Diagnosis and Management of the Metabolic Syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement

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The metabolic syndrome has received increased attention in the past few years. This statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) is intended to provide up-to-date guidance for professionals on the diagnosis and management of the metabolic syndrome in adults.

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—metabolic risk factors—that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD). Patients with the metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus. Another set of conditions, the underlying risk factors, give rise to the metabolic risk factors. In the past few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients who manifest the multiple components of the metabolic syndrome. These criteria also include a combination of both underlying and metabolic risk factors.

The most widely recognized of the metabolic risk factors are atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose. Individuals with these characteristics commonly manifest a prothrombotic state and a proinflammatory state as well. Atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apolipoprotein B (apoB), increased small LDL particles, and a reduced level of HDL cholesterol (HDL-C). The metabolic syndrome is commonly referred to as if it were a discrete entity with a single cause. Available data suggest that it truly is a syndrome, ie, a grouping of ASCVD risk factors, but one that probably has more than one cause. Regardless of cause, the syndrome identifies individuals at an elevated risk for ASCVD. The magnitude of the increased risk can vary according to which components of the syndrome are present plus the other, non–metabolic syndrome risk factors in a particular person.

Underlying Risk Factors and Metabolic Syndrome

The predominant underlying risk factors for the syndrome appear to be abdominal obesity and insulin resistance; other associated conditions can be physical inactivity, aging, and hormonal imbalance. An atherogenic diet (eg, a diet rich in saturated fat and cholesterol) can enhance risk for developing cardiovascular disease in people with the syndrome, although this diet is not listed specifically as an underlying risk factor for the condition. One theory holds that insulin resistance is the essential cause of the metabolic syndrome. There is no doubt that insulin resistance predisposes to the hyperglycemia of type 2 diabetes mellitus. Multiple metabolic pathways have also been proposed to link insulin resistance and compensatory hyperinsulinemia to the other metabolic risk factors. It is recognized that some people who are not obese by traditional measures nevertheless are insulin resistant and have abnormal levels of metabolic risk factors. Examples are seen in individuals with 2 diabetic parents or 1 parent and a first- or second-degree relative; the same is true for many individuals of South Asian ethnicity. Although insulin-resistant individuals need not be clinically obese, they nevertheless commonly have an abnormal fat distribution that is characterized by predominant upper body fat. Upper-body obesity correlates with insulin resistance and other metabolic risk factors.

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on August 10, 2005, and by the National Heart, Lung, and Blood Institute in July 2005. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0336. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or E-mail kgray@lww.com. To complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

The Executive Summary of this Statement will also appear in the December 2005 issues of Critical Pathways in Cardiology and Cardiology in Review, the issue of Current Opinion in Cardiology, and the issue of Journal of Cardiovascular Nursing.

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strongly with insulin resistance. Excess upper body fat can accumulate either intraperitoneally (visceral fat) or subcutaneously. Many investigators claim that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment; other workers find that excess subcutaneous abdominal (or truncal) fat also carries a significant association with insulin resistance. Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper-body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity. An interesting feature of upper-body obesity is an unusually high release of nonesterified fatty acids from adipose tissue; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid metabolism in muscle and liver seemingly predisposes to insulin resistance and dyslipidemia.

According to many experts, the increasing burden of obesity in the United States is the driving force behind the rising prevalence of the metabolic syndrome. Abnormalities in adipose tissue metabolism may be the crux of the issue. Adipose tissue in obese people is seemingly hypermetabolic; in addition, the adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance and/or modify hepatic metabolism; in addition, the adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance and/or modify hepatic metabolism. Notable are many South Asians who appear to be inherently insulin resistant, but even people with little or no inherent insulin resistance can develop the metabolic syndrome if they accumulate marked abdominal obesity. Moreover, the population of the United States varies considerably in degree of insulin resistance; those having more inherent insulin resistance can develop the metabolic syndrome with only moderate excess in abdominal fat, but even people with little or no inherent insulin resistance can develop the metabolic syndrome if they accumulate marked abdominal obesity. These findings support the idea that body fat distribution, particularly excess abdominal fat, plays an important role in the etiology of the syndrome.

Recently, this syndrome has been noted to be associated with a state of chronic, low-grade inflammation. Some researchers speculate that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both adipose tissue and muscle. In the presence of obesity, adipose tissue indeed produces cytokines in excess, whereas output of adiponectin is diminished; these responses appear to heighten the connection between obesity and inflammation. Interestingly, insulin-resistant people manifest evidence of low-grade inflammation even without an increase of total body fat. Finally, considerable individual and ethnic variation exists in the clinical pattern of metabolic risk factors in obese/insulin-resistant subjects. It is likely that the expression of each metabolic risk factor falls partially under its own genetic control, which influences the response to different environmental exposures. For example, a variety of polymorphisms in genes affecting lipoprotein metabolism are associated with worsening of dyslipidemia in obese people. Similarly, a genetic predisposition to defective insulin secretion when combined with insulin resistance can raise plasma glucose to abnormal levels.

