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Primary Care Reports

The Practical, Peer-Reviewed Journal for Primary C

NEWSLETTER & ELECTRONIC PUBLISHERS FOUNDATION
EDITORIAL EXCELLENCE AWARD WINNER

Volume 8, Number 26 **December 23, 2002**

The Insulin Resistance Syndrome—Syndrome X

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Editor's Note—*The quintet of abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism, and coagulopathy has been called "syndrome X" or "metabolic syndrome."*[1,2] *Some have referred to this grouping as the "insulin resistance syndrome," the "obesity dyslipidemia syndrome," and the "deadly quartet," the end result being atherosclerosis, which leads to coronary artery disease and its sequelae.*[3-5]

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes (DM2) and in the associated metabolic abnormalities, such as dyslipidemia and hypertension. Insulin resistance is strongly linked to obesity (mainly abdominal visceral obesity), which is growing in major proportions within the developed world, especially the United States.[6]

DM2 is caused by a dual defect: insulin resistance and β-cell failure. Insulin resistance is a state in which a given concentration of insulin is associated with a subnormal glucose response.[7] *Thus, the β-cells of the pancreas secrete increased amounts of insulin to maintain euglycemia. However, over time, functional defects in insulin secretion prevent the β-cells from maintaining high rates of insulin secretion, resulting in impaired glucose tolerance and eventually DM2.*[8] *In addition to causing hyperglycemia in DM2, insulin resistance and compensatory hyperinsulinemia also play a role in other metabolic abnormalities culminating in atherosclerosis and its sequelae (discussed later).*

During the past decade, the cardiovascular complications associated with DM2 have attracted increasing attention. In fact, macrovascular complications account for 80% of the mortality in patients with DM2.[9] *Although aggressive glycemic control can delay or prevent the microvascular complications of the disease, which may eventually lead to renal failure, blindness, and neuropathy, there are no concrete data linking glycemic control to macrovascular complications.*[10,11] *The reason is that the cardiovascular disease that accompanies diabetes is multi-factorial, including obesity, dyslipidemia and hypertension, and impaired hemostasis, eventually culminating in atherosclerotic vascular disease. It has been estimated that atherosclerosis has been progressing for 10-20 years before the clinical onset of DM2.*[2-5] *In 2001, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program recognized diabetes as a cardiovascular risk equivalent; a new definition for the metabolic syndrome (or syndrome X) as a treatment target in patients at risk for heart disease also was established.*[12]

This review article will focus on the clinical spectrum of the metabolic syndrome, including obesity, abnormal glucose metabolism, hypertension, dyslipidemia, impaired hemostasis, macrovascular disease, and other associated features. The pathogenesis of each component in relation to insulin resistance and atherosclerosis and a brief overview of the therapeutic implications will be discussed, stressing appropriate early aggressive therapy of all risk factors.

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Introduction

The metabolic syndrome is observed in at least 25% of adults 20-70 years of age in the United States,[13] and occurs with increasing frequency in individuals with impaired glucose tolerance (approximately 45-65%) and DM2 (approximately 75-85%).[14] The prevalence of the metabolic syndrome has an age-dependent increase (6.7% for ages 20-29, as opposed to 42% for ages > 70 years).[13] Mexican-Americans had the highest age-adjusted prevalence (31.9%). Among African-Americans and Mexican-Americans, the prevalence was higher in women than in men (57% and 26% higher prevalence, respectively). The high prevalence of this syndrome and its strong association with obesity highlights the importance of appropriate lifestyle intervention (diet and exercise).

The ATP III tabulates 5 clinically determined characteristics of the metabolic syndrome and notes that the presence of any 3 is sufficient to confirm the diagnosis (*see Table*).[12] Other components of the metabolic syndrome might include impaired hemostasis, cardiovascular disease, cutaneous abnormalities, hepatic steatosis, hyperandrogenism and reproductive abnormalities.[6]

Clinical Spectrum

Obesity

In the United States, the prevalence of obesity has reached epidemic proportions in the past decade. Obese patients are often insulin-resistant and hyperinsulinemic, and these 3 factors are characteristic of the prediabetic phase. Obesity, in particular increased adiposity in the visceral compartment (ie, central or abdominal obesity), is negatively correlated with insulin sensitivity.[15] There are several mechanisms to explain how obesity, especially visceral obesity, leads to insulin resistance and contributes to cardiovascular disease. Visceral adipocytes are far more metabolically active than subcutaneous adipocytes. Lipolysis (ie, release of free fatty acids) from visceral fat is more pronounced than from subcutaneous fat, and visceral fat cells are less sensitive to suppression of lipolysis by insulin.[16] The released free fatty acids can directly block insulin-signaling pathways,[17] leading to insulin resistance. In addition, visceral fat has direct access to the portal circulation. Increased amounts of free fatty acids being released into the portal circulation may impair the metabolism and action of insulin and increase gluconeogenesis in the liver.[18] Also, different mediators secreted by the adipocytes have been implicated in the pathogenesis of insulin resistance associated with obesity. These mediators or chemical messengers, collectively known as "adipocytokines," include tumor necrosis factor (TNF)-α, adiponectin, resistin, and leptin (*see Figure 1*).[19,20]

