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The Metabolic Syndrome and Glucose Intolerance

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The clustering of several metabolic factors in the metabolic syndrome increases the risk of both cardiovascular disease (CVD) and glucose intolerance. Persons with more components of the syndrome are likely to have progressively severe insulin resistance and are more likely to exhibit glucose intolerance. This article reviews the association between the metabolic syndrome and the development of insulin resistance and glucose intolerance and discusses an approach to screening persons at risk for impaired glucose tolerance.

CASE PRESENTATION

A 46-year-old African-American man presents for a check up as a new patient. The patient leads a sedentary lifestyle. His father developed diabetes at age 50 years and died of a heart attack at age 67 years. The patient's history is otherwise unremarkable, but he has gained 40 lb in the past 5 to 10 years. On examination, he is 5 ft 8 in tall and weighs 220 lb, with a waist circumference of 41 in. His blood pressure is 142/88 mm Hg. Aside from obesity, his examination is unremarkable. His electrocardiogram shows left axis deviation with large complexes in leads V₂ through V₅. A blood sample obtained at the time of the visit reveals a serum alanine aminotransferase level of 42 U/L (normal, 10–40 U/L) and a glucose level of 146 mg/dL; however, the patient finished lunch 1 hour before the appointment. A fasting blood sample reveals the following: glucose, 112 mg/dL; total cholesterol, 210 mg/dL; triglyceride, 150 mg/dL; high-density lipoprotein (HDL) cholesterol, 45 mg/dL; and low-density lipoprotein (LDL) cholesterol, 135 mg/dL.

Given the patient's increased waist circumference, blood pressure, and fasting glucose level, the physician makes a diagnosis of metabolic syndrome.

- Is this patient likely to have insulin resistance?

This patient meets the Adult Treatment Panel III criteria for metabolic syndrome (ie, at least 3 of 5 criteria: obesity determined by waist circumference, hyper-

TAKE HOME POINTS

- The metabolic syndrome is associated with an increased risk for glucose intolerance.
- In patients with insulin resistance, glucose intolerance (impaired glucose tolerance [IGT] and type 2 diabetes) develops if insulin secretion from pancreatic beta cells is insufficient to overcome insulin resistance.
- Individuals older than 45 years and with a body mass index over 25 kg/m² or those younger than 45 years who have additional risk factors should undergo an oral glucose tolerance test to screen for IGT and unrecognized diabetes.
- Treatment of the metabolic syndrome should be aimed at decreasing insulin resistance, preserving beta-cell function, and minimizing cardiovascular risk.
- Lifestyle change via proper diet and increased physical activity should be the primary therapeutic strategy along with correcting hypertension and dyslipidemia to low-risk targets. Aspirin should be used to optimize risk reduction.

tension, fasting glucose level \geq 110 mg/dL, increased triglycerides, and low HDL cholesterol). Insulin resistance has been considered as a possible unifying factor that may lead to the development of the components of the metabolic syndrome. Several epidemiologic studies have shown that markers of insulin resistance (eg, plasma insulin, glucose parameters, measures of

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obesity, and lipid abnormalities) are intercorrelated, suggesting that insulin resistance may be a common underlying mediator.¹ Although insulin resistance and hyperinsulinemia have been associated with hypertension,² blood pressure in many of these studies is less intercorrelated,¹ suggesting that blood pressure may involve different etiologic pathways.

Obese persons as well as lean persons with normal glucose tolerance and a family history of diabetes often have insulin resistance, which may be mediated by several factors. The adverse effects of obesity reflect the metabolic and hormonal activity of the adipose organ, particularly visceral adipose tissue. Visceral fat has greater metabolic effects than fat in other sites,³ and waist circumference is a stronger predictor of diabetes risk than body mass index (BMI) or waist/hip ratio.⁴ Obesity is associated with detrimental changes in adipocyte secretion of adipocytokines, with increased levels of free fatty acids, tumor necrosis factor (TNF)- α , interleukin (IL)-6, plasminogen-activator inhibitor-1 (PAI-1), leptin, and resistin as well as decreased adiponectin levels. In the liver, the excess delivery of fatty acids leads to increased triglyceride content (fatty liver), increased hepatic gluconeogenesis and glycogenolysis, and increased synthesis and secretion of very low-density lipoprotein (VLDL) cholesterol, leading to abnormalities in glucose metabolism and increased triglyceride levels. Intramyocellular triglyceride accumulation in muscle tissue has been associated with insulin resistance,⁵ but the mechanism is not known. It is highly likely that this obese patient with the metabolic syndrome and elevated alanine aminotransferase level has insulin resistance and a fatty liver.

- Should insulin sensitivity be measured in this patient?

Accurate, practical measures of insulin resistance are not available to most clinicians. However, having such a tool would not alter management decisions in most patients with the metabolic syndrome for 2 reasons. First, insulin resistance alone is not a sufficient predictor of the development of type 2 diabetes. Although insulin resistance is an important component in the pathogenesis of type 2 diabetes, it must be accompanied by beta-cell dysfunction for the disease to occur. Second, most patients with the metabolic syndrome already exhibit clinical manifestations of insulin resistance that by themselves would warrant management to prevent the development of CVD and diabetes—the major adverse outcomes related to the metabolic syndrome—without quantitation of the degree of insulin resistance. Patients with the metabolic syndrome usually have increased BMI and waist circumference, and the presence of these markers is an

Table 1. Glucose Tolerance (American Diabetes Association Criteria)

	Fasting	OGTT*
Normal	< 100 mg/dL	< 140 mg/dL
Impaired	100–125 mg/dL	140–199 mg/dL
Diabetes	≥ 126 mg/dL	≥ 200 mg/dL

IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

*2-Hr glucose, 75 g.

indication that hypertension, dyslipidemia, and other abnormalities should be treated aggressively.

- What is the likelihood that the patient has glucose intolerance or diabetes?

