diagnosis and intervention. When initiating a therapeutic plan that includes drugs that may likely increase the risk of diabetes, physicians should be committed to monitoring and counseling for incident diabetes. Prevention of diabetes in patients at risk is based on intensive counseling on alteration of lifestyle. Pharmacologic interventions addressing insulin resistance, weight management, or postprandial glycemia are promising but have not yet gained wide acceptance. Intensive cardiovascular risk factor management, including drug therapy, is an important part of the treatment plan.

REFERENCES

- Engelgau M, Geiss L, Saaddine J, et al. The evolving diabetes burden in the United States. *Ann Intern Med.* 2004;140:945–950.
- Narayan K, Boyle J, Thompson T, et al. Lifetime risk for diabetes mellitus in the United States. *JAMA.* 2003; 290:1884–1890.
- Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004;5:1047–1053.
- Pinhas-Hamiel O, Dolan L, Daniels S, et al. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr.* 1996;128:608–615.
- Macaluso C, Bauer U, Deeb L, et al. Type 2 diabetes mellitus among Florida children and adolescents, 1994 through 1998. *Public Health Rep.* 2002;117:373–379.
- Keenan H, El Deirawi K, Walsh M, et al. Are trends in diabetes incidence changing for minority children? *Ann Epidemiol.* 2000;10:459.
- Gerich J. Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. *Mayo Clin Proc.* 2003;78:447–456.

8. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917–932.
9. Centers for Disease Control and Prevention Web site. Available at: <http://www.cdc.gov/diabetes/statistics/index.htm#prevalence>. Accessed October 15, 2004.
10. Kannel W, McGee D. Diabetes and cardiovascular disease. The Framingham Study. *JAMA*. 1979;241:2035–2038.
11. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
12. Lorenzo C, Okoloise M, Williams K. The metabolic syndrome as predictor of type 2 diabetes: The San Antonio Heart Study. *Diabetes Care*. 2003;26:3153–3159.
13. Zieve F. The metabolic syndrome: Diagnosis and treatment. *Clin Cornerstone*. 2004;6(Suppl 3):S5–S13.
14. Reaven G. Importance of identifying the overweight patient who will benefit the most by losing weight. *Ann Intern Med*. 2003;138:420–423.
15. McLaughlin T, Allison G, Abbasi F, et al. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. *Metabolism*. 2004;53:495–499.
16. Laaksonen D, Lakka H, Niskanen L, et al. Metabolic syndrome and development of diabetes mellitus: Application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol*. 2002;156:1070–1077.
17. Nauck M, Meier J, Wolfersdorff A, et al. A 25-year follow-up study of glucose tolerance in first-degree relatives of type 2 diabetic patients: Association of impaired or diabetic glucose tolerance with other components of the metabolic syndrome. *Acta Diabetol*. 2003;40:163–172.
18. Mykkanen L, Kuusisto J, Pyorala K, Laakso M. Cardiovascular disease risk factors as predictors of type 2 (non-insulin-dependent) diabetes mellitus in elderly subjects. *Diabetologia*. 1993;36:553–559.
19. Hanley A, Festa A, D'agostino R Jr, et al. Metabolic and inflammation variable clusters and prediction of type 2 diabetes: Factor analysis using directly measured insulin sensitivity. *Diabetes*. 2004;53:1773–1781.
20. Hanley A, Williams K, Gonzalez C, et al. Prediction of type 2 diabetes using simple measures of insulin resistance: Combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. *Diabetes*. 2003;52:463–469.
21. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414–419.
22. Klein B, Klein R, Lee K. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care*. 2002;25:1790–1794.
23. Meigs J, Williams K, Sullivan L, et al. Using metabolic syndrome traits for efficient detection of impaired glucose tolerance. *Diabetes Care*. 2004;27:1417–1426.
24. Hanson RL, Imperatore G, Bennett P, Knowler WC. Components of the “metabolic syndrome” and incidence of type 2 diabetes. *Diabetes*. 2002;51:3120–3127.
25. Grundy S. What is the contribution of obesity to the metabolic syndrome? *Endocrinol Metab Clin North Am*. 2004;33:267–282.
26. Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
27. Einhorn D, Reaven G, Cobin R, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract*. 2003;9:237–252.
28. Ruderman N, Schneider S, Berchtold P. The “metabolically-obese,” normal-weight individual. *Am J Clin Nutr*. 1981;34:1617–1621.
29. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: New definition of the metabolically obese, normal-weight individual. *Diabetes Care*. 2004;27:2222–2228.