TNF-α is overexpressed in the adipose tissue of obese humans, and increases free fatty acid secretion.[21] Adiponectin appears to enhance insulin action; as an individual becomes more obese, the adiponectin concentration in the blood is decreased and insulin resistance increases.[22] Resistin is another recently identified adipocyte-specific protein found in mouse cells.[23] Resistin is associated with insulin resistance and work to date has shown that resistin itself appears to be limited in expression to rodents, but there is a family of related molecules expressed in human fat tissue that may have effects similar to those of resistin.[24] Treatment of rodents with rosiglitazone results in decrease in resistin and resultant decrease in insulin

Table. Definition of the Metabolic Syndrome (based on ATP-III Guidelines)

Clinical Identification of the Metabolic Syndrome—Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity†	Waist circumference†
Men	102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL

† The presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index.

† Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (37-39 in).

Primary Care Reports™, ISSN 1040-2497, is published biweekly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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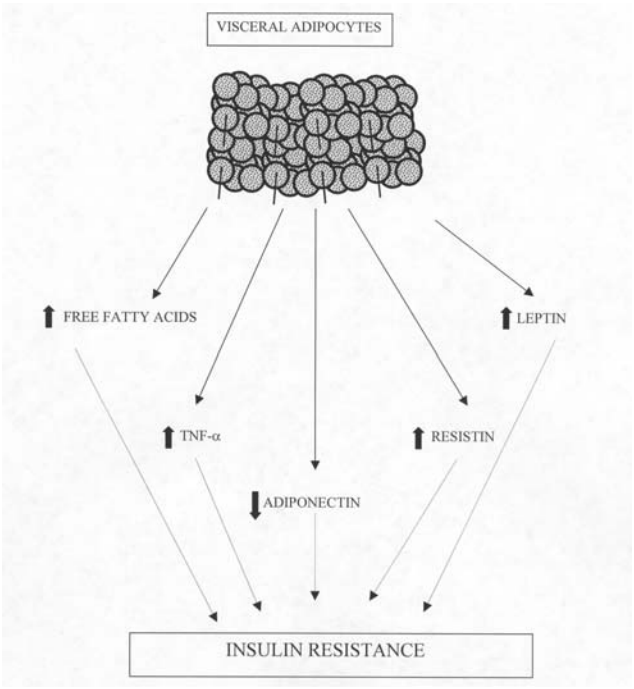
Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief) serves as a consultant to Aventis and Sanofi and does research for Astrazeneca. Dr. Jabbour (author) is on the speaker's bureau of Pfizer. The peer reviewer reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Figure 1. Visceral Obesity and Insulin Resistance



resistance.[23] Leptin is another adipose-specific hormone that contributes to appetite regulation and has been proposed to affect insulin sensitivity. Some investigators have suggested that hyperleptinemia plays a crucial role in insulin resistance.[25]

Finally, aging is also associated with a higher prevalence of type 2 diabetes. This can be attributed to loss of lean body mass and an increase in adipose tissue, especially in sedentary individuals. This results in less muscle tissue available for glucose disposal and relatively more adipose tissue, leading to insulin resistance in susceptible individuals.

Visceral obesity, besides promoting the development of insulin resistance and DM2, is also an independent significant predictor of coronary heart disease morbidity and mortality.[15,26]

Hyperglycemia

In order to maintain normal glucose levels in the blood circulation, insulin must be available and capable through its cellular action to promote the uptake and metabolism (disposal) of glucose into skeletal muscle and adipose tissue. In addition, sufficient insulin action must occur in the liver to suppress hepatic glucose production, the major source of circulating glucose in the fasting state.[27] Several pathophysiologic changes have been shown to precede the development of the hyperglycemia of DM2.[18] One essential factor is the appearance of insulin resistance, such as seen in patients with metabolic syndrome, impairing the use of glucose by peripheral tissues. Insulin resistance can be worsened by a variety of factors, including increases in body mass due to excess adiposity, sedentary lifestyle, age, and glucocorticoids. To compensate, the pancreas attempts to overcome the underlying defect of insulin resistance by increasing insulin secretion with subsequent hyperinsulinemia.[8] If β-cells are normal, people remain euglycemic; but in the presence of functional defects in glucose-stimulated insulin secretion in the β-cells (mostly genetic in origin), hyperglycemia ensues.[18,28] The compensated state of insulin resistance and hyperinsulinemia may last for a decade or more, but ultimately, insulin secretion decreases because of β-cell failure (*see Figure 2*). Free fatty acids (released from visceral fat) not only seem to interfere with insulin action but also with insulin secretion.[28a] It has been suggested that alterations in the expression of metabolic enzymes by free fatty acids may account for β-cell insensitivity to glucose or for alterations in insulin secretion.[28a] At least part of the reason behind β-cell failure is insulin resistance leading to elevated free fatty acids which result in β-cell apoptosis (*see Figure 3*). Hyperglycemia and DM2 develop when these 2 defects, insulin resistance and impaired β-cell function, are present.[18] An early defect is a relative insulin deficiency leading to an increase in postmeal glucose levels, due to decrease in glucose use. A later effect is the increase in glucose production by the liver, especially in the fasting state, which is due to insufficient insulin action in the liver. Thus, persons with DM2 have 3 major pathophysiologic features that provide a useful framework on which to design the basis of a "stepped" therapeutic approach: insulin resistance with defective glucose disposal after meals in muscle and fat tissue, insulin resistance with increased glucose output by the liver and impaired β-cell function[27] (*see Figure 4*). During the development of DM2, β-cell function is progressively lost. At the time of the diagnosis of diabetes, up to 50% of β-cell function has already been lost, and declines progressively over time (4% per annum).[29] The degree of β-cell function is critical,