GLUCOSE INTOLERANCE AND BETA-CELL DYSFUNCTION

The increasing prevalence of diabetes in the United States can be attributed to changes in demographics: we have become older, heavier, and more sedentary—more likely to be insulin resistant—and the population is enriched with racial/ethnic groups with a genetic predisposition to diabetes. Because of these trends, the lifetime risk of developing diabetes for individuals born in 2000 is estimated at 33% for men and 38% for women.⁶

Although the case patient has a normal level of triglycerides, he has increased waist size and impaired fasting glucose (IFG) by either World Health Organization (WHO) or American Diabetes Association (ADA) criteria (Table 1), evidence of early glucose intolerance. The Baltimore Longitudinal Study of Aging characterized the appearance of glucose intolerance during the natural history of beta-cell dysfunction.⁷ In individuals with normal glucose tolerance at baseline, 14% had progressed to abnormal fasting plasma glucose (110 mg/dL) after 10 years, but 48% had developed abnormal postchallenge glucose (140 mg/dL) by this time, showing that impaired glucose tolerance (IGT) precedes IFG in the natural history of the development of beta-cell failure. Studies in other populations also indicate that postchallenge glucose (and presumably postprandial glucose) tends to rise earlier than fasting glucose as glucose intolerance develops.

When glucose levels rise, the normal beta cell responds with both first- and second-phase secretion of insulin. First-phase insulin secretion (rapid) reflects release of insulin previously synthesized and stored in secretory granules, for which the glucose signal triggers exocytosis, while second-phase insulin secretion (slow) requires synthesis of new insulin molecules. As shown in

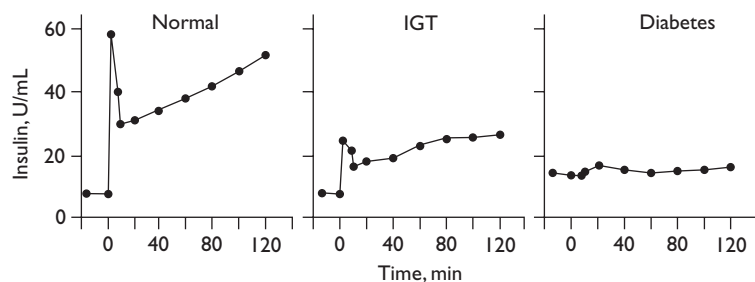


Figure 1. Reduced first- and second-phase insulin secretion in individuals with impaired glucose tolerance (IGT) and diabetes. (Adapted with permission from Stumvoll M, Fritsche A, Stefan N, Haring H.A 60 minute hyperglycemic clamp is sufficient to assess both phases of insulin secretion. *Horm Metab Res* 2000;32:231.)

Figure 1, individuals with IGT have extensive loss of first-phase insulin secretion and a reduced second phase, and individuals with type 2 diabetes have little first-phase insulin release at all.⁸ Impaired first-phase insulin release due to early beta-cell dysfunction results in inadequate suppression of hepatic glucose output, which is a major cause of postchallenge/postprandial hyperglycemia.

Postprandial hyperglycemia, resulting from the combination of insulin resistance and early beta-cell dysfunction, is associated with increased oxidative stress. Administration of streptozocin to induce diabetes in monkeys leads to the accumulation of the reactive nitrogen species *ortho*-tyrosine and *meta*-tyrosine in vascular tissue, and the tissue concentrations of these products are strongly correlated with circulating levels of glycosylated hemoglobin (HbA_{1c}) in the animals. Patients with diabetes also have elevated circulating levels of nitrotyrosine compared to nondiabetic subjects.⁹ Following a meal, patients with type 2 diabetes exhibit a rise in circulating levels of both malondialdehyde and nitrotyrosine.⁹ Although nondiabetic persons have less of a response to such meal challenges, induction of acute but sustained hyperglycemia with a glucose clamp leads to a progressive rise in nitrotyrosine even in healthy persons.¹⁰ In combination, these findings indicate that acute hyperglycemia produces oxidative stress, and that the oxidative stress responses are increased in individuals with diabetes, who have exaggerated postprandial hyperglycemia.

MECHANISMS OF THE DEVELOPMENT OF BETA-CELL DYSFUNCTION WITH THE METABOLIC SYNDROME

Systemic Oxidative Stress

Obesity results in increased local oxidative stress in adipocytes. In an elegant report from Furukawa et al,¹¹ the development of preadipocytes into adipocytes was shown to be associated with increased production of reactive oxygen species (ROS), such as H₂O₂ and superoxide. ROS production in white adipose tissue of obese mice reflects underlying increases in NADPH oxidase and decreases in antioxidant enzymes. There is also increased expression of the transcription factor PU.1, which stimu-

lates NADPH oxidase gene transcription, and increased expression of NADPH oxidase 4 (NOX4), which is involved in generation of H₂O₂. Accumulation of fatty acids increases production of ROS by steps requiring NADPH oxidase, and accumulation of ROS further stimulates expression of PU.1 and NOX4—a vicious cycle.

Systemic “messages” from the adipose organ (ie, free fatty acids, adipocytokines, and systemic oxidative stress) can challenge beta-cell function both indirectly (via increased insulin resistance in fat, muscle, and liver) and directly (via local effects). As outlined above, increased adiposity leads to insulin resistance, which reflects both the accumulation of triglycerides in muscle and liver, and the effects of increased levels of adipocytokines and free fatty acids. Obese humans have increased circulating oxidative stress, which is associated with increases in free fatty acids, TNF- α , IL-6, and leptin as well as decreases in adiponectin; these adipocytokines are significantly correlated with increases in BMI and waist circumference. Measures of oxidative stress are also inversely correlated with adiponectin levels, and similar abnormalities are present in animal models of obesity.¹¹ In obese KKAy mice, the decrease in circulating adiponectin reflects underlying decreases in expression in adipose tissue. Such alterations in adiponectin appear to be secondary to increased local oxidative stress, as its secretion from adipocytes is decreased by administration of H₂O₂ and enhanced by administration of the antioxidant N-acetylcysteine (NAC). Moreover, administration of apocynin, an NADPH oxidase inhibitor that decreases adipose tissue lipid peroxidation and production of H₂O₂, increased expression of adiponectin and decreased expression of TNF- α . In this animal model, apocynin also reduced hepatic and circulating triglycerides and lowered glucose levels, supporting the hypothesis that such features of the metabolic syndrome and associated development of glucose intolerance reflect pivotal contributions from oxidative stress in adipose tissue.

