

# The Metabolic Syndrome: An Emerging Health Epidemic in Women

Suzanne R. Steinbaum

---

The metabolic syndrome is a compilation of factors characterized by insulin resistance and the identification of 3 of the 5 criteria of abdominal obesity, elevated triglycerides, decreased high-density lipoprotein (HDL) level, elevated blood pressure, and elevated fasting plasma glucose. According to census data from 2000, these criteria have led to the diagnosis of approximately 47 million Americans with the metabolic syndrome, correlating with the 61% increase in the incidence of obesity between 1991 and 2000.

Insulin resistance occurs when target tissues cannot respond properly to normal concentrations of insulin. The results are hypercoagulability, endothelial dysfunction, inflammation, and eventually coronary artery disease.

Treatment involves lifestyle modification, including diet and exercise, to treat obesity and prevent the development of diabetes. Patients who meet the criteria for the metabolic syndrome may also be treated with insulin-sparing and insulin-sensitizing medications that help to improve endothelial function, vascular reactivity, and vascular inflammation. Ultimately, treatment goals are to prevent cardiovascular disease by both altering the risk factors that are components of the syndrome, and treating the lifestyle issues inherent to the disease process, such as caloric restriction and increased physical activity.

There are 2 million more women than men in the United States categorized as being obese, with the trend of obesity and diabetes increasing. In the last decade there has been a 74% increase in obesity, mostly in women. This epidemic needs to be understood and managed to prevent further morbidity and mortality owing to diabetes and cardiovascular disease.

© 2004 Elsevier Inc. All rights reserved.

---

**T**he metabolic syndrome is a compilation of factors characterized by insulin resistance combined with other risk factors associated with

coronary artery disease. These risk factors include those outlined by The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) guidelines, such as hypertension, obesity, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol. The metabolic syndrome is the identification of 3 of the following 5 risk factors: abdominal obesity, elevated triglycerides ( $>150$  mg/dL), decreased HDL levels ( $<40$  mg/dL in men and  $<50$  mg/dL in women), elevated blood pressure ( $>130/85$ ), and elevated fasting plasma glucose levels ( $>110$  mg/dL). According to census data from 2000, these criteria have led to the diagnosis of approximately 47 million Americans with the metabolic syndrome, correlating with the 61% increase in the incidence of obesity between 1991 and 2000.<sup>1,2</sup>

The Centers for Disease Control and Prevention (CDC) performed a study based on surveys conducted with 195,005 adults by telephone. These telephone surveys indicated that 21 million men and 23 million women living in the United States are obese. There has been an increase in the prevalence of obesity among U.S. adults from 19.8% in 2000 to 20.9% in 2001. In turn, the prevalence of diabetes has also increased. This trend of obesity has increased by at least 74% in the last decade; more women than men have this condition.<sup>3</sup> Obesity has been clearly linked to cardiovascular disease and is becoming an alarming public health issue. The distinction has been made

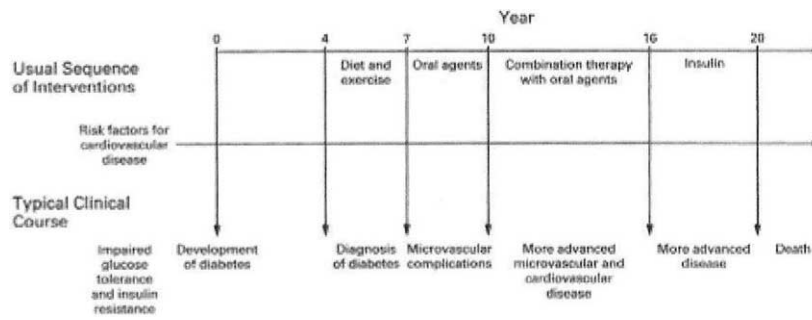
---

From the Albert Einstein College of Medicine, Division of Cardiology, Beth Israel Medical Center, New York, NY. Address reprint requests to Suzanne R. Steinbaum, MD, 35 E. 75th Street, New York, NY 10021.

0033-0620/\$ - see front matter

© 2004 Elsevier Inc. All rights reserved.

doi:10.1016/j.pcad.2003.08.005



**Fig 1. Typical clinical course of type 2 diabetes including the progression of glycemia and the development of complications and the usual sequence of interventions.**

between overweight, with a body mass index (BMI) of greater than 25, and obesity, with a BMI of greater than 30. Obesity kills approximately 300,000 Americans per year, with an estimated expense of \$117 billion each year.<sup>4</sup> The increased incidence of type 2 diabetes is not only explained by the increase in obesity, but also by the increase in sedentary lifestyle.<sup>5</sup> Lifestyle issues besides obesity and a sedentary lifestyle include a diet of which greater than 60% of the total caloric intake are carbohydrates, and has been demonstrated to be another reversible contributor to the metabolic syndrome. These lifestyle trends translate to a greater percentage of people exhibiting the complications associated with these multiple risk factors, such as coronary artery disease.

Data from the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994 define the metabolic syndrome. The metabolic syndrome, through that study, is defined as having 3 or more of the following criteria: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting glucose. Based on data from the 8814 participants, it is approximated that roughly 22% of U.S. adults have the metabolic syndrome. This increases with age, with the age-adjusted prevalence being 6.7% for those 20 to 29 years old, and 42% for those 60 to 69 years old. Among African Americans, women have a 57% higher prevalence than men.<sup>1</sup>

The Framingham study also provides data regarding the population at risk for cardiovascular disease, including diabetes and obesity. With the growing incidence of both these risk factors, the role of the metabolic syndrome in the development of cardiovascular disease becomes a public health concern.<sup>6</sup> The ATP III is the first report to detail the metabolic syndrome, including the def-

inition and its implications for coronary disease. These initial data, collected between 1988 and 1994, do not reflect this increasing incidence of obesity, and allow one to only speculate the current growth in the prevalence of this disease cluster.<sup>7,8</sup>

In 2001, the National Cholesterol Education Program (Adult Treatment Panel III) included into the guidelines type 2 diabetes as a cardiovascular risk equivalent. Patients with type 2 diabetes have a 2- to 5-fold greater risk of developing cardiovascular disease, and essentially 75% of these patients will die of some form of cardiovascular event. Manifestations of diabetes actually precede the diagnosis and the diabetes itself, and may in fact begin with subdiabetic levels of hyperglycemia early in the disease process. It has been shown that there is a delay of 4 to 7 years in diagnosing type 2 diabetes, which leads to approximately 20% of these patients already having a microvascular or neurologic manifestation by the time of diagnosis (Figure 1).<sup>9</sup> Macrovascular complications, such as coronary artery disease, account for 80% of the mortality in patients with type 2 diabetes.<sup>2</sup> Statistics from the American Diabetes Association from 1993 revealed that 4 out of 5 patients with coronary artery disease will die of cardiovascular causes and have a significantly worse prognosis than those patients without diabetes.<sup>10,11</sup> Insulin resistance, a prediabetic state, is associated with many of the factors that are also implicated in the development of atherosclerosis such as hypertension, sedentary lifestyle, obesity, left ventricular hypertrophy, dyslipidemia, and impaired fibrinolysis. All of these factors are both associated with the metabolic syndrome and with the development of atherosclerosis, and subsequent cardiovascular events.<sup>12,13</sup> Glucose intolerance and insulin resistance have become important in the

treatment goals of preventing development to diabetes and further cardiovascular incidents.