Figure 2. Natural History of Diabetes, Depicting the Increasing Blood Glucose with Progressive Beta-Cell Dysfunction

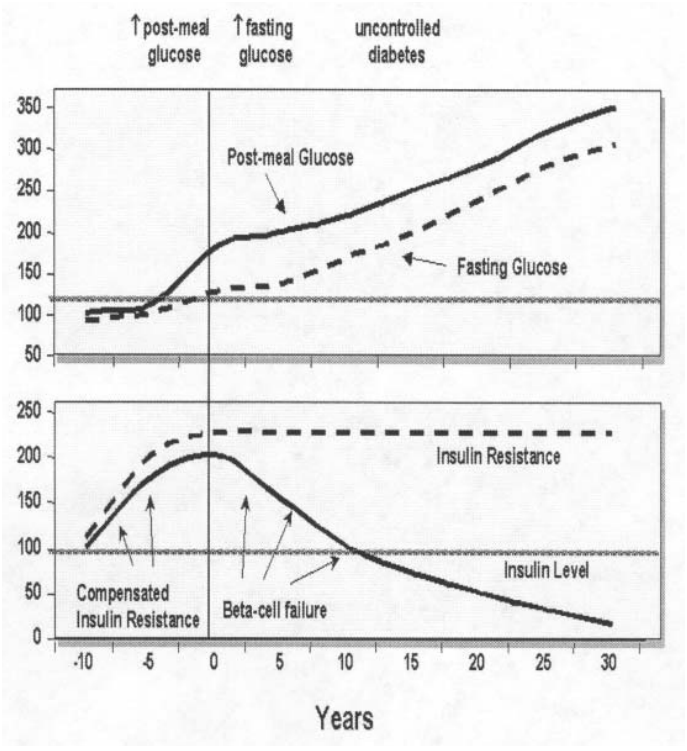


Figure 3. Dual Defects

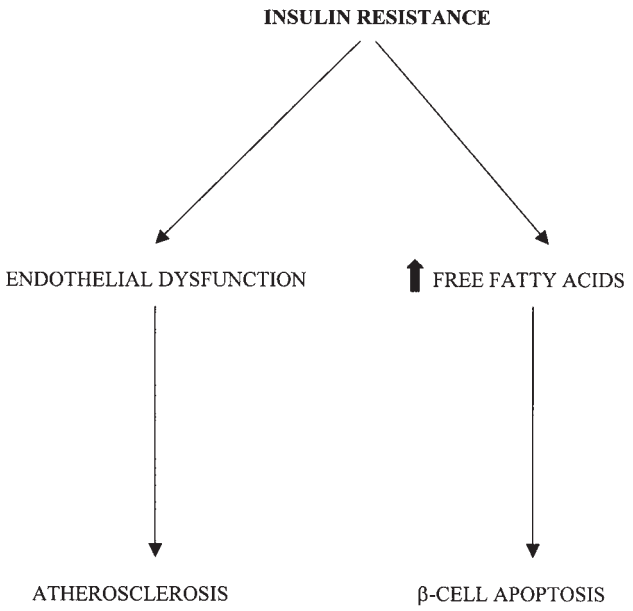
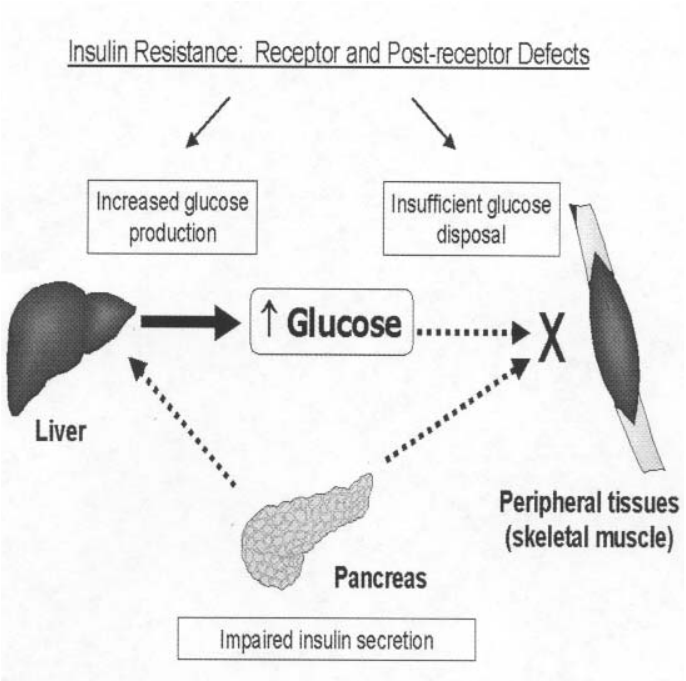