30. Carey DG, Jenkins AB, Campbell LV, et al. Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes*. 1996;45:633–638.
31. Snijder M, Dekker J, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: The Hoorn study. *Am J Clin Nutr*. 2003;77:1192–1197.
32. Carr D, Utzschneider K, Hull RL, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004;53:2087–2094.
33. Taniguchi A, Nakai Y, Sakai M, et al. Relationship of regional adiposity to insulin resistance and serum triglyceride levels in nonobese Japanese type 2 diabetic patients. *Metabolism*. 2002;51:544–548.
34. Laaksonen DE, Kainulainen S, Rissanen A, Niskanen L. Relationships between changes in abdominal fat distribution and insulin sensitivity during a very low calorie diet in abdominally obese men and women. *Nutr Metab Cardiovasc Dis*. 2003;13:349–356.
35. Tulloch-Reid MK, Williams DE, Looker HC, et al. Do measures of body fat distribution provide information on the risk of type 2 diabetes in addition to measures of general obesity? Comparison of anthropometric predictors of type 2 diabetes in Pima Indians. *Diabetes Care*. 2003;26:2556–2561.
36. Tripathy D, Carlsson M, Almgren P, et al. Insulin secretion and insulin sensitivity in relation to glucose tolerance: Lessons from the Botnia study. *Diabetes*. 2000;49:975–980.
37. Bonora E, Kiechl S, Willeit J, et al. Population-based incidence rates and risk factors for type 2 diabetes in

- white individuals: The Bruneck Study. *Diabetes*. 2004;53:1782–1789.
38. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*. 2004;109:433–438.
 39. Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes*. 1999;48:2197–2203.
 40. Festa A, D'agostino R Jr, Hanley AJ, et al. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. *Diabetes*. 2004;53:1549–1555.
 41. Hanefeld M, Koehler C, Fuecker K, et al. Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: The risk factor in impaired glucose tolerance for atherosclerosis and diabetes study. *Diabetes Care*. 2003;26:868–874.
 42. Pontiroli AE, Pizzocri P, Caumo A, et al. Evaluation of insulin release and insulin sensitivity through oral glucose tolerance test: Differences between NGT, IFG, IGT, and type 2 diabetes mellitus. A cross-sectional and follow-up study. *Acta Diabetol*. 2004;41:70–76.
 43. Larsson H, Lindgarde F, Berglund G, Ahren B. Prediction of diabetes using ADA or WHO criteria in post-menopausal women: A 10-year follow-up study. *Diabetologia*. 2000;43:1224–1228.
 44. Vaccaro O, Ruffa G, Imperatore G, et al. Risk of diabetes in the new diagnostic category of impaired fasting glucose: A prospective analysis. *Diabetes Care*. 1999;22:1490–1493.
 45. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003;26:3160–3167.
 46. Borch-Johnsen K, Colagiuri S, Balkau B, et al. Creating a pandemic of prediabetes: The proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia*. 2004;47:1396–1402.
 47. Shaat N, Ekelund M, Lernmark A, et al. Genotypic and phenotypic differences between Arabian and Scandinavian women with gestational diabetes mellitus. *Diabetologia*. 2004;47:878–884.
 48. Albareda M, Caballero A, Badell G, et al. Diabetes and abnormal glucose tolerance in women with previous gestational diabetes. *Diabetes Care*. 2003;26:1199–1205.
 49. Bian X, Gao P, Xiong X, et al. Risk factors for development of diabetes mellitus in women with a history of gestational diabetes mellitus. *Chin Med J (Engl)*. 2000;113:759–762.
 50. Di Cianni G, Volpe L, Lencioni C, et al. Prevalence and risk factors for gestational diabetes assessed by universal screening. *Diabetes Res Clin Pract*. 2003;62:131–137.
 51. Lauenborg J, Hansen T, Jensen DM, et al. Increasing incidence of diabetes after gestational diabetes: A long-term follow-up in a Danish population. *Diabetes Care*. 2004;27:1194–1199.
 52. Dunaif A. Insulin action in the polycystic ovary syndrome. *Endocrinol Metab Clin North Am*. 1999;28:341–359.
 53. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab*. 1999;84:165–169.
 54. Oh J, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo Study. *Diabetes Care*. 2002;25:55–60.
 55. Flier JS, Eastman RC, Minaker KL, et al. Acanthosis nigricans in obese women with hyperandrogenism. Characterization of an insulin-resistant state distinct from the type A and B syndromes. *Diabetes*. 1985;34:101–107.