Treatment involves lifestyle modification, including diet and exercise to treat obesity and prevent the development to diabetes. Patients who meet the criteria for the metabolic syndrome may also be treated with insulin-sparing and insulin-sensitizing medications, which help to improve endothelial function, vascular reactivity, and vascular inflammation. Ultimately, treatment goals are to prevent cardiovascular disease by both altering the risk factors that are components of the syndrome, and treating the lifestyle issues inherent to the disease process, such as caloric restriction and increased physical activity.<sup>14</sup>

### Pathophysiology

Impaired glucose tolerance arises from 2 possible defects: either impaired insulin action on the target cells, or impaired  $\beta$ -cell function leading to decreased insulin secretion. Insulin resistance occurs when target tissues cannot respond properly to normal concentrations of insulin. Initially, as the cells fail to respond, pancreatic  $\beta$ -cells secrete increased amounts of insulin. As insulin resistance worsens, insulin secretion continues to increase. Insulin resistance, along with overproduction of glucose by the liver, impaired peripheral glucose utilization, and increased lipolysis leading to elevated free fatty acids are all hallmarks of the insulin resistance found in the metabolic syndrome.<sup>2</sup> In time, the  $\beta$ -cells are unable to maintain high rates of insulin secretion. Then, there is an increase in hepatic glucose output in both the fasting and postprandial states, and the development of decreased glucose absorption. This process eventually leads to type 2 diabetes. Insulin resistance may be demonstrated within families, and in fact, may be present in patients with normal glucose tolerance who are relatives of patients with type 2 diabetes.<sup>2</sup> Abnormal fatty acid metabolism, with an increase in abdominal adiposity, leads to an increase in glucose production. The visceral adipose tissue is insensitive to the actions of insulin, and therefore undergoes lipolysis, leading to the development of free fatty acids. In the liver, free fatty acids increase glucose production and form triglycerides. Impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia, and visceral adiposity are components of the met-

abolic syndrome, which ultimately become part of what is implicated in the development of coronary disease.

The proposed mechanism of hyperinsulinemia in association with cardiovascular disease has potentially been due to an increase in the hypercoagulable state, and the effect of insulin on thrombosis. With impaired glucose tolerance and hyperinsulinemia, there is impaired fibrinolysis, as seen with elevated levels of plasminogen activator inhibitor-1 antigen (PAI-1) and tissue plasminogen activator antigen (t-PA).<sup>15</sup> PAI-1 prevents clot dissolution by inhibiting actions of t-PA. In general, it has been shown that, in fact, women have a greater fibrinolytic potential than men, but with the development of insulin-resistant diabetes, this fibrinolytic potential is significantly reduced.<sup>16</sup> Many studies have demonstrated that in patients with elevated insulin levels and normal glucose tolerance, as in the metabolic syndrome, these factors were elevated. In addition, these factors have been implicated in increasing the risk for CAD, even in patients who are not diabetic.<sup>17,18</sup> In fact, elevated markers of impaired hemostasis have been shown to precede an acute infarction.<sup>19-21</sup> The conclusion is that the acute thrombosis that occurs with glucose intolerance and insulin resistance is due to ineffective fibrinolysis because of the increased levels of PAI-1 and t-PA.

The Framingham Offspring Study conducted between January 1991 and June 1995 stratified 1331 men and 1631 women by glucose tolerance, adjusted hemostatic factor levels, obesity, lipid levels, and traditional cardiovascular disease risk factors. This study also demonstrated the correlation between elevated levels of fasting insulin and impaired fibrinolysis and hypercoagulability.<sup>21</sup>

Other factors such as fibrinogen, factor VII, and von Willebrand factor, along with PAI-1 and t-PA antigens, show a strong positive association between levels of fasting insulin and viscosity in both men and women (Figure 2).<sup>14</sup> Elevations in fibrinolytic factors causing hypercoagulability are also associated with elevated markers of inflammation and endothelial dysfunction, and are commonly seen in atherosclerosis, as well as insulin resistance and glucose intolerance.<sup>22</sup> With impaired hemostasis, there is also potential for unstable plaque formation, and chronic inflamma-

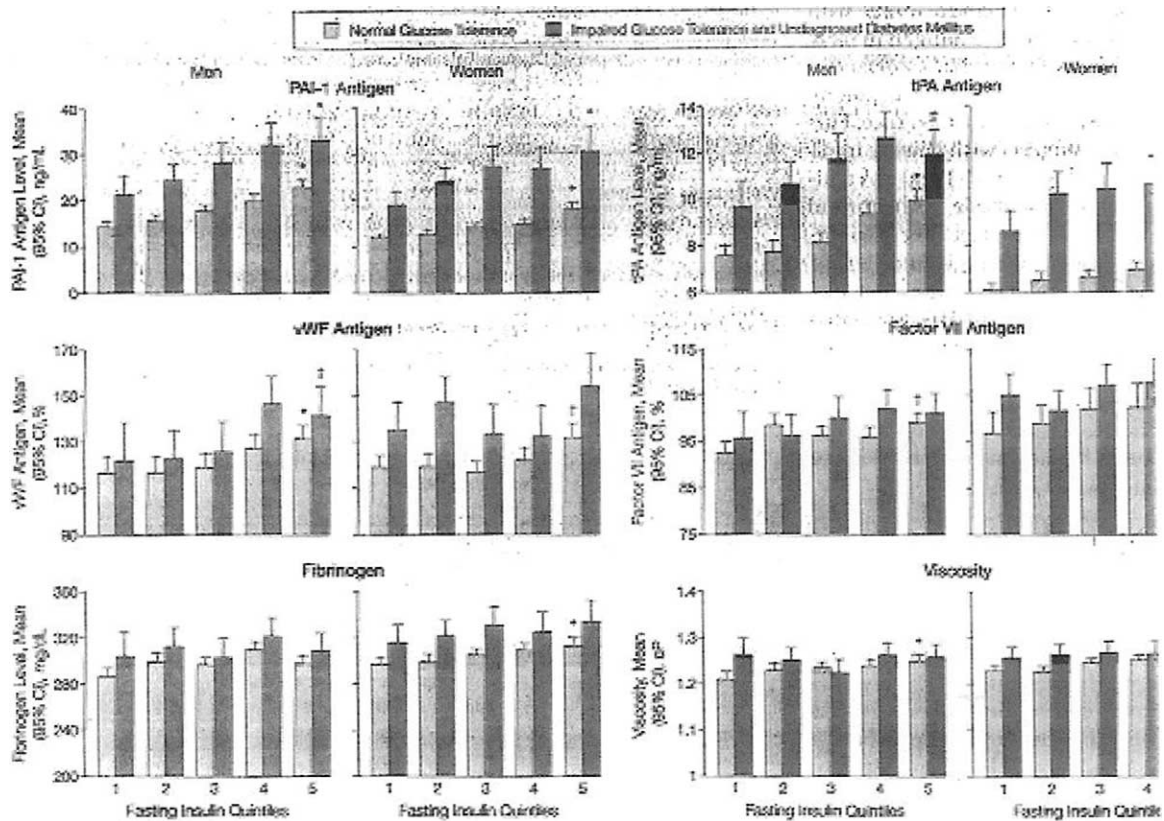


Fig 2. Association of hemostatic factors with fasting insulin levels by sex and glucose tolerance category.

tion also eventually leading to the process of atherosclerosis.<sup>14</sup>

The metabolic abnormalities associated with insulin resistance favor proliferation, inflammation, and plaque formation. Insulin effects 2 essential cell pathways. The first is the phosphatidylinositol 3-kinase pathway (PI3), which is associated with the metabolism of insulin causing glucose transport, glycogen synthesis, and lipid metabolism. The second is the mitogen-activated protein (MAP) kinase, which is associated with cell growth and proliferation. With insulin resistance, there is a reduced effect of the PI3 kinase-mediated pathways, while the MAP kinase activity stays the same. This leads to proliferation of cells and increased inflammation.