Figure 4. Insulin Resistance: Receptor and Post-Receptor Defects



Sites of the 3 major pathogenic defects that lead to type 2 diabetes. Insulin resistance in the muscle causes reduced glucose disposal from the bloodstream, and insulin resistance in the liver causes increased glucose production. Impaired insulin secretion by the pancreas is a critical feature that leads to hyperglycemia when the amount of insulin secreted and the timing of the insulin response to glucose are effective.

because therapeutic approaches to prevent or treat diabetes are more effective earlier in the disease, most likely because β-cell response is more robust.[6,29]

Hypertension

Insulin resistance and subsequent hyperinsulinemia cause exaggerated responses in tissues that remain sensitive to insulin, underlying many of the pathophysiologic features of the insulin resistance syndrome, such as hypertension. Insulin resistance and hypertension are associated, although not as strongly as insulin resistance and dyslipidemia. Patients with DM2 are almost twice as likely to have hypertension as patients without diabetes, and approximately 50% of patients with hypertension are insulin-resistant and hyperinsulinemic.[4] The rise in plasma insulin levels may elevate the blood pressure by one or more of the following mechanisms:[4,5]

- Hyperinsulinemia acts centrally to enhance the activity of the sympathetic nervous system.[4,30] This hyperadrenergic state stimulates thermogenesis, thereby minimizing further weight gain. However, the price paid for this maintenance of energy balance is a sympathetically induced rise in the systemic blood pressure.
- Insulin and increased sympathetic activity can stimulate renal sodium reabsorption,[3,5,31,32] leading to volume expansion, and elevation in systemic blood pressure.
- There may be a difference in the action of insulin on the vasculature. Insulin normally causes vasodilatation and enhanced muscle blood flow, an effect that appears to be mediated in part by nitric oxide; this effect is regulated by an enzyme involved in glucose metabolism.[33,34] These effects are blunted in both obese and hypertensive subjects.[33] Insulin resistance may result in proportionate reductions in glucose use and nitric oxide production (and therefore vasodilation).[35]

Despite all of these suggestive findings, there are several observations that do not confirm a tight causal relationship between insulin and hypertension:[32]

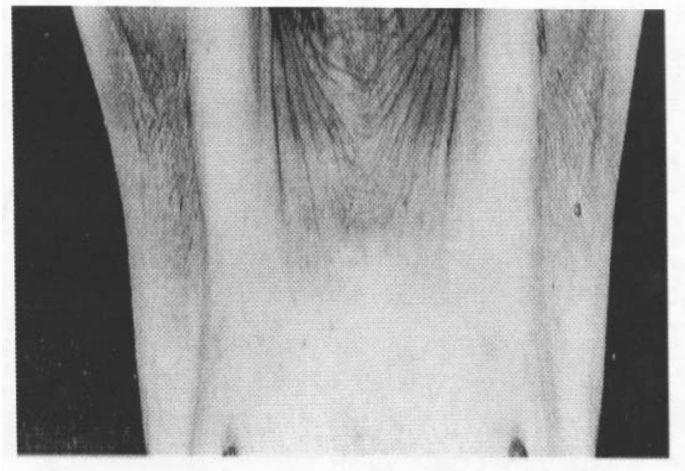
- Some epidemiologic studies have not been able to demonstrate a strong correlation between hyperinsulinemia and hypertension.[36]
- High insulin levels alone appear to be insufficient to substantially raise the blood pressure. As an example, chronic hyperinsulinemia (by infusion) does not induce hypertension in dogs.[37] Similarly, humans with insulinoma do not become hypertensive and their blood pressure does not fall after successful surgery.[38]

These negative findings suggest that, if insulin is important in the pathogenesis of hypertension, there is substantial interpatient variability and that some additional factor or factors must also be present.[30,39] One possibility is genetic susceptibility to the development of hypertension or to the effects of insulin on blood pressure.