Although the metabolic syndrome unequivocally predisposes to type 2 diabetes mellitus, many investigators of cardiovascular diseases consider this syndrome to be a multidimensional risk factor for ASCVD. Several recent reports show that the metabolic syndrome is associated with greater risk for cardiovascular disease but once type 2 diabetes mellitus emerges, cardiovascular risk increases even more. Finally, insulin resistance and the metabolic syndrome are associated with a variety of other conditions; some of these are fatty liver, polycystic ovary syndrome, cholesterol gallstones, sleep apnea, lipodystrophies, and protease-inhibitor therapy for HIV. These associations are generating considerable interest in several other fields of medicine.

**Metabolic Risk Factors, ASCVD, and Type 2 Diabetes Mellitus**

The metabolic risk factors consist of those factors that seemingly have a direct effect on atherosclerotic disease. Among these, as stated earlier, atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apoB, increased small LDL particles, and a reduced level of HDL-C. Among triglyceride-rich lipoproteins, remnant lipoproteins almost certainly are the most atherogenic. Many studies further suggest that the smallest particles in the LDL fraction carry the greatest atherogenicity. The atherogenic potential of lipoprotein remnants and small LDL could be confounded in part by their common association with an increased total number of apoB-containing lipoproteins in circulation; this increased number is reflected by an elevation of serum total apoB. Finally, the lipoprotein field widely holds that low levels of HDL are independently atherogenic; multiple mechanisms are implicated to explain this relationship.

Other metabolic risk factors likewise appear individually to be atherogenic. Among these are hypertension, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. Indeed, 3 of the metabolic risk factors—elevated apoB-containing lipoproteins, low HDL-C levels, and hypertension—are well established, major risk factors. Each imparts increased risk even when only marginally abnormal, as often observed in the metabolic syndrome. A growing body of data additionally implicates high circulating levels of prothrombotic factors in the causation of ASCVD events, possibly by predisposing to thrombotic episodes. Many reports also show that the presence of a proinflammatory state, as revealed by increased inflammatory markers, denotes a higher risk for acute cardiovascular syndromes.
TABLE 1. Previous Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

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<tr>
<td>Insulin resistance</td>
<td>IGT, IFG, T2DM, or lowered insulin sensitivity plus any 2 of the following</td>
<td>Plasma insulin &gt;75th percentile or &gt;85 and/or BMI &gt;30 kg/m²</td>
<td>None, but any 3 of the following 5 features</td>
<td>IGT or IFG plus any of the following based on clinical judgment</td>
<td>None</td>
</tr>
<tr>
<td>Body weight</td>
<td>Men: waist-to-hip ratio &gt;0.90; women: waist-to-hip ratio &gt;0.85 and/or BMI &gt;30 kg/m²</td>
<td>WC ≥84 cm in men or ≥80 cm in women</td>
<td>WC ≥102 cm in men or ≥88 cm in women</td>
<td>BMI ≥25 kg/m²</td>
<td>Increased WC (population specific) plus any 2 of the following</td>
</tr>
<tr>
<td>Lipid</td>
<td>TG ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TG ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TG ≥150 mg/dL and/or HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td>TG ≥150 mg/dL and/or HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td>TG ≥150 mg/dL or on TG Rx</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥140/90 mm Hg</td>
<td>≥140/90 mm Hg or on hypertension Rx</td>
<td>≥130/85 mm Hg</td>
<td>≥130/85 mm Hg</td>
<td>≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx</td>
</tr>
<tr>
<td>Glucose</td>
<td>IGT, IFG, or T2DM</td>
<td>IGT or IFG (but not diabetes)</td>
<td>&gt;110 mg/dL (includes diabetes)</td>
<td>IGT or IFG (but not diabetes)</td>
<td>≥100 mg/dL (includes diabetes)</td>
</tr>
<tr>
<td>Other</td>
<td>Microalbuminuria</td>
<td>Other features of insulin resistance</td>
<td></td>
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</table>

T2DM indicates type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; and TG, triglycerides. All other abbreviations as in text.

*Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (eg, 94 to 102 cm [37 to 39 in]). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases.

‡The 2001 definition identified fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L), in accordance with the American Diabetes Association’s updated definition of IGT.63–73

§Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

Finally, a variety of mechanisms to explain how elevated plasma glucose may promote atherosclerosis are postulated.97 Regardless, once type 2 diabetes mellitus compounds the metabolic syndrome, risk for ASCVD increases still more.