The PI3 pathway also plays a role in the anti-inflammatory effects of insulin and the release of nitric oxide synthase, leading to vasodilation.<sup>15,23</sup> With elevated insulin, the PI3 pathway is blocked, leading to adhesion of monocytes as well as cellu-

lar proliferation. There also occurs the associated inflammation, which is seen by and in increase of C-reactive protein (hs-CRP), which is an independent predictor of cardiovascular events and is often elevated in type 2 diabetes.<sup>24</sup> Prothrombotic inflammatory cells, such as PAI-1, are increased, leading to the formation of acellular thin-walled plaques, which often lead to rupture and myocardial infarction.<sup>25</sup> In the development of atherosclerosis initial plaque, the adhesion of monocytes and T cells begins an inflammatory cascade that eventually leads to the development of foam cells filled with oxidized low-density lipoprotein (LDL) cholesterol.<sup>26</sup> This is the beginning of plaque formation. PAI-1, causing both inflammation and impaired hemostasis, is not only triggered by elevated insulin, but also by an increase in visceral fat. PAI-1 is released by hepatocytes, endothelial cells, and adipocytes, particularly those in the abdominal distribution, in the setting of elevated glucose, insulin, and IV fat emulsion,

although not IV insulin alone.<sup>27,28</sup> The association of increased hip-to-waist ratio included in the metabolic syndrome is partially due to the predisposition of the visceral adipocytes to secrete PAI-1. With elevated insulin, PAI-1, and t-PA antigen in the setting of glucose intolerance and hypertriglyceridemia, it could be surmised that faulty fibrinolysis is due to the metabolic abnormalities associated with the metabolic syndrome.<sup>28</sup> These markers of inflammation, including PAI-1, plasma interleukin 6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are elevated in both obese subjects and patients with type 2 diabetes.<sup>29</sup>

The role of insulin resistance and obesity on endothelial function has been established through studies looking at endothelium-dependent vasodilation, endothelium-independent vasodilation, and insulin-mediated augmentation of endothelium-dependent vasodilation. In the normal setting, insulin mediates vasodilation by increasing the release of endothelium-derived nitric oxide.<sup>30,31</sup> In patients with type 2 diabetes, as well as those with insulin resistance, there was a blunted response to methacholine intrafemoral arterial infusions on the leg blood flow, demonstrating a decreased response to endothelium-dependent vasodilation.<sup>15</sup> In this study, methacholine was used to assess endothelium-dependent vasodilation, nitroprusside was used to assess endothelium-independent vasodilation, and verapamil was used as a nitric oxide-independent vasodilator. In patients with diabetes, forearm blood flow increased only  $6.4 \pm 0.9$  mL/min per 100 mL compared to  $10.1 \pm 1$  mL/min per 100 mL in nondiabetic subjects ( $P < .05$ ). Nitroprusside also revealed a decreased vasodilator response in the diabetic subjects, increasing blood flow by  $4.6 \pm 0.6$  mL/min in diabetics compared with  $8.4 \pm 1$  mL/min per 100 mL in nondiabetics. There were no differences between the two in the verapamil group. The study demonstrated that forearm blood flow in patients with insulin resistance and obesity is decreased in both situations where there is endogenous nitric oxide and direct-acting exogenous nitric oxide given.<sup>32</sup> In patients with euglycemia and hyperinsulinemia, there was also failure of the normal augmentation in endothelial vasodilation, owing to the effect of insulin on endothelial function.<sup>22</sup> After a period of forearm ischemia, it has been shown that the postischemic flow-mediated dilation is significantly decreased

in the brachial artery in patients with both type 1 and type 2 diabetes.<sup>32,33</sup>

Endothelial dysfunction is also part of the metabolic syndrome. Abnormalities in endothelial function are seen in dyslipidemia, causing a decrease in vasodilation and cellular proliferation, which prevent plaque formation. In fat cells, insulin causes lipolysis and a subsequent release of free fatty acids. This process leads to a further elevation of lipids, and causes worsening endothelial dysfunction. This process leads not only to endothelial dysfunction, but has a multifactorial effect in leading to the development of coronary artery disease.<sup>2</sup>

Ultimately, the damage that is done in the insulin-resistant patient is due to the hyperinsulinemic state. Excess insulin has multiple deleterious effects on several body sites. It causes further insulin resistance by increasing glucose output from the liver, and reducing glucose utilization by the skeletal muscle.<sup>2</sup> In the vascular tissues, insulin may stimulate endothelial and cell growth. In the kidney, insulin has been shown to cause renal sodium reabsorption and activate the sympathetic nervous system, both leading to hypertension.<sup>34</sup> In the ovaries, insulin resistance has been shown to increase androgen release, as is seen in polycystic ovary syndrome, where patients suffer with hyperandrogenism, infertility, and insulin resistance.<sup>35,36</sup>

### Obesity and Dyslipidemia

Insulin resistance is closely associated with obesity. Central obesity measured by waist-to-hip ratio and subscapular-to-triceps ratio is associated with hyperinsulinemia and the development of type 2 diabetes. The continuum of being overweight begins at a BMI of greater than 25, and obesity being reached at a BMI greater than 30. In obesity, the waist circumference is usually greater than 40 inches or 102 cm for men and 35 inches or 88 cm for women.<sup>1</sup> Obesity is also a risk factor for coronary artery disease, and is clearly associated with insulin resistance. In one study, the relationship of abdominal fat to insulin sensitivity was measured by direct and indirect measurements of fat by dual-energy x-ray absorptiometry (DEXA) and anthropometry, and insulin sensitivity was measured by an oral glucose tolerance test. Percentage of central abdominal fat was found to be a

significantly stronger correlate of insulin sensitivity than any other region of fat. Increased abdominal fat was associated with hyperinsulinemia, hyperlipidemia, and insulin resistance. In another study, central obesity in obese women has been associated with glucose intolerance, decline in insulin sensitivity, altered lipid metabolism, an increased risk of diabetes, and an increase in cardiovascular mortality. Central abdominal fat, as measured by DEXA, is a significant correlate of insulin resistance in both normal and overweight women, independent of other risk factors for diabetes.<sup>37</sup>

It has been shown that visceral fat is more resistant to the actions of insulin than other types of fat.<sup>38</sup> Visceral fat is less sensitive to insulin, causing the body to breakdown fat leading to the release of free fatty acids. Insulin-resistant fat cells are unable to store triglycerides, which also results in the development of free fatty acids.<sup>30</sup>

Fat cells themselves release free fatty acids that can block the insulin signaling pathways by their direct release into the portal circulation. These free fatty acids not only decrease the action of insulin, they also increase gluconeogenesis in the liver.<sup>38</sup> There are several hypotheses explaining the mechanism by which free fatty acids block insulin signaling. Recently, it has been shown that free fatty acids stimulate protein kinase C isoforms, which interrupt the cellular mechanism of insulin signaling and inhibit glucose transport activity. When there is an impairment in insulin-stimulated glucose transport to the skeletal muscle, there is the subsequent development of insulin resistance.<sup>39</sup>

In the liver there is synthesis of triglycerides and very low-density lipoprotein (VLDL) cholesterol with apolipoprotein B. With insulin resistance, there is an exchange of cholesterol esters from HDL and LDL to VLDL from triglyceride molecules, which causes the HDL particles to become completely ineffective in removing cholesterol from peripheral cells. This pattern favors development of smaller LDL particles, which is shown to be associated with insulin resistance and an increase in triglycerides.<sup>40,41</sup> Reaven et al<sup>35</sup> studied 100 subjects, revealing that patients with small, dense LDL particle size had an associated increase in insulin and glucose levels after a 75-g oral glucose load. This pattern B type of small, dense LDL particles is also associated with lower

HDL levels. The LDL that is seen is enriched with triglycerides, and is converted to small, dense LDL particles. These types of particles are greatly atherogenic because they are potentially easily oxidized.<sup>42</sup> Oxidized LDL has been implicated in the development of endothelial dysfunction, and the progression of vascular inflammation leading to development of the atherosclerotic plaque.

Fat cells, known as adipocytes, synthesize and secrete several messengers that help to mediate insulin action. TNF- $\alpha$  is associated with obesity and the development of insulin resistance. In obese subjects, elevated TNF- $\alpha$  also leads to increased free fatty acid secretion, and decreased effects of insulin signaling, leading to downregulation of glucose transporters.<sup>2</sup> Adiponectin has been shown to increase insulin activity, and is decreased in patients with type 2 diabetes. It is indirectly related to the amount of obesity, and in fact, levels of adiponectin have been associated with increased weight loss. It has been hypothesized to interact with receptors at the muscle or liver where it interrupts the action of other substances, such as TNF- $\alpha$ , eventually rendering insulin ineffective. It has also been shown to enhance oxidation of intracellular fatty acids in the muscle and liver, thereby decreasing muscle and liver triglyceride content.

