Metabolic Syndrome: Overview and Current Guidelines

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TAKE HOME POINTS

- Metabolic syndrome is a cluster of risk factors for cardiovascular disease (CVD) that includes abdominal obesity, dyslipidemia, elevated blood pressure, and impaired glucose tolerance.
- CVD is considered the principal clinical end point of the metabolic syndrome, while type 2 diabetes mellitus is considered another important sequelae.
- The principal determinant of the syndrome is obesity, particularly visceral/abdominal obesity.
- Lifestyle interventions with intensive dietary modifications and increased physical activity are first-line therapy.
- Drug therapies are recommended following lifestyle modification in patients with a CVD risk greater than 20% or in those with another indication for drug therapy targeting specific risk factors.

The cluster of risk factors for atherosclerosis that constitute the metabolic syndrome was first recognized in 1983. In 1988, Reaven introduced the term syndrome X to highlight insulin resistance as a common denominator for the dyslipidemia, elevated blood pressure, and impaired glucose tolerance in the context of abdominal obesity that characterize this syndrome. Other notable features of the syndrome include a proinflammatory state, microalbuminuria, and hypercoagulability. Although other terms have been used to describe this cluster of risk factors, metabolic syndrome is now the accepted term.

Up to 50 million people in the United States are believed to have the metabolic syndrome and are thus at increased risk of developing atherosclerotic disease. Because of this high prevalence and in order to increase awareness of the syndrome among practicing physicians, several expert bodies (eg, the World Health Organization [WHO] and the American Association of Clinical Endocrinologists [AACE]) have published diagnostic criteria for the metabolic syndrome. The criteria developed in the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) are the most widely used in US clinical practice.

The purpose of this article, the first in a series on the metabolic syndrome, is to provide the reader with an understanding of how to recognize patients with and at risk for developing the metabolic syndrome and to review current strategies for treatment of these individuals. We present a typical case of a patient presenting with the metabolic syndrome to illustrate several key issues in the management of this condition.

COMPONENTS OF METABOLIC SYNDROME AND CARDIOVASCULAR RISK

ATP III considers risk of atherosclerotic disease according to underlying, major, and emerging risk factors. Underlying risk factors for coronary heart disease (CHD) include (abdominal) obesity, an atherogenic diet, and physical inactivity. Major risk factors for CHD include aging, tobacco use, increased serum concentration of low-density lipoprotein (LDL) cholesterol, low serum concentration of high-density lipoprotein (HDL) cholesterol, high blood pressure, and a history of premature CHD in a first-degree relative (male, < 55 years; female, < 65 years). Emerging risk factors include hypertriglyceridemia, small, dense LDL particles, insulin resistance with glucose intolerance, inflammation, and a prothrombotic state.
These risk factors are comprised in the 6 central components of the metabolic syndrome ATP III identified as relevant to clinical development of CHD:

1. **Abdominal obesity.** This is characterized clinically as increased waist circumference; abdominal or visceral obesity is the form of obesity most strongly associated with metabolic syndrome and risk of CHD.

2. **Atherogenic dyslipidemia.** This is characterized in routine lipoprotein analysis by raised triglycerides and low concentrations of HDL cholesterol. Further detailed analysis often reveals other abnormalities, including small, dense LDL particles, small HDL particles, increased levels of apolipoprotein B, and increased remnant lipoproteins, all of which have independent atherogenic potential.

3. **Increased blood pressure.** Obesity is an important predisposing factor for hypertension, particularly in those with insulin resistance. Although hypertension is multifactorial in origin and other causes should be considered in patients with metabolic syndrome, increased blood pressure should be considered as a principal component of this syndrome.

4. **Insulin resistance with glucose intolerance.** The majority of patients with metabolic syndrome exhibit evidence of insulin resistance, typically characterized by glucose intolerance. Despite the strong association between insulin resistance, glucose intolerance, and other metabolic risk factors, mechanisms underlying the link to CHD risk factors are uncertain, and the associated constellation of risk factors may drive atherogenesis to a greater extent than impaired insulin signaling and glucose intolerance per se. When glucose intolerance evolves into hyperglycemia sufficient to diagnose type 2 diabetes mellitus, this is considered to be a major, independent CHD risk factor.