Dyslipidemia

A central component of the insulin resistance syndrome is a characteristic pattern of lipid abnormalities, including elevated plasma triglyceride concentrations and decreased high-density lipoprotein (HDL) cholesterol. Although plasma concentrations

Figure 5. Acanthosis Nigricans



The skin of the neck and axillae shows the typical velvey-textured, brown changes of acanthosis nigricans.

of low-density lipoprotein (LDL) cholesterol may not differ from those in normal subjects, there is an increase in small, dense LDL particles in patients with insulin resistance.[40,41] Elevated triglycerides, low levels of HDL and the presence of small, dense LDL are each independent risk factors for cardiovascular disease,[12,42,43] and represent a set of lipoprotein abnormalities that promote atherosclerosis.[44]

Dyslipidemia associated with insulin resistance is thought to be initiated by the resistance of adipose cells to the effects of insulin. The inability of insulin-resistant fat cells to store triglycerides results in hydrolysis of triglycerides and release of fatty acids.[45] The resulting availability of free fatty acids to the liver leads to increased hepatic synthesis and release of triglycerides and very low-dense lipoprotein (VLDL) cholesterol. Exchange of cholesterol esters from HDL and LDL to VLDL for triglyceride molecules renders HDL unavailable to remove cholesterol from peripheral cells. Thus, hypertriglyceridemia leads to low levels of HDL cholesterol. Furthermore, triglyceride-enriched LDL is readily converted to small, dense LDL, which has greater atherogenic potential, because it is more readily oxidized. Oxidized LDL is more readily scavenged by vascular scavenger LDL receptors and has a longer residence time in the vascular matrix. This leads to enhanced lipid deposition in the arterial wall. Oxidized LDL cholesterol also is toxic to endothelial cells, leading to decreased nitric oxide release and enhanced expression of cytokines and adhesion molecules. These effects in turn lead to vascular inflammation.[46]

The presence of small, dense LDL cholesterol has been associated with worsened cardiovascular outcomes. In the Quebec Cardiovascular Study, 2103 men without ischemic heart disease were followed during a period of 5 years.[43] LDL particle size was measured in 103 patients who developed ischemic heart disease to determine the relationship between ischemic heart disease and presence of small, dense LDL. Notably, small, dense LDL composition, as described in the metabolic syndrome, was associated with a 3.6-fold increase in the risk of developing ischemic heart disease.

Individuals who are insulin-resistant or have DM2 uncommonly have elevated total LDL cholesterol levels,[45] which suggests that the increased atherogenicity associated with diabetes is related to specific aspects of the LDL cholesterol lipid profile. The elevation in small, dense LDL composition is associated with increased triglycerides and reduced HDL cholesterol, all of which are risk factors for development of heart disease.[43,45,46]

Impaired Hemostasis

A more recently recognized component of the insulin resistance syndrome is a prothrombotic state. Patients with insulin resistance often have evidence of alterations in coagulation that predispose to arterial thrombosis.[44,47] One of these alterations is increased levels of plasminogen activator inhibitor type 1 (PAI-1).

Maintenance of hemostasis is mediated through such factors as PAI-1 and tissue plasminogen activator (tPA). tPA mediates clot lysis by activating the fibrinolytic system. PAI-1 blocks the action of tPA and is the primary inhibitor of endogenous fibrinolysis.[40] Elevated PAI-1 plasma concentrations are associated with cardiovascular disease and appear to be important in the pathogenesis of thrombosis and myocardial infarction. In persons with type 2 diabetes and in nondiabetic persons with insulin resistance, PAI-1 concentrations are elevated. There is a significant direct correlation between PAI-1 concentrations and insulin resistance.[41] There are also strong, positive associations between fasting insulin concentrations and other markers of hemostatic function (eg, von Willebrand factor antigen, factor VII antigen, fibrinogen, and plasma viscosity).[47]

Thus, insulin resistance and hyperinsulinemia may increase the risk of cardiovascular disease by impairing hemostatic function and enhancing the potential for acute thrombosis.

Macrovascular Disease

Although many of the individual components of the metabolic syndrome predict increased risk for cardiovascular disease, presence of the metabolic syndrome is clearly associated with a high relative risk for coronary artery disease (CAD) (2.96), myocardial infarction (2.63), and stroke (2.27). This risk is greater than the risk associated with any of the individual components of the metabolic syndrome. For example, the relative risks for CAD for obesity, hypertension or dyslipidemia are 1.44, 1.57, and 1.73, respectively.[48,49]

The fact that individuals with metabolic syndrome have a markedly increased risk of CAD was also illustrated in a prospective epidemiologic study of 970 men with no CAD who were followed for 22 years; the presence of hyperinsulinemia was associated with an increased risk of a major coronary event, death or nonfatal myocardial infarction, although its predictive value diminished with time.[50] The hazard ratios, adjusted for other risk factors, at 5, 10, 15, and 22 years were 2.3, 2.4, 1.8, and 1.3, respectively. Hyperinsulinemia was associated with increases in both cardiovascular and noncardiovascular mortality.[51] Of note, there are little data supporting insulin itself as being atherogenic. The likely culprit might be some other atherogenic factors (? pro-insulin) secreted by the β-cells or the other components of the metabolic syndrome (dyslipi-

demia, hypertension. . .). In fact, aggressive insulin therapy may lead to a reduction in mortality from cardiovascular disease, as shown in the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial.[51a]