Other proteins are also associated with obesity. Resistin is another recently discovered protein specific to adipocytes found in mouse cells. This substance is also associated with insulin resistance, and has been shown to be reduced with the thiazolidinediones. Although specifically seen in rodents, there are related types of proteins seen in fat cells in humans. Leptin has also been implicated in insulin resistance. It contributes to appetite regulation and effects insulin sensitivity.<sup>2</sup>

### **Coronary Artery Disease and the Metabolic Syndrome**

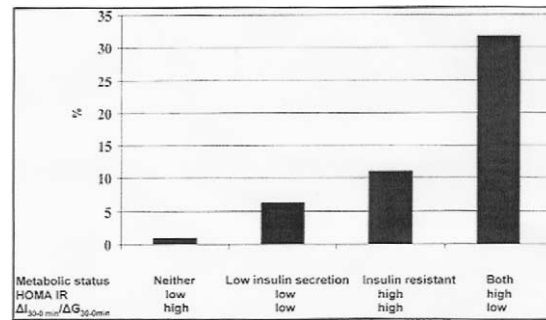
Many factors determine the risk of developing coronary artery disease, many of which have also been implicated in insulin resistance and the metabolic syndrome. Increases in inflammatory mediators, stimulation of the sympathetic nervous system, hypertension, and dyslipidemia are several mechanisms contributing to the development of both disease states. In patients with insulin resistance, the dyslipidemia seen is manifested by an

elevation in triglycerides and a decrease in HDL cholesterol. Additionally, the LDL particles are small and dense, more difficult to be effectively cleared by the liver, and easily oxidized, increasing their potential to lead to coronary artery disease.<sup>29</sup>

Several studies have shown the correlation between insulin resistance and coronary artery disease. In 1971, the Helsinki Policemen Study began as one of the first prospective studies clearly showing a correlation between hyperinsulinemia and the risk of heart disease. This initial study included 970 men, ages 34 to 64, who had no history of coronary disease or diabetes. An oral glucose tolerance test was performed, using the area under the plasma insulin response curve as a reflection of plasma insulin levels. Those men in the highest area under the curve quintile—with the highest insulin levels—were more likely to suffer from a cardiovascular event. In the 22-year follow-up, the study continued to show that elevated insulin levels, as seen in insulin resistance, are positively correlated with an increased risk of a major coronary heart disease event. Hyperinsulinemia was independent of other cardiovascular risk factors, although through this study, other risk factors including blood glucose, cholesterol, triglycerides, blood pressure, obesity, smoking, and physical activity were often prevalent along with hyperinsulinemia, and contribute to the multifactorial causes of the increase in cardiovascular disease.<sup>43</sup>

The Paris Prospective Study, was an 11-year study involving 7028 men, also showed a positive correlation between insulin resistance and incidence of CAD. In analyzing causes of death, there was a clear correlation between the patients with known diabetes and CAD mortality rates compared with patients with newly diagnosed diabetes, impaired glucose tolerance, or normal glucose tolerance ( $P < .02$ ). The study also demonstrated a correlation between increased fasting insulin and the prediction of CAD mortality.<sup>42</sup>

This same correlation between the insulin level and risk of coronary artery disease was seen in several prospective epidemiologic studies and case-control studies. Because of these studies, insulin resistance subsequently became a risk factor independent of other cardiovascular risk factors.<sup>44</sup> In other studies, there has been a clear association between insulin resistance and evi-



**Fig 3. Seven-year incidence of type 2 diabetes by baseline status for insulin resistance (HOMA IR surrogate for insulin resistance) and insulin secretion ( $\Delta I_{30-0}/\Delta G_{30-0}$ ).**

dence of atherosclerosis as seen by Doppler ultrasound of the coronary arteries.<sup>45,46</sup> An association between insulin resistance and coronary artery disease has also been seen in studies utilizing coronary angiography.<sup>47</sup>

In analyzing the development of coronary heart disease, the San Antonio Heart Study assessed the 2 types of abnormalities that occur in the prediabetic state: those with decreased insulin secretion due to  $\beta$ -cell dysfunction and those that have insulin resistance. In a 7-year follow-up study, an analysis was performed to determine which metabolic abnormality, or both, would lead to the atherogenesis often seen with coronary artery disease.<sup>2</sup> Of the 1734 subjects studied, 195 converted to type 2 diabetes. These patients at baseline had a higher BMI, greater waist circumference, higher triglycerides, lower HDL levels, and higher blood pressures. Analysis was then performed using a homeostasis model assessment of insulin resistance ( $HOMA\ IR = \text{fasting insulin} \times \text{fasting glucose}$ ) and the ratio of early insulin increment to early glucose increment during a glucose tolerance test, over a 30-minute period ( $\Delta I_{30-0}/\Delta G_{30-0}$ ). Those patients with insulin resistance had a high HOMA IR and a high  $\Delta I_{30-0}/\Delta G_{30-0}$ , and those with a decreased insulin secretion demonstrated low values for both of these variables<sup>48</sup> (Fig 3). Those subjects that did convert to type 2 diabetes had a greater compilation of risk factors for coronary artery disease, including higher triglycerides, elevated BMI, increased systolic and diastolic blood pressures, and lower HDL levels. Insulin resistance and the prediabetic state have been clearly

shown to increase the risk of atherosclerosis and the risk for coronary artery disease.<sup>49</sup>

In a 6-year analysis of the Atherosclerosis Risk in Communities Study, over 15,000 men and women were examined to evaluate the etiology of the atherosclerosis. The study examined arterial stiffness; insulin, glucose, and lipid levels; and cardiovascular risk factors. Arterial stiffness was correlated with the development of hypertension, a risk factor for coronary artery disease. The final analysis demonstrated that increased fasting insulin and glucose levels, and insulin resistance correlated with an increase in arterial stiffness in both men and women.<sup>50</sup> This correlation demonstrated the association of insulin resistance as a risk factor of coronary artery disease.

The different methods of clustering the variables by factor analysis revealed 3 types of factors. The first factor, the central metabolic syndrome, includes hyperinsulinemia, hyperglycemia, high triglycerides, low HDL, high BMI, and high waist-to-hip ratio. The second factor was defined as hyperinsulinemia and hyperglycemia, and the third was hypertension.<sup>51</sup>

In recent studies, factor analysis has been performed, which includes intercorrelating variables in statistical analyses, and has been used to study the insulin resistance syndrome.<sup>13,52</sup> Between the sexes, there are conflicting data regarding the association between insulin and cardiovascular risk. In several studies, the risk was observed in men, but not women, and another showed no association with men, only in women.<sup>53</sup>

In a study of 1069 subjects from eastern Finland, there were 151 CHD events during the 7-year follow-up period. In this particular study, previous stroke, and low HDL and high triglyceride levels portended greater risk than the insulin resistance factors, as in relation to the factor analysis of the three types of factors depicted above.<sup>13</sup> Despite this separation of factors, there is clearly an overlap between these distinctions, and the individual criteria that make up the metabolic syndrome and the risk of coronary artery disease.

Clearly, more studies need to be performed and more women need to be included in the analyses. The largest trials of coronary artery disease have, thus far, been directed at men. In extrapolating these data, we have surmised its effects on women. Further large randomized trials need to be performed to adequately evaluate and assess the role

of the risk factors in the development of the metabolic syndrome, as well as coronary artery disease.

## Treatment

### Medication

Insulin resistance is seen in a patient who has an ability to secrete insulin, which is relatively ineffective, although in the initial stages of its dysfunction does not lead to hyperglycemia. Overt diabetes develops at the level of the  $\beta$ -cell in the pancreas, where there are functional defects in insulin secretion. At the level of the diagnosis of diabetes, there is at least 50% loss of  $\beta$ -cell function. During the earlier stages of disease, when there is some  $\beta$ -cell function remaining, the treatment strategies are more effective because they are directed at  $\beta$ -cell function.<sup>2</sup> After hyperglycemic stimulation, there is a sudden release of insulin, followed by a steady secretion until the hyperglycemia is resolved. The first biochemical defect in patients with type 2 diabetes is the loss of the first-phase initial insulin secretion, which occurs at a fasting glucose level as low as 115 mg/dL. The normal insulin response is delayed, with the insulin secretion occurring later and at lower levels.

In treating the metabolic syndrome, one of the key goals is lowering endogenous insulin concentrations. The mainstay of therapy includes diet and weight loss, exercise, and medical treatment with medications that increase the body's sensitivity to insulin.