Animal models of diabetes also exhibit increased triglyceride content and oxidative stress as measured by 8-OHdG and hydroxynonenal (HNE)-modified proteins,

and direct exposure of islets and/or beta cells to fatty acids or ROS decreases beta-cell function. Glucose-sensitive insulin secretion (GSIS) is decreased by exposure of islets or cultured beta cells to high levels of fatty acids¹² and to HNE or lipid peroxidation products.¹³ Such observations provide evidence that adipose organ “messages,” such as fatty acids and ROS, can have direct adverse effects on beta-cell function.

Local Production of ROS

Individuals with glucose intolerance characteristically exhibit decreased islet and beta-cell mass, decreased islet insulin content, and decreased GSIS. Current evidence indicates that beta-cell oxidative stress, especially high levels of superoxide, plays an important role in causing important functional abnormalities: increased apoptosis mediated in part by a fall in levels of the antiapoptotic Bcl-2 protein, decreased insulin synthesis mediated in part by a fall in the transcription factor PDX-1 (a regulator of insulin gene transcription), and decreased GSIS mediated by a rise in uncoupling protein-2 (UCP-2) (Table 2).

Increased apoptosis. Individuals with type 2 diabetes have a decrease in islet and beta-cell mass, reflecting an imbalance between apoptosis and generation of new beta cells. Animal models of diabetes exhibit increased islet apoptosis, as seen in both diabetic and prediabetic Zucker diabetic fatty (ZDF) rats. Oxidative stress appears to mediate the increase in apoptosis and fall in beta-cell mass because treatment of spontaneously diabetic *db/db* mice with the antioxidant NAC reduces islet apoptosis without affecting beta-cell proliferation.¹⁴ It seems likely that the increase in apoptosis is due in part to a superoxide-induced fall in the antiapoptotic protein Bcl-2 (which prevents caspase activation). In T cells, there is a strong inverse correlation between superoxide levels and Bcl-2 levels, and antioxidant treatment increases Bcl-2 expression.¹⁵

Decreased insulin synthesis In the ZDF rat, a well-accepted model of type 2 diabetes, the development of hyperglycemia is associated with a progressive fall in levels of insulin messenger RNA (mRNA) in their pancreatic islets, attributed to an underlying decrease in expression of PDX-1, which regulates insulin gene transcription. Treatment of the animals with troglitazone, an insulin-sensitizing agent, reduces hyperglycemia and partially restores levels of PDX-1 and insulin mRNA. Treatment with NAC partially restores levels of PDX-1 and insulin mRNA, evidence for mediation by increased oxidative stress. The promotion of insulin synthesis requires movement of PDX-1 from the cytoplasm to the nucleus, but exposure of cultured beta cells to H₂O₂ in

Table 2. Beta-Cell Oxidative Stress Leads to Glucose Intolerance: Underlying Mechanisms

Superoxide Process	Impact
↓ Bcl-2	↑ Apoptosis, ↓ beta-cell mass
↓ PDX-1	↓ Insulin synthesis
↑ UCP-2	↓ Glucose-sensitive secretion

UCP-2 = uncoupling protein-2.

vitro causes PDX-1 to translocate from the nucleus to the cytoplasm.¹⁶ Thus, oxidative stress appears to decrease synthesis of insulin both by decreasing PDX-1 expression and by retaining PDX-1 in the cytoplasm, where it is transcriptionally inactive.

Decreased GSIS. The normal beta cell is metabolically constituted to respond promptly to a rise in circulating glucose levels (Figure 2). The high-*K_m* glucose transporter GLUT2 moves glucose into the cell, and the high-*K_m* hexokinase isoform glucokinase facilitates glycolytic processing. Reducing equivalents are generated via the tricarboxylic acid (TCA) cycle, which increases the ATP/ADP ratio via oxidative phosphorylation. This closes an ATP-sensitive potassium channel, depolarizing the cell, and results in activation of a voltage-gated calcium channel. The rise in intracellular calcium triggers exocytosis of insulin secretory granules, releasing insulin.

The production of ATP involves flux through the mitochondrial electron-transport chain (Figure 3), in which electrons are donated from reducing equivalents (NADH and FADH₂) to complexes in the inner mitochondrial membrane, generating a proton gradient that provides energy to drive synthesis of ATP. However, when the proton gradient becomes too high (from exposure to high glucose levels), electron transport is partially inhibited, electrons back up to a free radical intermediate of coenzyme Q, and superoxide is generated.¹⁷ When islet cells are exposed to high glucose concentrations, superoxide levels rise^{18,19} as was demonstrated in ZDF rats both in the diabetic and prediabetic (normoglycemic) stage of development.¹⁹ Activation of UCP-2 by superoxide permits the energy in the proton gradient to be dissipated as heat rather than generation of ATP.²⁰

Increasing evidence indicates that the effect of oxidative stress to decrease GSIS is mediated by UCP-2. UCP-2 is a membrane protein that increases proton leak across the inner mitochondrial membrane, “uncoupling” the link between the electron transport chain and oxidative phosphorylation as well as reducing the electrochemical gradient that drives synthesis of ATP.^{21,22} It appears that superoxide activates UCP-2