Impaired glucose tolerance and DM2 are associated with increased risk for cardiovascular morbidity and mortality. The increased risk of macrovascular complications likely begins years before the development of clinical type 2 diabetes, when insulin resistance and hyperinsulinemia are present. Prediabetic subjects usually have hyperinsulinemia and a more atherogenic pattern of cardiovascular risk factors compared with subjects who do not develop diabetes.[52]

Atherosclerosis is now recognized as an inflammation of the arterial wall.[52a] It starts with abnormalities in the endothelium (from hypertension, dyslipidemia, diabetes and other factors), resulting in the adhesion of circulating monocytes and T-cells, and in the formation of an inflammatory nidus. The adherent monocytes are then activated and move into the subendothelial space, where they form "foam cells" loaded with oxidized low-density lipoprotein. These foam cells are active and secrete matrix metalloproteinase, which may lyse the fibrous cap of the atherosclerotic plaque to make the plaque unstable and to cause plaque rupture. Such a rupture leads to initiation of the thrombotic process.

After individuals have developed subclinical or clinical cardiovascular disease, the presence of the disease is far more predictive of future cardiovascular events than the components of the metabolic syndrome.[53] Therefore, it may be concluded that treatment of the metabolic syndrome is likely to maximally reduce future development of cardiovascular disease, if treatment begins before significant structural vascular damage has occurred. The common soil hypothesis linking DM2, hypertension, dyslipidemia, and atherosclerosis is inflammation.

Other Associated Features

Acanthosis nigricans and skin tags are commonly associated with primary insulin resistance, regardless of its molecular cause. Acanthosis nigricans is a skin lesion characterized by brown, velvety, hyperkeratotic plaques[54] (*see Figure 5*). The lesions are usually found on the back of the neck, the axilla, the groin, and over the elbows, but they may cover the entire surface of the skin, sparing only the palms and soles. The common denominator in all cases of acanthosis nigricans, with the possible exception of tumor-induced lesions, is insulin resistance.

Men with insulin resistance are not known to have disorders of the reproductive system. In contrast, women with insulin resistance commonly present with reproductive abnormalities.[55] Insulin resistance may lead to ovarian hyperandrogenism, a sequence that has been proposed in women with polycystic ovary syndrome (PCOS), where women present with hirsutism and irregular menses. Of course, hyperinsulinemia by itself is not enough to induce PCOS, which may arise as a complex genetic disorder in which an intrinsic ovarian genetic trait interacts with other congenital or cellular environmental factors (like insulin resistance) to cause dysregulation of steroidogenesis.[56]

The metabolic syndrome also has been associated with abnormal liver pathology in very obese patients including steatosis, fibrosis, and cirrhosis.[57]

Therapeutic Implications

Because syndrome X is associated with significant morbidity and mortality, early diagnosis and aggressive treatment are critical, especially in DM2, where complications often are present years before diagnosis. Adverse sequelae are easier to prevent than to reverse, and preservation of β-cell function may slow progression of the disease.

Weight Loss

Regardless of the mechanisms, avoidance of obesity, particularly abdominal obesity, should reduce the potential for the development of the various features of the insulin resistance syndrome. For most patients, weight reduction and increased physical activity will improve insulin resistance, hyperglycemia, hypertension, and dyslipidemia, and reduce the risk of cardiovascular disease.

Recently, the Diabetes Prevention Program Research Group[58] has shown that lifestyle changes can slow the conversion of pre-diabetes to DM2. This study randomized 3234 patients with impaired glucose tolerance to treatment with placebo, metformin (850 mg twice a day), or lifestyle modification (goal of at least 7% weight loss and at least 150 minutes of physical activity per week). Patients were monitored for a period of 2.8 years. Compared with placebo, patients who modified their lifestyle experienced a 58% reduction in the incidence of diabetes and patients treated with metformin had a 31% reduction.

Similarly, another study from Finland[59] randomized 522 overweight patients with impaired glucose tolerance to lifestyle modification (goal of at least 5% weight loss and moderate exercise for at least 30 minutes per day) or control group. After a follow-up of 3.2 years, the risk of diabetes was reduced by 58% in the intervention group.

These data suggest that lifestyle modification is extremely effective for preventing or delaying the onset of diabetes.

When present, DM2 is a disease associated with significant morbidity and mortality; so early diagnosis and aggressive treatment are critical. Early intervention in patients with DM2 is particularly important, because complications often are present before diagnosis, adverse sequelae are easier to prevent than to reverse, and preservation of β-cell function may slow progression of the disease. This is why treating the pre-diabetes state is paramount, primarily through weight loss and targeting the other cardiovascular risk factors.