In the initial stages of insulin resistance, where patients secrete adequate amounts of insulin, a thiazolidinedione and biguanide could be used. The biguanide functions to decrease hepatic glucose output. As the disease progresses and there is a decrease in insulin secretion, a sulfonylurea should then be added, which stimulates insulin secretion.<sup>2</sup> Both the biguanide and the sulfonylurea have the potential of lowering the glycosylated hemoglobin by 1.5 percentage points.<sup>8</sup>

In a prospective, randomized study performed in 1976 by the University Group Diabetes Program, there was an increase in cardiovascular events in patients who were treated with tolbutamide, a sulfonylurea, rather than placebo. The concern about sulfonylureas is their mechanism of action to lower glucose. They function to lower

glucose by closing the adenosine triphosphate-sensitive potassium channels causing an increased secretion of insulin by  $\beta$ -cells in the pancreas, ultimately leading to a reduction in glucose levels. One of the negative manifestations may be the development of arrhythmias through the closing of the potassium channels, which may prolong myocardial refractoriness. Sulfonylureas have been also shown to be vasoconstrictive, leading to greater endothelial dysfunction. In fact, in patients postangioplasty, it has been shown that sulfonylureas have been associated with an increased risk of death in both elective angioplasty and angioplasty for acute myocardial infarction.<sup>54</sup> Sulfonylureas also increase weight gain, and increase insulin levels, leading to atherogenesis and cardiovascular events, despite the reduction of the glucose.<sup>11</sup>

Thiazolidinediones have been shown to improve insulin resistance and decrease plasma glucose and insulin concentrations in patients with type 2 diabetes.<sup>55</sup> The drug inhibits the peroxisome proliferator-activated receptor- $\gamma$ , which is implicated in the development of adipose tissue, and also affects skeletal muscle and liver. This medication functions by increasing peripheral glucose uptake.

These medications have been effective in preventing diabetes by increasing insulin sensitivity and enhancing  $\beta$ -cell secretion. Thiazolidinediones have been shown to reduce intrahepatic and visceral fat, and increase fat oxidation. In one study, pioglitazone was shown to reduce visceral fat and increase subcutaneous fat after 16 weeks of treatment, demonstrating the beneficial role of thiazolidinediones on changing the distribution from central adiposity to peripheral fat.<sup>56</sup> It has been shown to decrease plasma free fatty acid levels by preventing lipolysis at the level of the adipocyte. In causing this, insulin-mediated glucose uptake by the skeletal muscle, which is inhibited by free fatty acids in the plasma, is better able to perform its function.<sup>29</sup> The increased sensitivity of the adipose cells to insulin may, in fact, enable the cells to again perform their function of storing triglycerides. All of these mechanisms decrease insulin resistance, and the factors implicated in the metabolic syndrome.<sup>57</sup> Not only have they been shown to decrease the release of free fatty acids from the adipocyte, the thiazolidinediones

have been shown to prevent the release of inflammatory adipocytokines.

These medications are able to suppress inflammation by decreasing inflammatory cells and molecules that have been shown to be part of the development of coronary artery disease. There is inhibition of the free oxygen radicals, which are generated by polymorphonuclear leukocytes and mononuclear cells. The thiazolidinediones also decrease the major regulator of transcription of the cytokines, TNF- $\alpha$ , and interleukin-6.<sup>21,29</sup> By inhibiting transcription of these pro-inflammatory markers, there is reduction in the plasma concentration of C-reactive protein (CRP), intracellular adhesion molecule-1, monocyte chemoattractant protein-1, and TNF- $\alpha$ .<sup>58</sup> After beginning this medical therapy, there is evidence in changes of the inflammatory indices and insulin resistance after 1 week. These benefits were not seen in the patients with overt type 2 diabetes.<sup>29</sup>

On the other hand, rosiglitazone has been beneficial in patients with or without diabetes. It has been shown to increase insulin-stimulated glucose metabolism, and is effective also as an anti-inflammatory agent.<sup>29</sup> It has been shown to improve peripheral adipocyte insulin responsiveness, and to enhance  $\beta$ -cell functioning, leading to increased insulin sensitivity.<sup>59</sup> Within the mononuclear cells, it prevents transcription of inflammatory hormones. There is shown to be a decrease in tumor necrosis factor-1 and PAI-1, as well as a 30% reduction in CRP.<sup>60,61</sup> In a 26-week study of patients with type 2 diabetes, there was statistically significant decreases in percent reduction in mean CRP and MMP-9, matrix metalloproteinases, which have been implicated in the pathogenesis of atherosclerotic plaque rupture ( $P < .01$ ).<sup>62</sup> Theoretically, the reduction of CRP may decrease the development to type 2 diabetes, and subsequently decrease the progression to coronary artery disease. The correlation between insulin resistance, by high HOMA IR, and the inflammatory markers IL-6 and MMP-9, have shown this relationship.<sup>63</sup> Changes in MMP-9 were correlated with changes in CRP, IL-6, WBC, HbA1c, fasting plasma glucose, insulin resistance, and BMI.<sup>63</sup>

In the location of the early developing plaque, rosiglitazone may also have an effect on decreasing the levels of the metalloproteinases, abundant in the early and vulnerable plaque. Rosiglitazone

**Table 1. Blood Pressure, Insulin Sensitivity, and Cardiovascular Risk Factors Before and After Rosiglitazone Treatment**

	Week 0	Week 16	P Value
24-h mean ABPM			
Systolic blood pressure (mm Hg)	138 ± 2	134 ± 2	<0.01
Diastolic blood pressure (mm Hg)	85 ± 2	80 ± 2	<0.0001
Daytime ABPM (0600-2300)			
Systolic blood pressure (mm Hg)	141 ± 2	137 ± 2	<0.05
Diastolic blood pressure (mm Hg)	87 ± 2	83 ± 2	<0.001
Nighttime ABPM (2300-0600)			
Systolic blood pressure	131 ± 3	126 ± 3	<0.02
Diastolic blood pressure (mm Hg)	80 ± 2	73 ± 2	<0.0001
Fasting glucose (mg/dL)	83 ± 2	82 ± 2	NS
Fasting insulin (units/mL)	16.1 ± 1.4	12.5 ± 0.9	<0.01
Basal hepatic glucose output (mg·kg <sup>-1</sup> ·min <sup>-1</sup> )	1.8 ± 0.1	1.8 ± 0.1	NS
Insulin-stimulated glucose disposal (mg·kg <sup>-1</sup> ·min <sup>-1</sup> )	5.0 ± 0.4	5.9 ± 0.5	<0.001
Residual hepatic glucose output (mg·kg <sup>-1</sup> ·min <sup>-1</sup> )	0.7 ± 0.1	0.7 ± 0.1	NS
Total cholesterol (mg/dL)	207 ± 7	187 ± 8	<0.001
LDL cholesterol (mg/dL)	129 ± 6	122 ± 8	0.18
HDL cholesterol (mg/dL)	51 ± 3	46 ± 3	<0.05
Triglycerides (mg/dL)	134 ± 16	89 ± 8	<0.04
CRP (mg/dL)	0.27 ± 0.05	0.15 ± 0.04	<0.002
PAI-1 (ng/mL)	16.7 ± 1.5	11.1 ± 1.5	<0.009

Data are means ± SE.

has also been shown to suppress an essential component in the conversion of molecular oxygen into free radicals. In a comparison with glyburide, rosiglitazone was more beneficial in reducing hemoglobin A1C and increasing HDL levels.<sup>42</sup> Its beneficial effects on LDL was seen in a study by Brunzell et al,<sup>64</sup> which demonstrated, after an 8-week period, a slight increase in LDL particles, with an alteration in the composition of LDL from small and dense to large and buoyant, which have less potential to lead to atherosclerosis.<sup>64</sup>