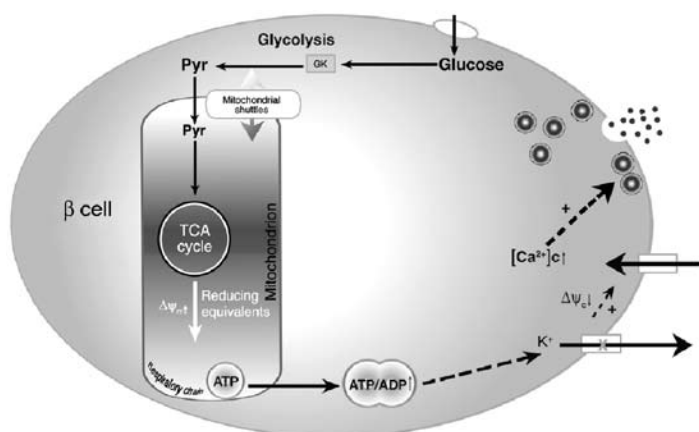
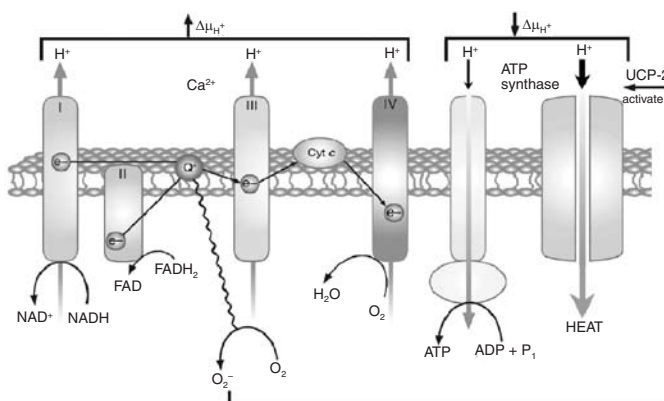


Figure 2. Normal insulin release by beta cells in response to glucose. ADP = adenosine diphosphate; ATP = adenosine triphosphate; TCA = tricarboxylic acid. (Adapted with permission from Brownlee M. A radical explanation for glucose-induced beta cell dysfunction. *J Clin Invest* 2003;112:1789.)

Figure 3. ATP production by the mitochondrial electron transport chain. ADP = adenosine diphosphate; ATP = adenosine triphosphate; Cyt c = cytochrome c; FAD = flavin adenine dinucleotide; NAD = nicotinamide adenine dinucleotide; UCP-2 = uncoupling protein-2. (Adapted with permission from Brownlee M. A radical explanation for glucose-induced beta cell dysfunction. *J Clin Invest* 2003;112:1789.)



from the matrix side of the mitochondrial membrane, but it may not activate UCP-2 directly. Instead, superoxide generates a cascade of lipid peroxidation reactions, and it is the lipid peroxidation products (eg, HNE) that activate UCP-2. Adenoviral overexpression of UCP-2 in cultured human islets leads to reductions in the proton gradient and ATP content,²³ with subsequent inhibition of GSIS.²¹ Conversely, UCP-2 knockout mice have higher islet ATP levels and improved GSIS, along with increased insulin and lower glucose levels in the circulation.²⁴ Exogenous superoxide increases proton leak in isolated wild-type mitochondria.²⁵ However, in UCP-2 knockout mice, superoxide has no effect on either mitochondrial proton leak or islet ATP levels and GSIS,¹⁸ thus confirming that the presence of UCP-2 is necessary for the detrimental effect of superoxide on these processes. Such tissue evidence for the physiologic significance of UCP-2 is reinforced by the observation that type 2 diabetes patients who carry a UCP-2 polymorphism that increases promoter activity are likely to need insulin, presumably reflecting early beta-cell failure.

Beta-Cell Defense Against Oxidative Stress

Beta cells express NADPH oxidase and can gener-

ate ROS but have low levels of the antioxidant enzymes required to ameliorate oxidative stress. Compared to liver, both islets and beta-cell lines have reduced levels of superoxide dismutase, which is needed to inactivate superoxide, and low levels of catalase and glutathione peroxidase, which are needed to inactivate H₂O₂.²⁶ Accordingly, beta cells are more likely than other tissues to exhibit functional abnormalities as a result of exposure to either systemic ROS or local ROS. Individuals with the metabolic syndrome tend to develop glucose intolerance partly due to the inability of the beta cell to defend against oxidative stress. Analogous to the “canary in the coal mine” (whose distress was regarded as a sign of the presence of toxic gases), hyperglycemia can be viewed as a signal of systemic oxidative stress that confers risk to other body tissues and organs such as the cardiovascular system.

- Is it important to screen for glucose intolerance in this patient?

SCREENING FOR GLUCOSE INTOLERANCE

Screening for glucose intolerance has largely been based on glycemic indicators. Because individuals with

IGT often have normal HbA_{1c} levels, it is not surprising that HbA_{1c} is not sensitive in detecting IGT in several different populations. Accordingly, screening should involve measurement of glucose levels with an oral glucose tolerance test (OGTT). There is a nonlinear quadratic rise in post-challenge glucose as fasting glucose increases, and fasting glucose measurements often fail to recognize both IGT and “isolated post-challenge hyperglycemia” (IPH-diabetes, or patients with normal fasting glucose levels who have diabetes as shown by OGTT).²⁷ Because of the intrinsic limitations of fasting glucose screening, poor sensitivity is obtained even with lower cutoff levels.²⁸ In addition, inability to recognize IPH-diabetes is a particular problem because the prevalence of IPH-diabetes increases with age. Finally, IGT is more likely than IFG to be associated with insulin resistance and the development of CVD. In the Insulin Resistance Atherosclerosis Study,²⁹ which used an intravenous glucose tolerance test to assess acute insulin response to glucose, IGT patients had higher insulin resistance than IFG patients, along with higher levels of triglycerides and C-reactive protein. These patterns were similar among non-Hispanic whites, African Americans, and Hispanics.³⁰ Consistent with these findings, IGT and higher postchallenge glucose also conferred higher cardiovascular mortality than IFG and elevated fasting glucose in the DECODE Study.³⁰ Given the increased risk conferred by IGT, it is particularly important when screening for glucose intolerance to use OGTT rather than fasting glucose measurements in order to recognize both IGT and early diabetes.