**Clinical Diagnosis of Metabolic Syndrome**

Many investigations confirm that multiple cardiovascular risk factors of endogenous origin commonly aggregate in one individual. Although this aggregation was originally observed many years ago,98,99 more recently, several terms have been proposed to describe this clustering: metabolic syndrome,100 syndrome X,101 the “deadly quartet,”102 insulin-resistance syndrome,103,104 and hypertriglyceridemic waist.105 The term **metabolic syndrome** is most commonly used in the cardiovascular field. Although the metabolic syndrome is often referred to as a discrete entity, it is important to recognize, as noted earlier, that it is a syndrome and not a defined uniform entity. No single pathogenesis has been elucidated, nor may one exist. Thus, the syndrome could range from a cluster of unrelated risk factors to a constellation of risk factors linked through a common underlying mechanism. From a clinical standpoint, presence of the metabolic syndrome identifies a person at increased risk for ASCVD and/or type 2 diabetes mellitus. Eventually, a better understanding of the specific cause(s) of the syndrome may provide an improved estimate of risk of developing ASCVD or type 2 diabetes mellitus for individuals. For now, however, the presence of the syndrome is a more general indicator of higher risk for these conditions.

Because of a documented high relative risk for ASCVD events and type 2 diabetes mellitus, the metabolic syndrome undoubtedly carries a relatively high lifetime risk for these disorders even when shorter-term (10-year) risk is in the low-to-moderate range.63–73

In the effort to introduce the metabolic syndrome into clinical practice, several organizations have attempted to formulate simple criteria for its diagnosis (Table 1). The first proposal came in 1998 from a consultation group on the definition of diabetes for the World Health Organization (WHO).106 This group emphasized insulin resistance as the major underlying risk factor and required evidence of insulin resistance for diagnosis. This followed on the widely held belief that insulin resistance is the primary cause of the syndrome. A diagnosis of the syndrome by WHO criteria could thus be made when a patient exhibited one of several more insulin resistance markers in the metabolic syndrome. Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference.

In 1999, the European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition.107 This group used the term **insulin resistance syndrome**
rather than metabolic syndrome. They likewise assumed that insulin resistance is the major cause and required evidence of it for diagnosis. By their criteria, plasma insulin levels in the upper quartile of the population defined insulin resistance. An elevated plasma insulin plus 2 other factors—abdominal obesity, hypertension, elevated triglycerides or reduced HDL-C, and elevated plasma glucose—constituted a diagnosis of the insulin-resistance syndrome. Notably, EGIR focused more on abdominal obesity than did WHO, but in contrast to WHO, EGIR excluded patients with type 2 diabetes mellitus from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced alternative clinical criteria for defining the metabolic syndrome. In so doing, the purpose of ATP III was to identify people at higher long-term risk for ASCVD who deserved clinical lifestyle intervention to reduce risk. The ATP III criteria did not require demonstration of insulin resistance per se. It was noted that direct measures of insulin resistance are laborious and not well standardized. Moreover, less-specific measures, such as glucose tolerance tests, are not routinely used in clinical practice. Although the ATP III panel recognized the phenomenon of clustering of metabolic risk factors, it did not draw conclusions on mechanistic pathogenesis. The ATP III criteria thus required no single factor for diagnosis, but instead made the presence of 3 of 5 factors the basis for establishing the diagnosis; these were abdominal obesity (also highly correlated with insulin resistance), elevated triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting glucose (IFG or type 2 diabetes mellitus).

Although ATP III did not make any single risk factor (eg, abdominal obesity) a requirement for diagnosis, it nonetheless espoused the position that abdominal obesity is an important underlying risk factor for the syndrome. Its cutpoints for abdominal obesity came from the definition in the 1998 National Institutes of Health obesity clinical guidelines; they were a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. These cutpoints identify approximately the upper quartile of the US population. Abdominal obesity at these cutpoints was not made a prerequisite for diagnosis because lesser degrees of abdominal girth often associate with other ATP III criteria. In fact, some individuals or ethnic groups (eg, Asians, especially South Asians) appear to be susceptible to development of the metabolic syndrome at waist circumferences below ATP III cutpoints. Thus, ATP III specifically noted that some individuals having only 2 other metabolic syndrome criteria appear to be insulin resistant even when the waist circumference is only marginally elevated, eg, 94 to 101 cm in men or 80 to 87 cm in women. If so, they should benefit from clinical intervention similarly to many others who have greater increases in waist circumference, ie, ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. ATP III, like WHO, allowed for a diagnosis of metabolic syndrome in the presence of type 2 diabetes because of the high risk for ASCVD among multiple-risk factor patients with diabetes. When type 2 diabetes mellitus is present, concomitant metabolic risk factors must not be overlooked because of strong evidence that intervention on them can substantially reduce risk for ASCVD.