One group of investigators observed the connection between hyperinsulinemia, insulin resistance, and hypertension. Raji et al<sup>65</sup> determined a subset of salt-sensitive essential hypertensive patients who are more insulin resistant than the subjects with low-renin hypertension. This group is called *the nonmodulators* owing to their inability to regulate their blood pressure, renal plasma flow, and responsiveness to angiotensin II when going from a high- to low-salt diet. They hypothesized that the nonmodulator subgroup of hypertensives would receive greater improvement in insulin sensitivity and reduction in blood pressure while taking rosiglitazone compared to those patients with high blood pressure and low renin, and there would be a reduction in cardiovascular risk factors. The group concluded that, in fact, rosiglita-

zone improves insulin sensitivity and lowers blood pressure in patients with essential hypertension. There were also improvements in the cardiovascular risk factors with the decline of triglycerides, total cholesterol, PAI-1, and CRP. There was no difference between the 2 groups, which was felt to be due to both the fact that the study was conducted with both groups on a low-salt diet and that both groups were moderately overweight. Although in both groups there was a significant relationship between the improvement in insulin sensitivity and reduction in blood pressure, surmising that the degree to which blood pressure is elevated owing to insulin resistance, an insulin sensitizer will cause a level of reduction in blood pressure (Table 1).<sup>65</sup>

Both troglitazone and rosiglitazone improve endothelium-dependent flow-mediated vasodilation of the brachial artery seen after ischemic conditions. This benefit is seen relatively quickly after beginning the medications, demonstrating its role in the improvement of endothelial dysfunction. Troglitazone is also effective in improving nitric oxide-induced vasodilation, and therefore has a role in the treatment of vasospastic angina.<sup>29</sup> Rosiglitazone was shown to increase brachial artery vasoactivity from 4% to 10% ( $P < .05$ ) in a small

study of 11 nondiabetic obese patients who received the medication for 6 weeks.<sup>61</sup>

Along with its benefits in endothelial function, this class of medications has also been shown to decrease levels of PAI-1. In a comparison between the effects of sulfonylureas alone or with rosiglitazone on PAI-1 levels in 114 patients with type 2 diabetes, after 26 weeks of treatment, there was a 21.8% decrease in PAI-1 antigen level and a 33.8% decrease in PAI-1 activity, compared with an increase in both on the sulfonylurea alone. Other studies also compared the effects of troglitazone with placebo for 26 weeks. In those receiving troglitazone therapy, there also was found to be lower levels of PAI-1 compared to those taking the placebo.<sup>29,42</sup>

Along with the thiazolidinediones, metformin has also been shown to improve insulin resistance. It reduces blood sugar by suppressing glucose production by the liver, and therefore decreases insulin levels. It also has been shown to cause weight loss, secondary to the anorexic effect of the medication.<sup>11</sup> Metformin has also demonstrated improvement in endothelial function in patients with type 2 diabetes. The study did not include patients with the metabolic syndrome to minimize the effects of the cardiovascular risk factors on endothelial dysfunction. After a 12-week period, there was improvement in acetylcholine-stimulated forearm blood flow in patients who received 500 mg of metformin 2 times per day compared with placebo. Forearm blood flow responses were determined using brachial arterial infusions of the endothelium-dependent vasodilator acetylcholine, the endothelium-independent vasodilator sodium nitroprusside, and the nitrate-independent vasodilator verapamil. Along with vasodilation, homeostasis model approximation was assessed to determine the measurement of insulin resistance. There was a 32% drop in HOMA IR and a significant improvement in endothelium-dependent vasodilator response.<sup>66</sup> These findings correlate with the understanding that insulin resistance is directly associated with endothelial dysfunction, and that improvement of the endothelium will help in treating type 2 diabetes, insulin resistance, and therefore the metabolic syndrome. The benefits of metformin and its ability to improve endothelial function, decrease insulin, and promote weight loss were demonstrated in the United Kingdom Prospective Diabetic

Study (UKPDS). The study consisted of 1293 obese patients with type 2 diabetes who were randomized to receiving sulfonylurea, insulin, or metformin. There was a 36% reduction in all-cause mortality compared to the other cohorts.<sup>67</sup>

### Lifestyle Management and Risk Factor Modification

Lifestyle management and behavior modification have a definite role in the treatment of the metabolic syndrome. The initial goal of treatment is weight loss, which could be achieved by a low-calorie diet along with exercise. A weight loss of merely 5 to 10 pounds has been shown to decrease elevated glucose levels to within the normal range.<sup>8</sup>

A 2001 study by the National Institutes of Health entitled the Diabetes Prevention Program analyzed the effect of intensive lifestyle changes with metformin in 3234 patients who had impaired glucose tolerance. In a study of 3234 patients without diabetes, but with elevated fasting and postload glucose, lifestyle management proved to be more effective than treatment with metformin. The participants were randomly assigned to placebo, metformin (850 mg 2 times per day), or a lifestyle modification program with the objectives of having a 7% weight loss and 150 minutes of physical activity per week. The lifestyle intervention included a 16-lesson curriculum on diet and exercise individually taught during the first 24 weeks of the program, and then occurred on a monthly basis. The mean age was 51, with a BMI of 34.0; 68% were women. After a 2.8-year follow-up, the lifestyle management program decreased the incidence of developing diabetes by 58%, and metformin by 31% compared to placebo.<sup>68</sup>

Over 25,000 men were followed for 10 years to determine the effect of low cardiovascular fitness on the incidence of cardiovascular disease and all-cause mortality in normal weight, overweight, or obese men. Independent of other risk factors such as diabetes, high cholesterol, hypertension, smoking, or BMI, low cardiovascular fitness was associated with a higher relative risk. In a small cohort from this study, more than 1000 men with type 2 diabetes were then evaluated over a 1-year period to assess the correlation between physical

activity and mortality. Low cardiovascular fitness was associated with a 2-fold increase in the risk of death compared to other men with type 2 diabetes who were physically fit.<sup>42,69</sup>

These same findings were seen in women by looking at the maximal oxygen consumption ( $VO_{2max}$ ). Women with type 2 diabetes had a decreased  $VO_{2max}$ , which was compared with overweight and lean women without diabetes.<sup>70</sup> Through this study, a clear correlation between exercise and the prevention of type 2 diabetes was established.<sup>68</sup>

Besides increasing cardiovascular health, regular exercise promotes weight loss, and with the loss of abdominal obesity, there is an improvement in insulin sensitivity, therefore reducing the development of type 2 diabetes. Not only is aerobic exercise recommended, but the addition of strength training to the endurance activity has effects in reducing body fat and improving insulin sensitivity.<sup>71</sup>

In addition to exercise, diet can also be beneficial in patients to prevent the development of type 2 diabetes and delay the progression to coronary artery disease. The ideal diet for these patients is one low in simple carbohydrates, low in saturated fat, and high in fiber. A diet low in fats and high in carbohydrates can lead to an elevation in glucose, insulin, and triglyceride levels.<sup>72</sup> In altering the diet to include monounsaturated or polyunsaturated fats instead of saturated fats or carbohydrates, the lipid profile can be improved and this can cause a resultant decrease in cardiovascular events. It has been shown that there is an inverse relationship between the consumption of polyunsaturated fat and the incidence of coronary artery disease, promoting the intake of vegetable oils rich in linoleic acid. Diets high in polyunsaturated fat have been shown to be more effective than low-fat, high-carbohydrate diets in reducing cholesterol and decreasing the incidence of coronary artery disease. On the other hand, diets high in trans unsaturated fat may increase the LDL cholesterol levels, lower HDL cholesterol, increase lipoprotein a [Lp(a)] metabolism, increase triglyceride levels, and interfere with fatty acid metabolism.<sup>73</sup>

Even in studies looking at medications to induce weight loss, such as sibutramine, a combined norepinephrine-serotonin reuptake inhibitor that causes increased satiation, those subjects treated

with medication along with exercise, achieved the greatest benefit. Wadden et al<sup>74</sup> demonstrated in a study of 53 women, that the drug plus a lifestyle intervention group (providing behavioral strategies for achieving weight loss) had a greater weight loss than those treated with diet alone. This benefit was noted even at the end of 1 year of study. In the group of drug along with lifestyle intervention and a strict caloric reduction to 1000 kcal/d, there was a greater than 10% decrease from the initial body weight at the end of the 12th month compared to the drug along group.<sup>74</sup>