At present, many patients at risk are not being screened. However, the Centers for Disease Control and Prevention (CDC) and the Diabetes Prevention Program (DPP) research group recently projected (1) that incremental increases in costs associated with screening and earlier treatment would be in a range generally acceptable to US health care systems and that there would be particular value in screening younger individuals and minority populations at high risk; and (2) that treatment should be especially cost-effective in younger individuals recognized early in their natural histories.^{31,32}

In addition to glucose, measurement of risk factors such as those found in the metabolic syndrome, as well as age, sex, ethnicity, and family history of diabetes, can help identify individuals who are at risk for diabetes and CVD. For example, 7.5-year incident diabetes in the San Antonio Heart Study (SAHS) could be predicted by a model including age, sex, ethnicity, fasting glucose, systolic blood pressure, HDL cholesterol, BMI, and first-degree family history of diabetes.³³ Although some have argued that the utility of such non-OGTT risk fac-

tors might make use of the OGTT unnecessary, recent SAHS studies showed IGT to be more powerful than the metabolic syndrome as a predictor of diabetes risk.³⁴ Moreover, the major issue is not predicting diabetes years later, but identification of IGT (and previously unrecognized diabetes) now, for which an OGTT is essential as pointed out by the CDC group.^{35,36} In addition, risk factors such as BMI and waist/hip ratio have varying pathophysiologic significance in different racial/ethnic groups, and risk-factor-based models may have limited applicability in multicultural populations.^{37,38} For example, 64% of African Americans have BMI of at least 25 and 40% have hypertension, which are indications for screening. Yet only 13% of patients demonstrated IGT in NHANES III,³⁹ whereas many individuals with IGT and hyperglycemia may actually have few risk factors.^{40–42} Such considerations argue in favor of OGTT-based screening of a wide population as currently recommended by the ADA and the National Institutes of Health,⁴³ including most individuals over 45 years of age and younger individuals who are overweight, such as the case patient.

Case Presentation Continued

Testing in the case patient show a fasting glucose level of 98 mg/dL and a 2-hour postchallenge glucose level of 161 mg/dL, indicating the presence of IGT.

- What risk does IGT confer?

RISKS ASSOCIATED WITH IGT

IGT carries a high risk for development of diabetes. In the SAHS, the risk of developing diabetes was signaled by the presence of IGT alone with a considerably higher positive predictive value as compared with the presence of the metabolic syndrome alone.³⁴ The rate of progression from IGT to diabetes in the control arm was 11% per year in the DPP,⁴⁴ and ranged from 2.5% to 9% per year in different populations. Saad et al⁴⁵ found in a Pima Indian population that even a single transient finding of IGT tripled the risk of developing diabetes. In 1245 Italian subjects, IGT had much greater sensitivity for determining progression to diabetes than IFG (33% versus 9%), with little difference in specificity (93% versus 97%).⁴⁶

IGT also confers risk for the development of CVD. Diabetes is a coronary heart disease risk equivalent,⁴⁷ and a strong correlation between hyperglycemia and CVD has been shown in numerous studies. IGT conferred a 2.2-fold increase in risk of cardiovascular death in the Funagata Diabetes Study,⁴⁸ but the contribution of IFG was not significant; similar results were obtained

in NHANES II.⁴⁹ In the Nurses Health Study, the authors concluded that the finding of a 2.6-fold increase in risk of myocardial infarction prior to diagnosis of diabetes may be due to a greater proportion of participants with IGT.⁵⁰ Thus, while individuals with IGT may not yet have developed microvascular complications, their cardiovascular risk is substantial.

Although individuals with diabetes or IGT often have the metabolic syndrome,⁵¹ hyperglycemia in the range of IGT impairs endothelial function and increases cardiovascular risk independently of other risk factors.^{49,51,52} The impact of postchallenge glucose on coronary artery disease and/or cardiovascular mortality persisted after adjustment for risk factors such as age, BMI, hypertension, lipids, and smoking in several studies.^{52–55} In mechanistic studies, increased carotid intima-media thickness (IMT) was more strongly associated with increased 2-hour plasma glucose levels than with increased HbA_{1c} levels, and IMT was greater in patients with IGT compared to individuals with normal glucose tolerance.⁵⁶ Moreover, IGT was a strong predictor of 5-year change in carotid IMT and was associated with increased coronary artery calcification.⁵⁷ Thus, since approximately 25% of patients with newly diagnosed type 2 diabetes already have evidence of CVD⁵⁸ and the beta-cell defects that underlie diabetes may begin approximately 12 years before the diagnosis is made,⁵⁹ it will be important to identify patients earlier, when they have IGT.

- How should the patient be managed?

TREATMENT

The goal of therapy in patients with the metabolic syndrome is to minimize the risk for the development of CVD and diabetes. To address CVD risk factors, optimal blood pressure control should be achieved as recommended in the JNC-VII report.⁶⁰ Additional benefit should be obtained by lowering LDL cholesterol levels,^{61–63} lowering triglyceride levels,^{64,65} and raising HDL cholesterol levels^{64,66} as recommended by the National Cholesterol Education Program. Since the benefit of aspirin therapy in CVD prevention is well-established,⁶⁷ aspirin should be used as well.

Approaches to prevent the development of CVD and type 2 diabetes should be considered in patients with the metabolic syndrome, particularly in those with IFG or IGT. Diets high in fruits, vegetables, and fiber are associated with lower risk of CVD,⁶⁸ improved glucose and lipid levels in patients with diabetes,⁶⁹ and improved endothelial dysfunction in patients with the metabolic syndrome.⁷⁰ In overweight individuals,

weight loss improves the risk factors for CVD⁷¹ and diabetes and reduces insulin resistance.⁷² In the DPP,⁴⁴ an intensive diet and exercise program led to a 58% reduction in the incidence of diabetes in patients with IGT. Thus, combining high fiber, low saturated fat diets with regular exercise and weight loss should reduce the risk of CVD and diabetes in patients with the metabolic syndrome.