 56. Litonjua P, Pinero-Pilona A, Aviles-Santa L, Raskin P. Prevalence of acanthosis nigricans in newly-diagnosed type 2 diabetes. *Endocr Pract*. 2004;10:101–106.
 57. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: A feature of the metabolic syndrome. *Diabetes*. 2001;50:1844–1850.
 58. Luyckx FH, Lefebvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: Association with obesity and insulin resistance, and influence of weight loss. *Diabetes Metab*. 2000;26:98–106.
 59. Okamoto M, Takeda Y, Yoda Y, et al. The association of fatty liver and diabetes risk. *J Epidemiol*. 2003;13:15–21.
 60. Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyl-transferase and diabetes—a 4 year follow-up study. *Diabetologia*. 2003;46:359–364.
 61. Jiang R, Manson JE, Meigs JB, et al. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA*. 2004;291:711–717.
 62. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*. 1998;21:518–524.
 63. Park YW, Zhu S, Palaniappan L, et al. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med*. 2003;163:427–436.
 64. Ferrannini E, Gastaldelli A, Matsuda M, et al. Influence of ethnicity and familial diabetes on glucose tolerance and insulin action: A physiological analysis. *J Clin Endocrinol Metab*. 2003;88:3251–3257.
 65. Tan CE, Ma S, Wai D, et al. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care*. 2004;27:1182–1186.
 66. Freeman DJ, Norrie J, Caslake MJ, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes*. 2002;51:1596–1600.

67. Han TS, Sattar N, Williams K, et al. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care*. 2002;25:2016–2021.
68. Thorand B, Lowel H, Schneider A, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: Results from the Monica Augsburg Cohort Study, 1984–1998. *Arch Intern Med*. 2003;163:93–99.
69. Nakanishi S, Yamane K, Kamei N, et al. Elevated C-reactive protein is a risk factor for the development of type 2 diabetes in Japanese Americans. *Diabetes Care*. 2003;26:2754–2757.
70. Tan KC, Wat NM, Tam SC, et al. C-reactive protein predicts the deterioration of glycemia in Chinese subjects with impaired glucose tolerance. *Diabetes Care*. 2003;26:2323–2328.
71. Hu FB, Meigs JB, Li TY, et al. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53:693–700.
72. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286:327–334.
73. Duncan BB, Schmidt MI, Pankow JS, et al. Adiponectin and the development of type 2 diabetes: The Atherosclerosis Risk in Communities Study. *Diabetes*. 2004;53:2473–2478.
74. Spranger J, Kroke A, Mohlig M, et al. Adiponectin and protection against type 2 diabetes mellitus. *Lancet*. 2003;361:226–228.
75. Lindsay RS, Funahashi T, Hanson RL, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet*. 2002;360:57–58.
76. Krakoff J, Funahashi T, Stehouwer CD, et al. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. *Diabetes Care*. 2003;26:1745–1751.
77. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA*. 2004;291:1978–1986.
78. Norman JE, Bild D, Lewis CE, et al. The impact of weight change on cardiovascular disease risk factors in young black and white adults: The Cardia Study. *Int J Obes Relat Metab Disord*. 2003;27:369–376.
79. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001;286:1195–1200.
80. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the US: 1990–1998. *Diabetes Care*. 2000;23:1278–1283.
81. Koh-Banerjee P, Wang Y, Hu FB, et al. Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol*. 2004;159:1150–1159.
82. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995;122:481–486.
83. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health*. 2000;54:596–602.
84. Van Dam RM, Rimm EB, Willett WC, et al. Dietary patterns and risk for type 2 diabetes mellitus in US men. *Ann Intern Med*. 2002;136:201–209.
85. Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2001;73:1019–1026.
86. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care*. 2001;24:1528–1535.
87. Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: An ecological study. *Diabetes Metab*. 2003;29:635–642.
88. Meyer KA, Kushi LH, Jacobs DR Jr, et al. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr*. 2000;71:921–930.
89. Mozaffarian D, Kumanyika SK, Lemaitre RN, et al. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA*. 2003;289:1659–1666.
90. Liu S, Manson JE, Stampfer MJ, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health*. 2000;90:1409–1415.
91. Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: Findings from the Third National Health and Nutrition Examination Survey. *Diabetes*. 2003;52:2346–2352.
92. Lopez-Ridaura R, Willett WC, Rimm EB, et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care*. 2004;27:134–140.
93. Liu S, Willett WC, Manson JE, et al. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr*. 2003;78:920–927.
94. Janket SJ, Manson JE, Sesso H, et al. A prospective study of sugar intake and risk of type 2 diabetes in women. *Diabetes Care*. 2003;26:1008–1015.
95. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care*. 1997;20:545–550.
96. Stevens J, Ahn K, Juhaeri J, et al. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The Aric Study. *Diabetes Care*. 2002;25:1715–1721.
97. Schulze MB, Liu S, Rimm EB, et al. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr*. 2004;80:348–356.
98. Stampfer MJ, Colditz GA, Willett WC, et al. A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol*. 1988;128:549–558.
99. Nakanishi N, Suzuki K, Tatara K. Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *Diabetes Care*. 2003;26:48–54.
100. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: A

- 20-year follow-up of the Finnish Twin Cohort Study. *Diabetes Care*. 2003;26:2785–2790.
101. Wannamethee SG, Camargo CA Jr, Manson JE, et al. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch Intern Med*. 2003;163:1329–1336.
 102. Manson JE, Nathan DM, Krolewski AS, et al. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA*. 1992;268:63–67.
 103. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*. 1991;338:774–778.
 104. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23:991–999.
 105. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: A prospective study. *JAMA*. 1999;282:1433–1439.
 106. Hu G, Lindstrom J, Valle TT, et al. Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. *Arch Intern Med*. 2004;164:892–896.
 107. Lynch J, Helmrich SP, Lakka TA, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med*. 1996;156:1307–1314.
 108. Wei M, Gibbons LW, Mitchell TL, et al. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med*. 1999;130:89–96.
 109. Sawada SS, Lee IM, Muto T, et al. Cardiorespiratory fitness and the incidence of type 2 diabetes: Prospective study of Japanese men. *Diabetes Care*. 2003;26:2918–2922.
 110. Carnethon MR, Gidding SS, Nehgme R, et al. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA*. 2003;290:3092–3100.
 111. Hu FB, Leitzmann MF, Stampfer MJ, et al. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med*. 2001;161:1542–1548.
 112. Hu FB, Li TY, Colditz GA, et al. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA*. 2003;289:1785–1791.
 113. Rimm EB, Chan J, Stampfer MJ, et al. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ*. 1995;310:555–559.
 114. Rimm EB, Manson JE, Stampfer MJ, et al. Cigarette smoking and the risk of diabetes in women. *Am J Public Health*. 1993;83:211–214.
 115. Manson JE, Ajani UA, Liu S, et al. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med*. 2000;109:538–542.
 116. Carnethon MR, Fortmann SP, Palaniappan L, et al. Risk factors for progression to incident hyperinsulinemia: The Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol*. 2003;158:1058–1067.
 117. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care*. 2001;24:1590–1595.
 118. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345:790–797.
 119. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
 120. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) Randomised Trial. *Lancet*. 1999;353:611–616.
 121. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. *JAMA*. 2001;286:1882–1885.
 122. Pepine CJ, Handberg EM, Cooper-Dehoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA*. 2003;290:2805–2816.
 123. Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year in newly detected hypertensives: Results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE Study). *J Hypertens*. 2003;21:1563–1574.
 124. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: The CHARM-Overall Programme. *Lancet*. 2003;362:759–766.
 125. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
 126. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
 127. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: The DREAM Trial. *Diabetologia*. 2004.
 128. Prisant LM. Preventing type II diabetes mellitus. *J Clin Pharmacol*. 2004;44:406–413.

129. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet*. 2000;356:366–372.
130. Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension*. 2004;43:963–969.
131. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry*. 2003;160:284–289.
132. Clark C, Burge MR. Diabetes mellitus associated with atypical anti-psychotic medications. *Diabetes Technol Ther*. 2003;5:669–683.
133. Gupta S, Steinmeyer C, Frank B, et al. Hyperglycemia and hypertriglyceridemia in real world patients on antipsychotic therapy. *Am J Ther*. 2003;10:348–355.
134. Baptista T, Kin NM, Beaulieu S, De Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration: Mechanisms, management and research perspectives. *Pharmacopsychiatry*. 2002;35:205–219.
135. Lean ME, Pajonk FG. Patients on atypical antipsychotic drugs: Another high-risk group for type 2 diabetes. *Diabetes Care*. 2003;26:1597–1605.
136. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003;160:290–296.
137. Regenold WT, Thapar RK, Marano C, et al. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar, affective and schizoaffective disorders independent of psychotropic drug use. *J Affect Disord*. 2002;70:19–26.
138. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161:1334–1349.
139. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *J Clin Psychiatry*. 2004;65:267–272.