5. **Proinflammatory state.** Low-grade systemic inflammation, characterized clinically by elevated levels of C-reactive protein (CRP), is commonly observed in the metabolic syndrome. Release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL) -6, and leptin from visceral adipocytes appears to be an important underlying mechanism. Multiple mechanisms seemingly underlie elevations of CRP. One cause is obesity, as excess adipose tissue releases inflammatory cytokines that may elicit increased CRP release from the liver.

6. **Prothrombotic state.** Increased plasma levels of plasminogen activator inhibitor-1 and fibrinogen are commonly associated with the metabolic syndrome. Increased levels of cytokines promote the generation of fibrinogen, which like CRP is an acute phase protein. Thus, a common metabolic pathway may explain the prothrombotic and proinflammatory changes observed in the metabolic syndrome.

The Framingham study and many other subsequent studies have shown that most individuals who develop cardiovascular disease (CVD) have multiple risk factors for atherosclerosis. Many of those at risk have the obesity-associated proatherogenic cluster of risk factors described above. Insulin resistance is a central feature in such individuals, which has led to use of the term “insulin resistance syndrome(s).” However, ATP III and other expert bodies have used the term “metabolic syndrome” to describe the cluster of risk factors in such individuals to avoid the implication that insulin resistance is the primary or only cause of risk factors that drive clinical events in this condition.

**CASE PRESENTATION**

A 45-year-old man is referred by his family physician for further evaluation of hypertension. The patient works as a truck driver. He reports that he currently feels well. His father developed type 2 diabetes mellitus at age 60 years and died at age 70 years of a myocardial infarction. His mother died of bowel cancer in her 70s. He has a 40-year-old sister who is well. He lives alone, drives for 8 to 10 hours per day, drinks 2 to 3 beers per day after work, and smokes between 10 and 15 cigarettes per day. He is not currently taking any medications and does not use recreational drugs.

He has a good appetite and typically eats large quantities of fried food in diners while driving. He gets minimal exercise. There is no history of headache, visual disturbance, or neurologic disturbance. He does not complain of sweatiness and intolerance of heat or cold. He does not bruise easily and has not noticed skin changes or other changes in appearance. He has not experienced chest pain, breathlessness, palpitations, or ankle swelling. There are no symptoms attributable to the respiratory, gastrointestinal or urinary system.

On examination, height is 6 ft 1 in and weight is 240 lb (body mass index [BMI] > 30). The patient’s waist circumference is 44 in. There is no evidence of jaundice, anemia, cyanosis, or lymphadenopathy. Hands, eyes, neck and mucus membranes are normal. There are no skin striae. Funduscopic examination is normal. Jugular venous pressure is not elevated. His pulse rate is 72 bpm and is regular with normal character. Peripheral pulses are all present and of normal quality. There is no
radio-radial or radio-femoral pulse delay and no vascular bruits. Blood pressure is 150/95 mm Hg with no postural drop. Precordial palpation reveals a normal quality left ventricular impulse without displacement of the point of maximal impulse. Cardiac auscultation is normal with both heart sounds present and no added sounds or murmurs. His chest is clear. Other than marked obesity, abdominal examination is unremarkable with no evidence of organomegaly, mass, aortic enlargement, or renal arterial bruits. There is no neurologic deficit.

- **What further evaluation is appropriate in this patient?**

This patient is clinically obese with marked abdominal obesity. There are no other symptoms or signs suggesting a primary cause for his hypertension. Routine evaluation would include complete blood count; measurement of urea; creatinine and electrolytes; assessment of fasting glucose; a lipid profile; 12-lead electrocardiogram (ECG); and dipstick testing of his urine. The need for further detailed investigations such as renal or cardiac imaging and endocrine evaluation are usually indicated only in the presence of abnormal findings in the clinical assessment or routine laboratory tests.