In treating the metabolic syndrome, there are three lifestyle issues—physical exercise, diet, and weight control—that need to be assessed.<sup>11</sup> In addressing the dyslipidemia that occurs in the metabolic syndrome, diet and exercise are important components of treatment. The dyslipidemia characterized in the metabolic syndrome includes an increase in triglycerides, a decrease in HDL, and a moderate increase in LDL. This triad is difficult to treat and portends a worse diagnosis than an isolated increase in LDL. After attempts are made to decrease weight and change the cholesterol profile without success, then medical therapy is recommended. Along with statins, troglitazone and metformin have also been shown to alter the lipid profile. Although LDL is not the worst offender in patients with insulin resistance, statins have been demonstrated to reduce the rate of cardiovascular events if LDL is reduced to <100 mg/dL. In the Scandinavian Simvastatin Survival Study (4S), in patients with diabetes there was a decrease of cardiovascular events by 55% and all-cause mortality by 43%.<sup>75</sup>

A similar benefit was seen in the Cholesterol and Recurrent Events (CARE) trial, where 4159 patients who suffered from a myocardial infarction with cholesterol levels that were relatively normal (mean, 209 mg/dL), were analyzed. The trial demonstrated a higher absolute risk of a cardiovascular event in the diabetes cohort, regardless of being in the treatment or placebo group. The patients were randomized to receive pravastatin or placebo. In the 586 patients who were classified as diabetic, there was a 25% reduction in major cardiovascular events and a 23% reduction in the nondiabetic group. The benefits were also more apparent in those patients with triglycerides of  $\leq 144$  mg/dL, demonstrating the challenge in treating those patients with diabetes or the dyslip-

idemia prevalent in the metabolic syndrome.<sup>11,76</sup> The Helsinki Heart Study demonstrated the benefits of gemfibrozil in the lipid disorder of an elevated triglyceride level and low HDL level like that seen in the metabolic syndrome and insulin resistance.<sup>77</sup>

Niacin as a medication for lipid-lowering possesses many characteristics that are beneficial in the insulin resistance syndrome. It has benefits in improving HDL, triglycerides, small dense LDL, Lp(a), fibrinogen, and plasminogen activator inhibitor-1. Along with all these positive attributes, niacin also has the potential of increasing hyperglycemia, creating difficulty in treating and maintaining glycemic control. Therefore, it is not the drug of choice in diabetes or in those with elevated glucose levels.<sup>11</sup>

Hypertension is often associated with the metabolic syndrome. In the complex of attributes in the metabolic syndrome, high blood pressure is prevalent, along with insulin resistance, obesity, sedentary lifestyle, and dyslipidemia. Along with standard hypertensive medications, troglitazone and metformin have been shown to decrease blood pressure in patients with type 2 diabetes.<sup>78</sup> Angiotensin-converting enzyme inhibitors have been shown to be beneficial in stabilizing coronary plaques in patients with endothelial dysfunction.<sup>79</sup> In patients who are at high risk for developing coronary artery disease, as are patients with insulin resistance and type 2 diabetes,  $\beta$ -blockers have also demonstrated a decrease in mortality.<sup>80</sup>

Part of the metabolic syndrome is impaired fibrinolysis and elevated plasminogen activator inhibitor-1 levels. Aspirin decreases the incidence of acute coronary events by reducing platelet-thrombus formation at the site of the ruptured plaque. Aspirin is now indicated by the American Diabetes Association for all patients with type 2 diabetes, owing to the high risk of coronary artery disease. Most effective doses for high-risk patients are between 165 and 325 mg/d.<sup>81,82</sup>

### The Future

Several trials are underway to assess the effects of early treatment for type 2 diabetes, or prevention of type 2 diabetes in impaired glucose tolerance patients with thiazolidinediones. A Diabetes Outcomes Progression Trial is a 4-year trial studying the effects of early treatment of type 2 diabetes

with the thiazolidinediones. There are three comparison medications including rosiglitazone, metformin, and glyburide with the primary end point of the study being time to monotherapy failure, based on loss of glycemic control. If there is a delay in this with the rosiglitazone, then the patients with insulin resistance would derive greater benefit from treatment. Other studies include the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trials with looks at both primary prevention of diabetes in those patients with insulin resistance and a head-to-head analysis of rosiglitazone, sulfonylurea, or metformin and the end points of heart disease and glycemic control.

### References

1. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: Findings from the Third National Health and Nutrition Examination Survey. *JAMA* 287:356-359, 2002
2. Goldstein BJ: Insulin resistance as the core defect in type 2 diabetes mellitus. *Am J Cardiol* 90(suppl):1G-10G, 2002
3. Mokdad AH, Ford ES, Bowman BA, et al: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 289:76-79, 2003
4. United States Department of Health and Human Services: The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity. Rockville, MD, US Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001
5. Mokdad AH, Bowman BA, Ford ES, et al: The continuing epidemics of obesity and diabetes in the United States. *JAMA* 286:1195-1200, 2001
6. Isomaa B, Almgren P, Tuomi T, et al: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683-689, 2001
7. Trevisan M, Liu J, Bahsas FB, et al: Syndrome X and mortality: a population based study. *Am J Epidemiol* 148:958-966, 1998
8. National Institutes of Health: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD National Institutes of Health, 2001, NIH Publication 01-3670
9. Nathan DM: Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med* 347:1342-1349, 2002
10. American Diabetes Association: Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. *Diabetes Care* 16:72-78, 1993 (Suppl 2)

11. Mak K-H, Moliterno DJ, Granger CB, et al: (GUSTO-1 Investigators): Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. *J Am Coll Cardiol* 30:171-179, 1997
12. O'Keefe JH, Miles JM, Harris WH, et al: Improving the adverse cardiovascular prognosis of type 2 diabetes. *Mayo Clin Proc* 74:171-180, 1999
13. Despres JP, Lamarche B, Mauriege P, et al: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952-957, 1996
14. Meigs JB, Mittleman MA, Nathan DM, et al: Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA* 283:221-228, 2000
15. Lempiainen P, Mykkanen L, Pyorala K, et al: Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 100:123-128, 1999
16. Thompson SG, Kienast J, Pyke SD, et al: Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med* 332:635-641, 1995
17. Folsom AR, Wu KK, Rosamond WD, et al: Prospective study of hemostatic factors and incidence of coronary heart disease. *Circulation* 96:1102-1108, 1997
18. Meade TW, Brozovic M, Chakrabarti RR, et al: Haemostatic function and ischaemic heart disease. *Lancet* 2:533-537, 1986
19. Ridker PM, Hennekens CH, Stampfer MJ, et al: Prospective study of endogenous tissue plasminogen activator and risk of stroke. *Lancet* 343:940-943, 1994
20. Pinkney JH, Stehouwer CD, Coppack SW, et al: Endothelial dysfunction: cause of the insulin resistance syndrome. *Diabetes* 46:S9-S13, 1997 (Suppl 2)
21. Meigs JB, D'Agosino RB Sr, Wilson OW, et al: Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 46:1594-1600, 1997
22. Garg R, Kumbkarni Y, Aljada A, et al: Troglitazone reduces reactive oxygen species generation by leukocytes and lipid peroxidation and improves flow-mediated vasodilatation in obese subjects. *Hypertension* 36:430-435, 2000
23. Sobel BE: Increased plasminogen activator inhibitor-1 and vasculopathy: a reconcilable paradox. *Circulation* 99:2496-2498, 1999
24. Ross R: Atherosclerosis: an inflammatory disease. *N Engl J Med* 340:115-126, 1999
25. Alessi MC, Peiretti F, Morange P, et al: Production of plasminogen activator inhibitor 1 by human adipose tissue. *Diabetes* 46:860-867, 1997
26. Calles-Escandon J, Mirza SA, Sobel BE, et al: Induction of hyperinsulinemia combined with hyperglycemia and hypertriglyceridemia increases plasminogen activator inhibitor 1 in blood in normal human subjects. *Diabetes* 47:290-293, 1998
27. Pickup JC, Mattock MB, Chusney GD, et al: NIDDM as a disease of the immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 40:1286-1292, 1997
28. Albert MA, Danielson E, Rifai N, et al, for the PRINCE Investigators: Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 286:64-70, 2001
29. Juhan-Vague, Alessi MC, Vague P: Increased plasminogen activator inhibitor 1 levels. *Diabetologia* 34:457-462, 1991
30. Dandona P, Aljada A: A rational approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, inflammation, and atherosclerosis. *Am J Cardiol* 90(suppl):27G-33G, 2002
31. Steinberg HO, Chaker H, Leaming R, et al: Obesity/insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance. *J Clin Invest* 97:2601-2610, 1996
32. Williams SB, Cusco JA, Roddy MA, et al: Impaired nitric oxide-mediated vasodilation in patients with non-insulin dependent diabetes mellitus. *J Am Coll Cardiol* 27:567-574, 1996
33. Johnstone MT, Creager SJ, Scales KM, et al: Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 88:2510-2516, 1993
34. Clarkson P, Celermajer DS, Donald JE: Impaired vascular reactivity in insulin dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. *J Am Coll Cardiol* 28:573-579, 1996
35. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334:374-381, 1996
36. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 15:318-368, 1992
37. Brownlee M, Cerami A, Vlassara H: Advanced glycosylation products in tissue and the biochemical basis of diabetic complications. *N Engl J Med* 318:1315-1321, 1988
38. Carey DG, Jenkins AB, Campbell LV, et al: Abdominal fat and insulin resistance in normal and overweight women. *Diabetes* 45:633-638, 1996
39. Zierath JR, Livingston JN, Thorne A, et al: Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: relation to insulin receptor phosphorylation and intracellular signaling through the insulin receptor substrate-1 pathway. *Diabetologia* 41:1343-1354, 1998
40. Cline GW, Falk Peterson K, Krssak M, et al: Impaired glucose transport as a cause of decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. *New Engl J Med* 341:240-246, 1999
41. Reusch J: Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol* 90:19-26, 2002
42. Marja P, Miettinen H, Laakso M, et al: Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of