140. Kino T, Mirani M, Alesci S, Chrousos GP. AIDS-related lipodystrophy/insulin resistance syndrome. *Horm Metab Res*. 2003;35:129–136.
141. Butt AA, Fultz SL, Kwoh CK, et al. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology*. 2004;40:115–119.
142. Calza L, Manfredi R, Chiodo F. Hyperlipidaemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: Epidemiology, pathogenesis, clinical course and management. *Int J Antimicrob Agents*. 2003;22:89–99.
143. Sax PE, Kumar P. Tolerability and safety of HIV protease inhibitors in adults. *J Acquir Immune Defic Syndr*. 2004;37:1111–1124.
144. Woerle HJ, Mariuz PR, Meyer C, et al. Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens. *Diabetes*. 2003;52:918–925.
145. Hansen BR, Haugaard SB, Iversen J, et al. Impact of switching antiretroviral therapy on lipodystrophy and other metabolic complications: A review. *Scand J Infect Dis*. 2004;36:244–253.
146. Bucher HC, Young J, Battegay M. Protease inhibitor-sparing simplified maintenance therapy: A need for perspective. *J Antimicrob Chemother*. 2004;54:303–305.
147. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant*. 2003;3:178–185.
148. Parikh CR, Klem P, Wong C, et al. Obesity as an independent predictor of posttransplant diabetes mellitus. *Transplant Proc*. 2003;35:2922–2926.
149. Hernandez D, Alvarez A, Torres A, et al. Cardiovascular risk profile in nondiabetic renal transplant patients: Cyclosporine versus tacrolimus. *Transplant Proc*. 2003;35:1727–1729.
150. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: A systematic review and meta-analysis. *Am J Transplant*. 2004;4:583–595.
151. Filler G, Neuschulz I, Vollmer I, et al. Tacrolimus reversibly reduces insulin secretion in paediatric renal transplant recipients. *Nephrol Dial Transplant*. 2000;15:867–871.
152. Montori VM, Basu A, Erwin PJ, et al. Posttransplantation diabetes: A systematic review of the literature. *Diabetes Care*. 2002;25:583–592.
153. Pascual J, Marcen R, Burgos FJ, et al. A low incidence of new-onset insulin-dependent diabetes mellitus using tacrolimus in kidney recipients in Europe. *Transplant Proc*. 2003;35:1760–1761.
154. Nanji SA, Shapiro AM. Islet transplantation in patients with diabetes mellitus: Choice of immunosuppression. *Biodrugs*. 2004;18:315–328.
155. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 international consensus guidelines. Proceedings of an international expert panel meeting, Barcelona, Spain, 19 February 2003. *Transplantation*. 2003;75(Suppl 10):S3–S24.
156. Li G, Hu Y, Yang W, et al. Effects of insulin resistance and insulin secretion on the efficacy of interventions to retard development of type 2 diabetes mellitus: The Da Qing IGT and Diabetes Study. *Diabetes Res Clin Pract*. 2002;58:193–200.
157. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
158. Lindstrom J, Louheranta A, Manninen M, et al. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care*. 2003;26:3230–3236.
159. Lindstrom J, Eriksson JG, Valle TT, et al. Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study:

- Results from a randomized clinical trial. *J Am Soc Nephrol*. 2003;14(Suppl 2):S108–S113.
160. Uusitupa M, Lindi V, Louheranta A, et al. Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-year results from the Finnish Diabetes Prevention Study. *Diabetes*. 2003;52:2532–2538.
161. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22:623–634.
162. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
163. Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518–2523.
164. Hernan WH, Brandle M, Zhang P, et al. Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:36–47.
165. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.
166. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27:155–161.
167. Glucose Tolerance and Mortality: Comparison of WHO and American Diabetes Association Diagnostic Criteria. The Decode Study Group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe. *Lancet*. 1999;354:617–621.
168. Temelkova-Kurktschiev TS, Koehler C, Henkel E, et al. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care*. 2000;23:1830–1834.
169. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol*. 2004; 24:816–823.
170. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072–2077.
171. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for the prevention of type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: Facts and interpretations concerning the critical analysis of the STOP-NIDDM trial data. *Diabetologia*. 2004;47:969–975.
172. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. *JAMA*. 2003;290:486–494.
173. Hanefeld M, Chiasson JL, Koehler C, et al. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke*. 2004;35:1073–1078.
174. Hanefeld M, Cagatay M, Petrowitsch T, et al. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: Meta-analysis of seven long-term studies. *Eur Heart J*. 2004;25:10–16.
175. Esposito K, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation*. 2004;110:214–219.