**CASE PRESENTATION: LABORATORY TEST RESULTS**

The complete blood count, concentrations of sodium and potassium, urea, and creatinine, urinalysis results, and ECG findings are all within normal limits. Fasting lipid profile reveals the following: total cholesterol, 230 mg/dL; triglycerides, 200 mg/dL; HDL cholesterol, 35 mg/dL; and LDL cholesterol, 155 mg/dL. Fasting glucose is 118 mg/dL. The physician makes a diagnosis of metabolic syndrome.

- **How is metabolic syndrome diagnosed?**

**CRITERIA FOR CLINICAL DIAGNOSIS OF METABOLIC SYNDROME**

Metabolic syndrome is diagnosed based on the presence of a combination of measures of body habitus, blood pressure, lipid profile, and glucose intolerance. CVD is considered the principal clinical end point of the metabolic syndrome, while type 2 diabetes mellitus is considered another important sequela.

**ATP Criteria**

Metabolic syndrome can be diagnosed if 3 or more of 5 ATP III criteria (Table) are fulfilled. Obesity, in particular abdominal obesity reflecting accumulation of visceral adipose tissue, underpins the development of the metabolic syndrome. The inclusion of waist circumference (>40 in for men; and >35 in for women) is a simple and reliable clinical test that identifies individuals with a high likelihood of developing associated metabolic abnormalities and increased CVD risk. Diagnostic thresholds for reduced levels of HDL cholesterol and elevated triglycerides, blood pressure, and plasma glucose are lower than usual diagnostic criteria required to identify these component elements as individual risk factors. The threshold is lower because the priority in diagnosis of metabolic syndrome is to identify individuals with this malign cluster of multiple “marginal” factors that individually contribute only a small incremental risk but interact synergistically to increase global cardiovascular risk substantially. Unlike other diagnostic criteria for metabolic syndrome, biochemical evidence of insulin resistance is not required by ATP III, although most individuals diagnosed by these criteria are insulin resistant.

**WHO Criteria**

A WHO consultation group proposed a working definition of the metabolic syndrome in their 1998 classification of diabetes mellitus, which was finalized in 1999. Unlike in the ATP III criteria, demonstration of insulin resistance (defined as either type 2 diabetes; impaired fasting glucose; impaired glucose tolerance; or normal fasting glucose but with a glucose uptake below the lowest quartile of the population under hyperinsulinemic, euglycemic conditions) is necessary for

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**Table. ATP III Clinical Identification of the Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (given as waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt; 102 cm (&gt; 40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt; 88 cm (&gt; 35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥ 130/≥ 85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥ 110 mg/dL</td>
</tr>
</tbody>
</table>

diagnosis of the metabolic syndrome by WHO criteria. Presence of 2 other risk factors is also required for diagnosis of the metabolic syndrome, including taking antihypertensive medication and/or presence of high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic); plasma triglycerides ≥ 150 mg/dL; HDL cholesterol < 35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) ratio > 0.9 in men and > 0.85 in women; and/or urinary albumin excretion rate ≥ 20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g.

AACE Criteria

Further clinical criteria for the “insulin resistance syndrome” were proposed by the AACE. However, in this set of criteria a defined number of risk factors is not required, and diagnosis is left to clinical judgment. Criteria are similar to those comprising the ATP III and WHO criteria and include the following: BMI ≥ 25 kg/m²; triglycerides ≥ 150 mg/dL; HDL cholesterol < 40 mg/dL (men), < 50 mg/dL (women); blood pressure ≥ 135/≥ 85; 2-hour postglucose challenge > 140 mg/dL; fasting glucose between 110 and 126 mg/dL; family history of type 2 diabetes, hypertension, or CVD; sedentary lifestyle; advancing age; ethnic groups having high risk for type 2 diabetes or CVD; and polycystic ovary syndrome.

The ATP III criteria are the most easily applied in clinical practice as they utilize simple and practical tests and do not require formal testing of glucose tolerance or urine collection. Thus, the diagnostic costs are minimized without significant loss of power to predict CVD risk. A strength of the WHO and ACCE guidelines is that impaired glucose tolerance is a good predictor of the risk of developing type 2 diabetes.

• How does metabolic syndrome develop?