For patients with DM2, specific treatment goals have been established:[62,63]

- HbA1c < 7% (American Diabetes Association);
- HbA1c < 6.5% (American College of Endocrinology);
- Blood pressure < 130/80; and
- LDL < 100 mg/dL.

Glycemic Control

The UK Prospective Diabetes Study (UKPDS) established that treatment of patients with DM2 with sulfonylureas, metformin, or insulin reduced the development of microvascular complications, including retinopathy and nephropathy.[11,60] In

patients receiving intensive therapy with either a sulfonylurea or insulin, the microvascular complication rate was reduced by 25% compared with patients who received conventional dietary therapy.[11] In overweight patients, metformin decreased the incidence of myocardial infarction by almost 39%. Sulfonylurea, metformin, and insulin therapies were similarly effective in improving glucose control; each therapeutic agent, as monotherapy, increased 2- to 3-fold the proportion of patients who attained HbA1c below 7% compared with diet alone.[61] However, the progressive deterioration of diabetes control was such that after 3 years, approximately 50% of patients could attain this goal with either monotherapy (sulfonylurea, metformin, or insulin), and by 9 years this declined to approximately 25%.[61] The big lesson we learned from the UKPDS was that the majority of patients needed multiple combination therapies to attain the glycemic target levels in the long term.

Insulin Resistance

The thiazolidinediones (TZDs) directly improve insulin resistance. Because their antihyperglycemic effect is less pronounced than metformin or sulfonylureas as monotherapy, their use in combination therapy is favored, preferably early in the treatment of DM2; because TZDs have been shown to relocate visceral to subcutaneous fat and have anti-inflammatory properties in the vascular endothelium, both of which are anticipated to be beneficial in reducing atherosclerotic heart disease.[41]

TZDs have been shown to reduce PAI-1 levels and decrease C-reactive protein levels. Also, they appear to reduce the intima-media thickness of the carotid arteries.[63a] The TZD troglitazone also has been shown to be effective in preventing DM2 in a high-risk group of women who recovered from gestational diabetes (Troglitazone in the Prevention of Diabetes study [TRIPOD]),[64] but no outcome data on other TZDs are available yet. In animal models, rosiglitazone, in addition to its anti-inflammatory properties, reduces free fatty acids (preventing β-cell apoptosis from high level of free fatty acids) and causes β-cell rejuvenation, explaining 3-3.5 year data with sustained β-cell efficacy.

In the UKPDS, the data demonstrated that for every 1% decrease in mean HbA1c levels, the risk of microvascular complications decreased by 37%, but the risk of myocardial infarction decreased by only 14%.[65] The reason why macrovascular complications were not very significantly affected by glycemic control is probably due to the presence of other cardiovascular risk factors including hypertension and dyslipidemia.

Hypertension

There is evidence that treatment with angiotensin-converting enzyme inhibitors exerts a vascular-protective effect and improves cardiovascular outcomes in high-risk or diabetic patients.[66,67] The Heart Outcomes Prevention Evaluation (HOPE) study evaluated the effects of ramipril on cardiovascular events in patients at high risk for cardiovascular disease (9297 patients, including 3577 with diabetes). After 5 years, treatment with ramipril reduced the rates of death from cardiovascular causes by 26%, myocardial infarction by 20%, and stroke by 32%; more importantly, ramipril reduced the risk of new cases of diabetes by 34%, which may be due to a differential effect on insulin resistance. Almost similar reductions were seen in the subgroup of patients with diabetes, where the ramipril treatment group also had a 16% reduction in overt nephropathy, dialysis, or laser therapy. Only a small part of the benefit could be attributed to a reduction in blood pressure.

Another study examined the effect of an angiotensin-II receptor antagonist (losartan) in 9193 patients (including 1195 with diabetes) with hypertension and left ventricular hypertrophy (Losartan Intervention For Endpoint reduction trial [LIFE]).[68] The trial was randomized against atenolol. After 4 years, losartan was better than atenolol in reducing the frequency of the primary composite end point of cardiovascular death, stroke, and myocardial infarction. Also, there was a lower rate of new-onset diabetes (difference of 25%) with losartan.

Dyslipidemia

As mentioned before, dyslipidemia is a major component of the metabolic syndrome and a risk factor for heart disease. It is well known from major clinical trials that lowering LDL to a target goal based on risk factors is beneficial and improves cardiovascular outcomes.[69,70] When diabetes is present, the patient is considered as having a CAD risk equivalent[12] and is at increased risk for developing subsequent cardiovascular complications. There is evidence to suggest that management of dyslipidemia in patients with diabetes can significantly reduce the incidence of both fatal and nonfatal coronary events.[71,72] A subgroup of 202 patients with diabetes and established CAD was evaluated in the Scandinavian Simvastatin Survival Study (4S).[71] After treatment with simvastatin, patients with diabetes had a 55% risk reduction for a major CAD event compared with a 32% reduction in patients without diabetes. The Cholesterol And Recurrent Events (CARE) trial evaluated the effect of pravastatin compared with placebo in 586 patients with diabetes and history of CAD.[72] Treatment with pravastatin reduced the relative risk of coronary events by 25% in patients with diabetes and 23% in patients without diabetes.