Diabetes-Related Medications

Metformin, a biguanide, acts by decreasing hepatic glucose production, increasing peripheral glucose utilization, and reducing intestinal glucose absorption. These actions are mediated largely by stimulation of AMP-activated protein kinase,⁷³ which inhibits lipolysis, lipogenesis, and cholesterol and triglyceride synthesis as well as stimulates fatty acid oxidation and glucose uptake. The resulting decrease in insulin resistance, gluconeogenesis, and VLDL production lowers glucose, fatty acid, and triglyceride levels⁷³ and should decrease the risk of CVD and diabetes in individuals with the metabolic syndrome. Metformin treatment reduced incidence of myocardial infarction in a subgroup of patients with diabetes in the UKPDS⁷⁴ and reduced the development of diabetes by 31% in IGT patients in the DPP.⁴⁴

Thiazolidinediones (TZDs; rosiglitazone, pioglitazone) bind to PPAR γ , a nuclear transcription factor, increase insulin sensitivity in adipose tissue, muscle, and liver, and improve lipid abnormalities by decreasing free fatty acid levels, enhancing lipogenesis, and increasing adipocyte differentiation. TZDs also help to preserve beta-cell function. TZD treatment reduced progression to diabetes by 55% in women with prior gestational diabetes⁷⁵ and reduced in-stent restenosis in diabetic patients with CAD.⁷⁶ Such evidence suggests that TZD treatment may decrease the incidence of diabetes and CVD in high-risk individuals with the metabolic syndrome.

Postprandial hyperglycemia is associated with increased oxidative stress, and agents that reduce postprandial hyperglycemia might improve CVD risk. α -Glucosidase inhibitors (acarbose, miglitol) inhibit the breakdown of disaccharides to absorbable monosaccharides, and in subjects with IGT, acarbose treatment reduced the development of diabetes by 36%⁷⁷ and cardiovascular events by 49%.⁷⁸ Rapid-acting, non-sulfonylurea insulin secretagogues (repaglinide and nateglinide) inhibit the ATP-dependent potassium channel on pancreatic beta cells, with subsequent stimulation of insulin release. These medications have a more rapid onset and shorter duration of action than sulfonylureas, are more effective in lowering postprandial hyperglycemia, and carry less risk of hypoglycemia.

In patients with type 2 diabetes, repaglinide reduced carotid IMT and C-reactive protein levels⁷⁹ and improved brachial reactivity and levels of oxidative stress.⁸⁰ The potential preventive utility of nateglinide in patients with IGT is currently under investigation. Along with the potential benefits of these agents in reducing risk of CVD and diabetes, it is important to consider the potential risks of therapy. The sulfonylureas, and to a lesser extent, repaglinide, carry a risk of hypoglycemia and weight gain, and sulfonylureas may also accelerate beta-cell apoptosis.⁸¹ Treatment with α -glucosidase inhibitors has been associated with gastrointestinal distress.

Targeting the Renin-Angiotensin System

Mounting evidence suggests that the renin-angiotensin system (RAS) may also be an important component underlying the development of CVD and diabetes. The RAS contributes to endothelial dysfunction, inflammation, and oxidative stress, and the importance of the RAS for CVD has been shown in patients with diabetes by a reduction of CVD events and mortality; these benefits are independent of effects on glucose and blood pressure by angiotensin-converting enzyme (ACE) inhibitors⁸² and angiotensin-receptor blockers (ARBs).⁸³ Moreover, ACE inhibition improves both insulin resistance⁸⁴ and beta-cell function,⁸⁵ and ACE inhibitors⁸⁶ and ARBs⁸⁷ reduced the incidence of diabetes in prospective studies. These studies suggest that RAS blockade in individuals with the metabolic syndrome may reduce the risk of both CVD and diabetes.

AN INTEGRATIVE VIEW

As patients experience life changes that predispose to insulin resistance (eg, aging, weight gain, and decrease in physical activity), many will develop the metabolic syndrome. It seems likely that lack of full congruence between the metabolic syndrome and insulin resistance^{88,89} reflects both variable contributions from the different components of the syndrome and genetic predisposition. At the same time, not all individuals who exhibit insulin resistance and/or the metabolic syndrome will develop glucose intolerance, also reflecting varying genetic predisposition. However, the beta cell has intrinsic metabolic vulnerability to the oxidative stress that results from insulin resistance. Although the metabolic syndrome is not a perfect indicator of insulin resistance, individuals with more components of the syndrome and more severe abnormalities are likely to have progressively severe insulin resistance and are correspondingly more likely to exhibit glucose intolerance.

When patients with the metabolic syndrome devel-

op hyperglycemia, the relative insulin secretory defect that underlies the hyperglycemia is likely to make the glucose intolerance worse. Relative insulin deficiency will accelerate lipolysis and raise free fatty acid levels, increasing triglyceride deposition in liver and muscle (increasing insulin resistance). The associated increase in oxidative stress will further compromise beta-cell function, increasing apoptosis and decreasing insulin synthesis and glucose-dependent insulin secretion. If left untreated, this “vicious cycle” will lead to progressive beta-cell failure and rising glucose levels.

Ideally, treatment of the metabolic syndrome should be aimed at decreasing insulin resistance, preserving beta-cell function, and minimizing cardiovascular risk. Lifestyle change via proper diet and increased physical activity should be the primary therapeutic strategy since this has been shown to be both efficacious and cost-effective in patients with IGT. Hypertension and dyslipidemia should also be corrected to reach low-risk targets, together with use of aspirin to optimize risk reduction. Further studies will be required to determine whether additional benefit can be obtained via use of antioxidants, ACE inhibitors, or ARBs.

It should be emphasized that it is easier to prevent the development of diabetes than to treat diabetes and that it is easier to treat diabetes early in its natural history than to treat it late; both lifestyle change and medical therapy can decrease the progression from IGT to diabetes. Accordingly, it is important to use OGTTs to screen for glucose intolerance in individuals with the metabolic syndrome to detect both IGT and previously unrecognized diabetes.

SUMMARY

The metabolic syndrome is associated with an increased risk for CVD and glucose intolerance. Almost one fourth of the US population has the metabolic syndrome, due predominantly to increasing prevalence of obesity with associated insulin resistance. In obesity, the adipose organ (particularly visceral fat) produces elevated levels of free fatty acids, tumor necrosis factor- α , interleukin-6, and plasminogen activator inhibitor-1, decreases adiponectin levels, and increases oxidative stress, all of which lead to insulin resistance, dyslipidemia, and a prothrombotic/proinflammatory state.