PATHOGENESIS

The principal determinant of the metabolic syndrome is obesity, particularly visceral/abdominal obesity. Insulin resistance and other metabolic correlates also mediate certain processes that characterize metabolic syndrome. Increasing age, a sedentary lifestyle, and certain endocrine conditions contribute as well.

Abdominal Obesity

Over recent years there has been a steady and dramatic rise in the prevalence of obesity in all demographic groups in the United States. According to the National Health and Nutrition Evaluation Surveys, the age-adjusted prevalence of obesity rose from 15% to 30% over the last 2 decades of the last century. Just under 40 million US adults are clinically obese (BMI ≥ 30 kg/m²), and over 60% are overweight or obese (BMI ≥ 25 kg/m²). Although there are multiple causes for obesity, including genetic, environmental, and psychological causes, the “obesity epidemic” is principally driven by increased consumption of cheap, calorie-dense food and reduced physical activity. Accumulation of excessive visceral adipose tissue (in the presence or absence of obesity) is associated with insulin resistance, hyperinsulinemia, and glucose intolerance. In addition, excess abdominal obesity is associated with a potentially atherogenic lipoprotein profile, which includes (1) hypertriglyceridemia; (2) elevated apolipoprotein B levels; (3) an increased proportion of small, dense LDL particles; and (4) reduced HDL cholesterol concentrations. Visceral fat releases nonesterified fatty acids that overload muscle and liver with lipids, enhancing insulin resistance. Levels of adiponectin are reduced in obesity and are associated with reduced insulin sensitivity and an adverse risk factor profile.

Insulin Resistance

Insulin resistance typically increases with increasing body fat composition and is an important predisposing mechanism for development of the metabolic syndrome. Most obese and many overweight individuals have reduced insulin sensitivity and evidence of postprandial hyperinsulinemia. However, a range of resistance to the effects of insulin is observed within these population subgroups. Certain ethnic groups, particularly South Asians, have an increased predisposition to exhibit insulin resistance and develop metabolic syndrome, even with BMI in the normal range. This variability implies an important genetic contribution towards insulin resistance and its common metabolic correlates. Indeed, these individuals are typically more susceptible to the adverse metabolic consequences of increasing abdominal obesity, making it difficult to distinguish the relative importance of obesity and insulin resistance in the development of metabolic syndrome.

At physiological concentrations, insulin has vasodilator and anti-inflammatory actions that are mediated in part through the release of nitric oxide (NO) and inhibition of the transcription factor nuclear factor-κB (NF-κB). Additionally, the PI3 kinase pathway mediates the vasodilator and anti-inflammatory effects of insulin via activation of NO synthase. The MAP kinase pathway promotes the mitogenic effects that lead to cell growth and proliferation. Insulin resistance is characterized by impaired activation of the PI3 kinase pathway, combined with preserved signaling via the MAP
kinase pathway, which shifts the balance in favor of the atherogenic actions of insulin, probably by differential signal amplification. Insulin resistance in muscle promotes glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver as well as by diverting excess free fatty acids to the liver. In parallel, insulin resistance in adipose tissue is associated with decreased uptake and increased release of free fatty acids, which are converted in the liver to triglyceride-rich very-low-density lipoprotein (VLDL) particles. The resulting hypertriglyceridemia drives the dyslipidemic triad by promoting the synthesis of small, easily oxidizable dense LDL and enhanced clearance of HDL, which is believed to be highly atherogenic. Low HDL may also be a consequence of decreased ATP-binding cassette transporter 1 expression, which mediates reverse cholesterol transport in peripheral cells.