- the Helsinki policemen study. *Circulation* 98:398-404, 1998
43. Howard G, O'Leary DH, Zaccaro D, et al, for the IRAS Investigators: Insulin sensitivity and atherosclerosis. *Circulation* 93:1809-1817, 1996
  44. Cullen P: Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol* 86:943-949, 2000
  45. Sacks FM: The relative role of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol in coronary artery disease: evidence from large-scale statin and fibrate trials. *Am J Cardiol* 88:14N-18N, 2001
  46. Laakso M, Sarlund H, Salonen R, et al: Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb* 11:1068-1076, 1991
  47. Young MH, Jeng C-Y, Sheu WHH, et al: Insulin resistance, glucose intolerance, hyperinsulinemia and dyslipidemia in patients with angiographically demonstrated coronary heart disease. *Am J Cardiol* 72: 458-460, 1993
  48. Haffner SM, Mykkanen L, Festa A, et al: Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation* 101: 975-980, 2000
  49. Haffner SM, Miettinen H: Insulin resistance implications for type II diabetes mellitus and coronary heart disease. *Am J Med* 193:152-162, 1997
  50. Salomaa V, Riley W, Kark JD, et al: Arterial disease/hypertension/angiotensin system: non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC study. *Circulation* 91: 1432-1443, 1995
  51. Edwards KL, Austin MA, Newman B, et al: Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb* 14:1940-1945, 1994
  52. Folsom AR, Szklo M, Stevens J, et al: A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 20:935-942, 1997
  53. Meigs JB, D'Agostino RB, Wilson PWF, et al: Risk variable clustering in the insulin resistance syndrome. *Diabetes* 46:1594-1600, 1997
  54. Garratt KN, Brady PA, Hassinger NL, et al: Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 33:119-124, 1999
  55. Saltiel AR, Olefsky JM: Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes* 45:1661-1669, 1996
  56. Miyazaki Y, Mahankali A, Matsuda M, et al: Relationship between visceral fat and enhanced peripheral/hepatic insulin sensitivity after pioglitazone in type 2 diabetes. *Diabetes* 50:A126, 2001 (Suppl 2)
  57. Arioglu E, Duncan-Morin J, Sebring N, et al: Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 133:263-274, 2000
  58. Ghanim H, Garg R, Alijada A, et al: Suppression of nuclear factor-kappa beta and stimulation of inhibitor kappa beta by troglitazone: evidence for an anti-inflammatory effect and a potential antiatherosclerotic effect in the obese. *J Clin Endocrinol Metab* 86:1306-1312, 2001
  59. Mayerson AB, Hundal RS, Dufour S, et al: The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* 51:797-802, 2002
  60. Ridker PM, Rifai N, Pfeffer MA, et al, for the Cholesterol and Recurrent Events (CARE) Investigators: Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 100:230-235, 1999
  61. Mohanty P, Alijada A, Ghanim H, et al: Rosiglitazone improves vascular reactivity, inhibits reactive oxygen species (ROS) generation, reduced p47 subunit expression in mononuclear cells (MNC) and reduces C reactive protein (CRP) and monocyte chemotactic protein-1 (MCP-1): evidence of a potent anti-inflammatory effect. *Diabetes* 50:A68, 2001 (Suppl 2)
  62. Haffner SM, Greenberg AS, Weston WM, et al: Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 106:679-684, 2002
  63. Festa A, D'Agostino R Jr, Howard G: Chronic sub-clinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 102:42-47, 2000
  64. Brunzell J, Cohen B, Kreider M, et al: Rosiglitazone favorable affects LDL-C and HDL-C heterogeneity in type 2 diabetes. *Diabetes* 50:A141, 2001 (Suppl 2)
  65. Raji A, Seely EW, Bekins SA, et al: Rosiglitazone improves insulin sensitivity and lowers blood pressure in hypertensive patients. *Diabetes Care* 26:172-178, 2003
  66. Mather KJ, Verman S, Anderson TJ: Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol* 37:1344-1350, 2001
  67. UK Prospective Diabetes Study Group (UKPDS): Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet* 352:854-865, 1998
  68. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002
  69. Wei M, Kampert JB, Barlow CE, et al: Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight and obese men. *JAMA* 282:1547-1553, 1999
  70. Brandenburg SL, Reusch JED, Bauer TA, et al: Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. *Diabetes Care* 22:1640-1646, 1999

71. Wallace MB, Mills BD, Browning CL: Effects of cross-training on markers of insulin resistance/hyperinsulinemia. *Med Sci Sports Exerc* 29:1170-1175, 1997
72. Knopp RH, Walden CE, Retzlaff BM, et al: Long-term cholesterol-lowering effects of 4 fat restricted diets in hypercholesterolemic and combined hyperlipidemic men: The Dietary Alternatives Study. *JAMA* 278: 1509-1515, 1997
73. Hu FB, Stampfer MJ, Manson JE, et al: Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 337:1491-1499, 1997
74. Wadden TA, Berkowitz RI, Sarwer DB, et al: Benefits of lifestyle modification in the pharmacologic treatment of obesity. *Arch Intern Med* 161:218-227, 2001
75. Pyorala K, Pedersen TR, Kjekshus J, et al: (Scandinavian Simvastatin Survival Study Group 4S): Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614-620, 1997
76. Sacks FM, Pfeffer MA, Moyer LA, et al: (Cholesterol and Recurrent Events Trial Investigators): The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001-1009, 1996
77. Tenkanen L, Manttari M, Manninen V: Some coronary risk factors related to the insulin resistance syndrome and treatment with gemfibrozil: experience from the Helsinki Heart Study. *Circulation* 92:1779-1785, 1995
78. Inzucchi SE, Maggs DG, Spollett GR, et al: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867-872, 1998
79. Mancini CBJ, Henry GC, Macay C, et al: Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: The TREND Study (Trial on Reversing Endothelial Dysfunction). *Circulation* 94: 258-265, 1996
80. Jonas M, Reicher-Reiss H, Boyko V, et al: (Bezafibrate Infarction Prevention Study Group BIP): Usefulness of beta-blocker therapy in patients with noninsulin-dependent diabetes mellitus and coronary artery disease. *Am J Cardiol* 77:781-786, 1996
81. O'Keefe JH Jr, Conn RD, Lavie CJ Jr, et al: The new paradigm for coronary artery disease: altering risk factors, atherosclerotic plaques, and clinical prognosis. *Mayo Clin Proc* 71:957-965, 1996
82. Antiplatelet Trialists' Collaboration: Collaborative overview of randomized trials of antiplatelet therapy: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 308:81-106, 1994