Insulin resistance leads to glucose intolerance, both prediabetes (largely IGT) and type 2 diabetes, if insulin secretion from pancreatic beta cells is insufficient to overcome the insulin resistance. Oxidative stress is a major contributor to the development of glucose intolerance. Underlying mechanisms include increased

apoptosis due to decreases in the antiapoptotic protein Bcl-2, decreased insulin secretion due to decreases in the transcription factor PDX-1, and decreased glucose-stimulated insulin secretion due to increases in uncoupling protein-2.

Because the metabolic syndrome increases the risk of glucose intolerance with associated CVD, individuals at risk (age > 45 years and BMI > 25 kg/m², age ≤ 45 years if additional risk factors are present) should be screened with an oral glucose tolerance test for optimal sensitivity. Management of patients with the metabolic syndrome should include the control of CVD risk factors (blood pressure, lipids), use of aspirin, a high-fiber, low-saturated fat diet, and regular exercise. Treatment with antihyperglycemic medications and agents that block the renin-angiotensin system offers promise for reducing the development of CVD and glucose intolerance in patients with the metabolic syndrome, but use of such agents also carries risk of side effects and requires further investigation to establish net benefit. **HP**

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REFERENCES

- Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 2000;152:908–12.
- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1596–607.
- Wagenknecht LE, Langefeld CD, Scherzinger AL, et al. Insulin sensitivity, insulin secretion, and abdominal fat: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. *Diabetes* 2003;52:2490–6.
- Wang Y, Rimm EB, Stampfer MJ, et al. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005;81:555–63.
- Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev* 2002;23:201–29.
- Narayan KM, Boyle JP, Thompson TJ, et al. Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003;290:1884–90.
- Meigs JB, Muller DC, Nathan DM, et al. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 2003;52:1475–84.
- Stumvoll M, Fritsche A, Stefan N, Haring H. A 60 minute hyperglycemic clamp is sufficient to assess both phases of insulin secretion. *Horm Metab Res* 2000;32:230–2.
- Ceriello A, Quagliaro L, Catone B, et al. Role of hyperglycemia in nitrotyrosine postprandial generation. *Diabetes Care* 2002;25:1439–43.
- Marfella R, Quagliaro L, Nappo F, et al. Acute hyperglycemia induces an oxidative stress in healthy subjects [letter]. *J Clin Invest* 2001;108:635–6.
- Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004;114:1752–61.
- Wang X, Li H, De Leo D, et al. Gene and protein kinase expression profiling of reactive oxygen species-associated lipotoxicity in the pancreatic beta-cell line MIN6. *Diabetes* 2004;53:129–40.
- Miwa I, Ichimura N, Sugiura M, et al. Inhibition of glucose-induced insulin secretion by 4-hydroxy-2-nonenal and other lipid peroxidation products. *Endocrinology* 2000;141:2767–72.
- Kaneto H, Kajimoto Y, Miyagawa J, et al. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. *Diabetes* 1999;48:2398–406.
- Hildeman DA, Mitchell T, Aronow B, et al. Control of Bcl-2 expression by reactive oxygen species. *Proc Natl Acad Sci U S A* 2003;100:15035–40.
- Kawamori D, Kajimoto Y, Kaneto H, et al. Oxidative stress induces nucleo-cytoplasmic translocation of pancreatic transcription factor PDX-1 through activation of c-Jun NH(2)-terminal kinase. *Diabetes* 2003;52:2896–904.
- Korshunov SS, Skulachev VP, Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. *FEBS Lett* 1997;416:15–8.
- Krauss S, Zhang CY, Scorrano L, et al. Superoxide-mediated activation of uncoupling protein 2 causes pancreatic beta cell dysfunction. *J Clin Invest* 2003;112:1831–42.
- Bindokas VP, Kuznetsov A, Sreenan S, et al. Visualizing superoxide production in normal and diabetic rat islets of Langerhans. *J Biol Chem* 2003;278:9796–801.
- Brownlee M. A radical explanation for glucose-induced beta cell dysfunction. *J Clin Invest* 2003;112:1788–90.
- Krauss S, Zhang CY, Lowell BB. A significant portion of mitochondrial proton leak in intact thymocytes depends on expression of UCP2. *Proc Natl Acad Sci U S A* 2002;99:118–22.
- Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005;307:384–7.
- Chan CB, De Leo D, Joseph JW, et al. Increased uncoupling protein-2 levels in beta-cells are associated with impaired glucose-stimulated insulin secretion: mechanism of action. *Diabetes* 2001;50:1302–10.
- Zhang CY, Baffy G, Perret P, et al. Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, beta cell dysfunction, and type 2 diabetes. *Cell* 2001;105:745–55.
- Echtay KS, Roussel D, St-Pierre J, et al. Superoxide