Inflammation and Adipocytokines

Adipose tissue is a rich source of cytokines, including TNF-α and IL-6, adiponectin, and resistin,\(^\text{11}\) which are collectively referred to as adipocytokines. Adipocytokines contribute to insulin resistance via putative endocrine, paracrine, and/or autocrine actions, which may also mediate the link between abdominal obesity and the metabolic syndrome. Relevant functions of TNF-α include modulation of lipid metabolism; reduction of tyrosine kinase activity in insulin receptors, inhibiting insulin signaling and sensitivity; downregulation of glucose transporter proteins; promotion of pancreatic beta-cell dysfunction; and impairment of endothelial function. Indeed, circulating and tissue levels of TNF-α are typically increased in association with hyperinsulinemia in obesity, with this relationship reversing after weight reduction. Approximately 30% of circulating IL-6 originates from adipose tissue in healthy individuals. Waist circumference correlates strongly with CRP and fibrinogen levels, explaining between 15% and 42% of the total variability for CRP levels, an association that is stronger in women.\(^\text{12}\) Levels of adiponectin, a protein with potential anti-atherosclerotic properties, are lower in obese and diabetic individuals and correlate inversely with the degree of insulin resistance, hyperinsulinemia, and CRP.\(^\text{13–15}\)

Together these cytokines induce an inflammatory response in the vessel wall, with circulating levels of CRP and other inflammatory markers serving as potential markers of an adverse cardiovascular prognosis and increased risk of developing type 2 diabetes in patients with and without the metabolic syndrome. Thus, the pathophysiology of insulin resistance, metabolic syndrome, and atherosclerotic cardiovascular events may have a common inflammatory origin (Figure 1).

- **What are the clinical consequences of the metabolic syndrome?**

**CLINICAL SEQUELAE**

The critical clinical sequelae of the metabolic syndrome are type 2 diabetes mellitus, hypertension, dyslipidemia, and atherosclerotic vascular disease, particularly coronary artery disease.

**Diabetes Mellitus**

Most patients who develop type 2 diabetes mellitus are obese, predominantly with abdominal obesity, and have either relative insulin deficiency or insulin resistance with an insulin secretory defect. Chronic hyperglycemia itself can inhibit expression of the insulin gene and thus impair glucose-stimulated insulin secretion, which is also inhibited by increased free fatty acid levels resulting from increased visceral adipose tissue lipolysis. Clinical manifestation of diabetes in these individuals may not occur for many years after development of glucose intolerance and metabolic syndrome abnormalities. Thus, the development of clinical macrovascular and microvascular disease is promoted long before the development of overt diabetes,\(^\text{16}\) with approximately 50% of type 2 diabetics already having some form of macrovascular or microvascular disease at the time of diagnosis of diabetes. Individuals with diabetes have a greatly increased risk of cardiovascular events, and those events are more likely to be fatal compared with events in nondiabetics.\(^\text{17}\) The ATP III guidelines recognize this increased risk and state that diabetes is a CHD risk equivalent and that preventive measures should be as aggressive in patients with diabetes as in those with established clinical atherosclerotic disease.

**Hypertension**

Blood pressure is particularly sensitive to sodium intake in obese patients. Insulin also has an antinatriuretic effect and promotes activation of the sympathetic nervous system. Vascular inflammation and impaired endothelium-dependent vasomotor function may cause vasoconstriction, increased cardiac output, and enhanced renal sodium absorption and thus may contribute to the development of hypertension in patients with metabolic syndrome.\(^\text{18}\) Of note, up to 50% of patients with hypertension have evidence of insulin resistance and peripheral tissue glucose intolerance,\(^\text{19}\) again suggestive of a common etiology.
Dyslipidemia

The lipid profile associated with metabolic syndrome is characterized by increased apolipoprotein B–containing lipoproteins, plasma triglyceride, and intermediate-density lipoprotein (IDL) levels as well as reduced HDL cholesterol and an increased proportion of small, dense, cholesteryl ester–depleted LDL particles with relatively normal or only mildly elevated LDL cholesterol concentration. This profile is also seen in patients with type 2 diabetes mellitus, and more commonly in patients without diabetes but with insulin resistance. Insulin resistant visceral adipocytes are more sensitive to the lipolytic effects of glucocorticoids and catecholamines, which increase release of free fatty acids into the portal system, promoting hepatic synthesis of triglycerides and VLDL. Lipoprotein lipase in peripheral tissues hydrolyses VLDL to form IDL and remnant particles. Triglyceride-rich LDL particles are also generated and are further modified by lipoprotein lipase to produce small, dense LDL particles that promote atherogenesis by various mechanisms, including increased susceptibility to oxidation, reduced hepatic-receptor–mediated clearance, increased scavenger-receptor–mediated uptake, and greater arterial wall retention. Furthermore, insulin resistance leads to increased hepatic lipase activity, which hydrolyzes and reduces levels of antiatherogenic HDL cholesterol.