Statins have also been shown to be effective in primary prevention of CAD. The West of Scotland Coronary Prevention Study (WOSCOPS) was designed to evaluate the effect of pravastatin for 4 years on the rate of nonfatal and fatal myocardial infarction (MI) in 6595 men without history of CAD. There was almost 31% reduction in the incidence of nonfatal MI and death from cardiac events.[72a]

Also, statins may have actions other than lipid lowering (antiinflammatory effect). In the Heart Protection Study (HPS),[72b] 20,536 subjects were assigned to simvastatin or placebo. Entry criteria included a history of CAD, diabetes or hypertension. Even in patients who had baseline LDL < 116 mg/dL, there was 18% reduction in deaths from heart disease and 24% reduction in major cardiovascular events.

Also, besides targeting LDL as a primary goal, increasing HDL as a secondary target improves cardiovascular outcomes. The Veterans Affairs HDL-Cholesterol Intervention Trial (VA-

HIT) recruited men who had a CAD event in the past and dyslipidemia profile that included HDL cholesterol of less than 40 mg/dL. Patients were randomized to treatment with placebo or gemfibrozil and were followed for 5.1 years.[73] Treatment with gemfibrozil decreased triglycerides by 31% and increased HDL cholesterol by 6% but had no effect on LDL cholesterol. The gemfibrozil-treated individuals had a 22% risk reduction for the combined end point of death from CAD and nonfatal myocardial infarction compared with the placebo-treated group.

Coagulopathy

Finally, because of the procoagulant state seen in metabolic syndrome, administration of aspirin has been shown to be beneficial in patients with coronary heart disease or diabetes.[62] The most plausible mechanism for the benefit of aspirin relates to its ability to irreversibly inhibit platelet dependent cyclooxygenase agreeability, thereby reducing the risk of thrombotic vascular events. Small amounts of aspirin (75-81 mg) have such a pronounced effect that higher doses appear to yield no additional benefit. Also, naproxen (a nonsteroidal anti-inflammatory drug) appears to share anti-platelet effects with aspirin.[74]

Conclusion

In the metabolic syndrome or syndrome X, the cornerstone for management is to reduce the underlying cause, mainly obesity, which is a growing epidemic in the United Sates. For most patients, weight reduction and increased physical activity will improve insulin resistance, hyperglycemia, hypertension, and dyslipidemia, and reduce the risk of cardiovascular disease. If weight loss is not achieved, specific therapies should be targeted against the different components of the syndrome for each individual patient.

As macrovascular (cardiovascular) disease is the major cause of morbidity and mortality, and as these complications are established well before development of type 2 diabetes, early aggressive treatment aimed at reduction of visceral adiposity, glucose lowering, attention to blood pressure, dyslipidemia and prothrombotic state are essential. As the common soil hypothesis between glycemia, hypertension, dyslipidemia and atherosclerosis (as occurs in the metabolic syndrome) is inflammation, early aggressive treatment with insulin sensitizers, statins, tissue-specific ACE inhibitors and aspirin favors these agents as specifically anti-inflammatory.

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CME Questions

68. According to ATP (Adult Treatment Panel)-III guidelines, which of the following is a characteristic of the metabolic syndrome?
    a. Men with waist circumference > 35 inches
    b. Triglycerides > 200 mg/dL
    c. Men with HDL < 35 mg/dL
    d. Blood pressure > 140/90
    e. Fasting glucose > 110 mg/dL

69. One of the mechanisms explaining the insulin resistance resulting from visceral obesity is:
    a. amino acids.
    b. free fatty acids.
    c. cortisol.
    d. growth hormone.
    e. epinephrine.

70. The dyslipidemia characteristic of syndrome X consists of:
    a. increased triglycerides, normal HDL and increased large, fluffy LDL.
    b. normal triglycerides, decreased HDL and increased small, dense LDL.
    c. increased triglycerides, decreased HDL and increased large, fluffy LDL.
    d. increased triglycerides, decreased HDL and increased small, dense LDL.
    e. normal triglycerides, normal HDL and increased small, dense LDL.

71. The impaired hemostasis in syndrome X is due to which one of the following?
    a. Increased platelet count
    b. Low levels of tPA
    c. High levels of PAI-1
    d. Increased coagulation factors VIII and IX
    e. Leptin

72. In the Diabetes Prevention Program, a 7% weight loss led to ___% reduction in the incidence of diabetes?
    a. 12
    b. 24
    c. 33
    d. 47
    e. 58

73. In the HOPE trial, ramipril reduced the risk of new cases of diabetes by:
    a. 12%.
    b. 23%.
    c. 34%
    d. 45%.

In Future Issues:

An Overview of the Science and Practice of Humor—Neil Shulman, MD, and Zoe Haugo, BA