- activates mitochondrial uncoupling proteins. *Nature* 2002;415:96–9.
26. Tiedge M, Lortz S, Drinkgern J, Lenzen S. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells. *Diabetes* 1997;46:1733–42.
 27. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA_{1c} levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care* 1997;20:785–91.
 28. Schmidt MI, Duncan BB, Vigo A, et al. Detection of undiagnosed diabetes and other hyperglycemia states: the Atherosclerosis Risk in Communities Study [published erratum appears in *Diabetes Care* 2003;26:2489]. *Diabetes Care* 2003;26:1338–43.
 29. 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;53:1549–55.
 30. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. DECODE Study Group, the European Diabetes Epidemiology Group. *Arch Intern Med* 2001;161:397–405.
 31. Teutsch S. The cost-effectiveness of preventing diabetes [editorial]. *Diabetes Care* 2003;26:2693–4.
 32. 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 Prevention Program Research Group. *Diabetes Care* 2003;26:36–47.
 33. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med* 2002;136:575–81.
 34. Lorenzo C, Okoloise M, Williams K, et al. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 2003;26:3153–9.
 35. Engelgau MM, Narayan KM, Vinicor F. Identifying the target population for primary prevention: the trade-offs [editorial]. *Diabetes Care* 2002;25:2098–9.
 36. Benjamin SM, Valdez R, Geiss LS, et al. Estimated number of adults with prediabetes in the US in 2000: opportunities for prevention. *Diabetes Care* 2003;26:645–9.
 37. Anand SS, Razak F, Vuksan V, et al. Diagnostic strategies to detect glucose intolerance in a multiethnic population. *Diabetes Care* 2003;26:290–6.
 38. McNeely MJ, Boyko EJ, Leonetti DL, et al. Comparison of a clinical model, the oral glucose tolerance test, and fasting glucose for prediction of type 2 diabetes risk in Japanese Americans. *Diabetes Care* 2003;26:758–63.
 39. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998;21:518–24.
 40. Lindahl B, Weinehall L, Asplund K, Hallmans G. Screening for impaired glucose tolerance. Results from a population-based study in 21,057 individuals. *Diabetes Care* 1999;22:1988–92.
 41. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity [published erratum appears in *N Engl J Med* 2002;346:1756]. *N Engl J Med* 2002;346:802–10.
 42. Brickman WJ, Holland JS, Silverman BL. Prevalence of postprandial hyperglycemia in adolescents: a population-based study [letter]. *Diabetes Care* 2002;25:1887–8.
 43. The prevention or delay of type 2 diabetes [published erratum appears in *Diabetes Care* 2002;25:947]. American Diabetes Association, National Institute of Diabetes, Digestive and Kidney Diseases. *Diabetes Care* 2002;25:742–9.
 44. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. *N Engl J Med* 2002;346:393–403.
 45. Saad MF, Knowler WC, Pettitt DJ, et al. Transient impaired glucose tolerance in Pima Indians: is it important? *BMJ* 1988;297:1438–41.
 46. 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;22:1490–3.
 47. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34.
 48. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 1999;22:920–4.
 49. Saydah SH, Miret M, Sung J, et al. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care* 2001;24:1397–402.
 50. Hu FB, Stampfer MJ, Haffner SM, et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 2002;25:1129–34.
 51. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–9.
 52. Qiao Q, Jousilahti P, Eriksson J, Tuomilehto J. Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care* 2003;26:2910–4.
 53. 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;354:617–21.
 54. Meigs JB, Nathan DM, D'Agostino RB Sr, Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care* 2002;25:1845–50.
 55. de Vegt F, Dekker JM, Ruhe HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia*

- 1999;42:926–31.
56. Goff DC Jr, D'Agostino RB Jr, Haffner SM, et al. Lipoprotein concentrations and carotid atherosclerosis by diabetes status: results from the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2000;23:1006–11.
 57. Meigs JB, Larson MG, D'Agostino RB, et al. Coronary artery calcification in type 2 diabetes and insulin resistance: the framingham offspring study. *Diabetes Care* 2002;25:1313–9.
 58. Clark CM Jr, Perry RC. Type 2 diabetes and macrovascular disease: epidemiology and etiology. *Am Heart J* 1999;138(5 Pt 1):S330–3.
 59. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease [published erratum appears in *Diabetes* 1996;45:1655]. U.K. Prospective Diabetes Study Group. *Diabetes* 1995;44:1249–58.
 60. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [published erratum appears in *JAMA* 2003;290:197]. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. *JAMA* 2003;289:2560–72.
 61. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
 62. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301–7.
 63. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. CARDS investigators. *Lancet* 2004;364:685–96.
 64. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. Veterans Affairs High-Density Lipoprotein Intervention Trial. VA-HIT Study Group. *JAMA* 2001;285:1585–91.
 65. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;81:7B–12B.
 66. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–92.
 67. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published erratum appears in *BMJ* 2002;324:141]. *BMJ* 2002;324:71–86.
 68. Rimm EB, Ascherio A, Giovannucci E, et al. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;275:447–51.
 69. Chandalia M, Garg A, Lutjohann D, et al. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med* 2000;342:1392–8.
 70. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004;292:1440–6.
 71. Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. American Heart Association Council on Nutrition, Physical Activity, and Metabolism, American College of Cardiology Foundation. *Circulation* 2004;110:2952–67.
 72. Weinstock RS, Dai H, Wadden TA. Diet and exercise in the treatment of obesity: effects of 3 interventions on insulin resistance. *Arch Intern Med* 1998;158:2477–83.
 73. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001;108:1167–74.
 74. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published erratum appears in *Lancet* 1999;354:602]. UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53.
 75. 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;51:2796–803.
 76. Choi D, Kim SK, Choi SH, et al. Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes. *Diabetes Care* 2004;27:2654–60.
 77. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. STOP-NIDDM Trial Research Group. *Lancet* 2002;359:2072–7.
 78. 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. STOP-NIDDM Trial Research Group. *JAMA* 2003;290:486–94.
 79. Esposito K, Giugliano D, Nappo F, Marfella R. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Campanian Postprandial Hyperglycemia Study Group. *Circulation* 2004;110:214–9.
 80. Manzella D, Grella R, Abbatecola AM, Paolisso G. Repaglinide administration improves brachial reactivity in type 2 diabetic patients. *Diabetes Care* 2005;28:366–71.
 81. Efanova IB, Zaitsev SV, Zhivotovsky B, et al. Glucose and tolbutamide induce apoptosis in pancreatic beta-cells. A process dependent on intracellular Ca²⁺ concentration.

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- J Biol Chem 1998;273:33501–7.
82. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy [published erratum appears in Lancet 2000;356:860]. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:253–9.
 83. Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. LIFE Study Group. Lancet 2002;359:1004–10.
 84. Vuorinen-Markkola H, Yki-Jarvinen H. Antihypertensive therapy with enalapril improves glucose storage and insulin sensitivity in hypertensive patients with non-insulin-dependent diabetes mellitus. Metabolism 1995;44:85–9.
 85. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. Diabetologia 1998;41:127–33.
 86. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. HOPE Study Investigators. JAMA 2001;286:1882–5.
 87. 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. LIFE Study Group. Lancet 2002;359:995–1003.
 88. Cheal KL, Abbasi F, Lamendola C, et al. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. Diabetes 2004;53:1195–200.
 89. McLaughlin T, Abbasi F, Cheal K, et al. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003;139:802–9.

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