Other factors associated with metabolic syndrome...
Lifestyle Measures

The majority of patients with metabolic syndrome are obese or overweight and should lose weight by increasing physical activity and reducing calorie intake. A realistic goal is a 7% to 10% reduction in body weight after 6 to 12 months.1,2,4 ATP III recommends a generally healthy diet, including low intake of refined and simple sugars, cholesterol, saturated fats, and trans fatty acids and increased consumption of fruits, vegetables, and whole grains. Experts have recommended that reduced-energy diets (500–1000 Kcal/day reduction) should be favored over more extreme diets, including low-calorie and high-fat/low-carbohydrate diets, as they appear to be more effective in achieving persistent weight reduction and maintenance of healthy weight loss over the long-term, particularly when regular physical exercise is also included in the weight-loss program.1,24 The benefits of sensible eating habits (regular meals including breakfast, reading labels, meal planning), psychosocial stress management, and social support should be emphasized, and specialist help should be offered where appropriate.

Over two thirds of the US population have a sedentary lifestyle, which contributes to an increased risk of developing metabolic syndrome and its sequelae as well as other chronic diseases. Current American Heart Association physical activity guidelines recommend a daily minimum of 30 minutes of moderate-intensity physical activity.25 The emphasis should be on practical and moderate regimens that are more likely to be achieved by patients. Exercise modalities such as brisk walking or cycling, including several short bouts of more vigorous physical activity, avoidance of common sedentary activities such as television watching and computer gaming, walking or cycling rather than driving, and using stairs rather than elevators where possible, making exercise part of a daily routine. Recording/monitoring activity may help to increase activity levels and improve compliance. Increasing the total amount of exercise performed, whether high or low intensity, appears to confer further benefit.26

Specific Management of Metabolic Risk Factors

The aim of treating metabolic syndrome is to reduce the risk of clinical CVD and to reduce progression to type 2 diabetes mellitus. After implementation of therapeutic lifestyle changes, the multiple residual pathologic processes occurring in metabolic syndrome must be addressed. Clearly, implementation of drug therapy, often with multiple agents, may be required in many patients in order to achieve national targets:
blood pressure < 125/75 mm Hg; LDL cholesterol concentration < 100 mg/dL; triglyceride level < 150 mg/dL; and HDL cholesterol concentration > 40 mg/dL in men and > 50 mg/dL in women. Specific drug classes that are necessary in treating metabolic syndrome include statins, ACE inhibitors or angiotensin receptor blockers (ARBs), fibrates, and thiazolidinediones. N-3 fatty acids may also have an important role.

Elevated blood pressure. In the ATP III classification, a blood pressure level of ≥ 130/≥ 85 mm Hg is included as one of the criteria for diagnosis of metabolic syndrome. This slightly lower blood pressure threshold recognizes the important contribution of even small increases in blood pressure above 120/80 mm Hg to the pathogenesis of arterial disease, particularly in the presence of multiple risk factors. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) also recognized this issue by introducing the concept of “prehypertension” (120–139/80–89 mm Hg).

27 Individuals with prehypertension require more careful blood pressure surveillance and attention to levels of other risk factors. Patients with metabolic syndrome who fulfill the diagnostic criteria for hypertension (blood pressure ≥ 140/≥ 90 mm Hg, and ≥ 130/≥ 80 mm Hg in patients with diabetes) should be treated according to JNC 7 recommendations. JNC 7 recognizes the particular importance of therapeutic lifestyle changes, including weight loss, physical exercise, implementation of the low-sodium DASH diet, and limitation of alcohol consumption. If blood pressure remains uncontrolled, pharmacologic therapy should be implemented. Some recent trials with ACE inhibitors and ARBs have shown a reduction in the development of type 2 diabetes, making use of these agents more compelling in metabolic syndrome.28,29

Insulin resistance and glucose intolerance. Resistance to the effects of insulin with associated glucose intolerance and elevated glucose levels is a principal feature of metabolic syndrome. Treatment of insulin resistance can improve not only glucose tolerance but also the associated dyslipidemia and other associated metabolic abnormalities. A low-calorie diet that is low in refined carbohydrates and saturated fats together with a sensible exercise program should be the mainstay of treatment of insulin resistance. Drugs that enhance insulin sensitivity, such as metformin and the thiazolidinediones (eg, rosiglitazone and pioglitazone, which are peroxisome proliferator activated receptor γ agonists), have the potential to delay the onset of type 2 diabetes and improve the metabolic profile, and thus reduce the risk of atherosclerosis. In the Finnish Dia-
Diabetes Prevention Study, which included 522 participants with metabolic syndrome, intensive therapeutic lifestyle changes reduced the risk of type 2 diabetes mellitus by 58% compared to controls.\textsuperscript{30} In the Diabetes Prevention Program, metformin 850 mg twice daily reduced the progression from impaired glucose tolerance to type 2 diabetes mellitus by 31%, whereas intensive therapeutic lifestyle changes reduced this risk by 58% compared to placebo.\textsuperscript{31} Despite promising initial results, insulin sensitizers have not been shown to reduce the risk of cardiovascular events, and until results from ongoing studies persuade us otherwise, these agents cannot at present be recommended for preventive therapy.

**Lipid abnormalities.** Lifestyle modification with diet and exercise remains the first-line therapy of lipid abnormalities in metabolic syndrome (Figure 3). Although elevated LDL cholesterol is not a defining feature of the abnormal lipid profile in metabolic syndrome, this and other apolipoprotein B–containing lipoproteins are highly atherogenic. Intensity of LDL lowering should be guided by the cardiovascular risk score; in those at high risk (\geq 20% as determined by presence of CHD or CHD risk equivalents or Framingham risk score), the LDL target is < 100 mg/dL; others with metabolic syndrome should be considered at intermediate risk (10%–20% or 2 or more risk factors) and treated to a target LDL < 130 mg/dL.\textsuperscript{1} Furthermore, patients with high triglyceride levels (> 200 mg/dL, very common in metabolic syndrome) also have increased levels of atherogenic remnant particles (eg, VLDL and IDL cholesterol) that are not addressed by focusing solely on LDL cholesterol. Therefore, ATP III introduced the concept of non-HDL cholesterol, which incorporates all the potentially atherogenic lipoprotein subfractions. Non-HDL cholesterol targets are 30 mg/dL greater than those for LDL cholesterol and should be used when triglyceride levels exceed 200 mg/dL.

In patients who do not achieve LDL cholesterol targets with therapeutic lifestyle changes, statin therapy should be initiated. Statin therapy improved survival and reduced cardiac events and strokes in several large, randomized placebo-controlled clinical trials.\textsuperscript{32–34} The Collaborative Atorvastatin Diabetes Study and subgroup analyses in the Heart Protection Study demonstrated added benefits in diabetics, even when cholesterol levels were not significantly elevated.\textsuperscript{32,33} Statins reduce all apolipoprotein B–containing lipoproteins and will usually be able to achieve ATP III targets for both LDL and non-HDL cholesterol in patients with metabolic syndrome.

Fibric acid derivatives improve most components of the atherogenic lipid profile in metabolic syndrome, particularly the low HDL level, high triglycerides, and small, dense LDL particles, and their use should be considered in patients at high risk (\geq 20%) or with CHD. High-dose niacin can also improve HDL and triglyceride levels with similar efficacy to fibrates but can also impair glucose tolerance and increase uric acid levels and therefore should be used with caution in patients with metabolic syndrome.

**Prothrombotic and proinflammatory state.** In metabolic syndrome, levels of proinflammatory cytokines (eg, IL-6 and TNF–\alpha) and acute phase reactants (eg,
CRP and fibrinogen) are typically increased. Plasminogen activator inhibitor-1 levels are also typically elevated, and tissue plasminogen activator levels are reduced, contributing to the characteristic proinflammatory and prothrombotic milieu of metabolic syndrome. The clinical value of measuring these factors is controversial and is an evolving area of interest in preventive cardiovascular medicine. Although measurement of fibrinogen and other coagulation factors is not currently recommended in routine practice, the American Heart Association recommends routine aspirin prophylaxis in patients with a 10-year coronary risk of 10% or more.35,36

CASE PRESENTATION: INITIATION OF THERAPY

Using the ATP III online risk calculator (available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp?user=pub), the physician calculates the patient’s 10-year cardiovascular risk to be 20%, which can be considered a CHD risk equivalent. However, the patient does not have clinical atherosclerotic disease, and if the risk is recalculated omitting smoking, his 10-year risk would be estimated at 6%. The physician therefore advises aggressive lifestyle intervention to include diet, exercise, and smoking cessation. The patient receives counseling from a nurse practitioner specializing in prevention of vascular disease to improve his understanding of his risk status, with a focus on the contribution of and importance of treatment of the multiple risk factors acting synergistically to increase his risk of heart attack and stroke. He is advised to start a program of moderate exercise for 10 to 15 minutes 3 times per week, with the aim of increasing the duration and frequency to at least 30 minutes per day at least 5 times per week as his fitness level improves. He is advised to follow a therapeutic lifestyle changes diet (low in saturated fat and cholesterol and high in fruit, vegetables, fiber and complex carbohydrates) as recommended in the ATP III report. A consult is requested from the local smoking cessation service, who prescribe a course of nicotine replacement therapy patches, supported by counseling.

The patient is reviewed after 6 weeks. He has not smoked for 1 month and is reasonably but not fully compliant with his diet and exercise regimen. He weighs 234 lb, his blood pressure is 146/88 mm Hg, and his fasting glucose level is 116 mg/dL. Fasting lipid profile is as follows: total cholesterol, 220 mg/dL; triglycerides, 180 mg/dL; HDL, 37 mg/dL; and LDL cholesterol, 147 mg/dL. The patient is estimated to have a 10-year risk of 5%.

It is important to note that the patient’s global risk score places him in the “low risk” category, despite the presence of 3 additional major risk factors according to ATP III criteria (hypertension, low HDL, and male ≥ 45 years old). This is largely explained by his relatively young age, which has a major influence on the 10-year risk estimate. Nonetheless, he is at high relative risk for his age-group, and in view of these additional risk factors would be a potential candidate for lipid-lowering drug therapy to reduce his LDL cholesterol level to a target of 130 mg/dL or less. However, he has made some progress with therapeutic lifestyle changes, and the physician elects to continue with these measures at this juncture. The physician plans to reassess progress at 3 and 6 months after the initial consultation, with consideration of starting pharmacologic therapy with a statin and/or angiotensin-converting-enzyme (ACE) inhibitor if LDL and/or systolic blood pressure remain elevated. Lifestyle recommendations will continue to be reinforced during follow-up, and no specific pharmacologic therapy will be recommended to treat his low HDL or insulin resistance in the near future.

SUMMARY

Metabolic syndrome is a cluster of risk factors for atherosclerosis, including abdominal obesity, elevated blood pressure, dyslipidemia, and glucose intolerance. Metabolic syndrome increases the risk of type 2 diabetes and atherosclerotic cardiovascular disease. Development of metabolic syndrome is driven predominantly by abdominal obesity with increasing age and genetic factors (eg, South Asian and Hispanic ethnicity also contribute). Therapeutic lifestyle interventions focusing on dietary modification and increased physical activity to maximize weight loss are the mainstay of clinical management of metabolic syndrome. Drug therapy should be considered to achieve therapeutic goals for lipids, particularly low-density lipoprotein cholesterol, and blood pressure in patients with metabolic syndrome who do not achieve targets with lifestyle interventions. Low-dose aspirin should be considered in patients with a 10-year coronary risk of 10% or more. Treatment of insulin resistance with metformin or thiazolidinediones is not currently recommended in the absence of type 2 diabetes.

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