In 2003, the American Association of Clinical Endocrinologists (AACE) modified ATP III criteria to refocus on insulin resistance as the primary cause of metabolic risk factors. Like the EGIR, they used the name insulin resistance syndrome. Major criteria were IGT, elevated triglycerides, reduced HDL-C, elevated blood pressure, and obesity. No specified number of factors qualified for diagnosis, which was left to clinical judgment. Other factors used to inform clinical judgment were a family history of ASCVD or type 2 diabetes mellitus, poly cystic ovary syndrome, and hyperuricemia. By the AACE’s definition, once a person develops type 2 diabetes mellitus, the term insulin resistance syndrome no longer applies.

In 2005, the International Diabetes Foundation (IDF) published new criteria that again modified the ATP III definition. The IDF writing group included several members of the original WHO consultation group. They liked the ATP III definition because of its clinical simplicity. They furthermore considered that abdominal obesity is so highly correlated with insulin resistance that other, more laborious measures of insulin resistance are unnecessary. The IDF clinical definition thus makes the presence of abdominal obesity necessary for diagnosis. When such is present, 2 additional factors originally listed in the ATP III definition are sufficient for diagnosis. IDF recognized and emphasized ethnic differences in the correlation between abdominal obesity and other metabolic syndrome risk factors. For this reason, criteria of abdominal obesity were specified by nationality or ethnicity based on best available population estimates. For people of European origin (Europid), the IDF specified thresholds for abdominal obesity to be waist circumferences ≥94 cm in men and ≥80 cm in women. These thresholds apply to Europids living in the Americas as well as Europe. For Asian populations, except for Japan, thresholds were ≥90 cm in men and ≥80 cm in women; for Japanese they were ≥85 cm for men and ≥90 cm for women.

The present AHA/NHLBI statement, in contrast to IDF, maintains the ATP III criteria except for minor modifications (Table 2). This decision is based on the conclusion that ATP III criteria are simple to use in a clinical setting and have the advantage of avoiding emphasis on a single cause. No compelling reasons were found for making a change. In addition, a large number of studies have been carried out to evaluate the ATP III criteria for the metabolic syndrome. The majority of these reports are supportive of the present structure of ATP III criteria. It must be noted in Table 2, however, that the threshold for IFG was reduced from 110 to 100 mg/dL; this adjustment corresponds to the recently modified American Diabetes Association (ADA) criteria for IFG. Otherwise, the statement maintains that continuity with the original ATP III definition, which has been widely adopted in the United States and elsewhere, is appropriate in the absence of new evidence to the contrary. Present diagnostic criteria thus accord with ATP III by defining abdominal obesity as a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. As noted in ATP III, some people will manifest features of
Clinical Management of the Metabolic Syndrome

Goals of Clinical Management

The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-C above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for ASCVD. The prime emphasis in management of the metabolic syndrome per se is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. Effective lifestyle change will reduce all of the metabolic risk factors. Then, if absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, blood pressure, and glucose; current guidelines for their management should be followed. Moreover, efforts should be made to bring about smoking cessation in any cigarette smokers.

Table 3 summarizes the current goals and recommendations for management of each of the risk factors of the metabolic syndrome. These recommendations are derived in large part from existing NHLBI, AHA, and ADA guidelines for management of specific risk factors. It is important to note that individuals who have established ASCVD and/or diabetes can still have the metabolic syndrome. The evidence bases for most of the recommendations have been presented in background documents for obesity, physical inactivity, and atherogenic diet through lifestyle changes. Effective lifestyle change will reduce all of the metabolic risk factors. Then, if absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, blood pressure, and glucose; current guidelines for their management should be followed. Moreover, efforts should be made to bring about smoking cessation in any cigarette smokers.

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statement attempts to provide an integrated approach to the management of a multidimensional risk factor condition.

**Risk Assessment**

**ASCVD**

A series of studies have found that many middle-aged people with the metabolic syndrome are at increased absolute risk for ASCVD in the near future (eg, 10-year risk). Moreover, as stated previously, because of the high relative risk for ASCVD, long-term (lifetime) risk for ASCVD is increased even when 10-year risk is not considered to be high, eg, in young adults who develop the syndrome. An exacerbating factor raising lifetime risk for ASCVD is an increased likelihood for developing premature type 2 diabetes mellitus.

To reduce lifetime risk for ASCVD, all individuals found to have the metabolic syndrome deserve long-term management and follow-up in the clinical setting. The primary aim is to reduce the underlying risk factors. Such individuals need to be categorized according to absolute 10-year risk. Individuals with any clinical form of ASCVD or with diabetes belong in the high-risk category. For metabolic syndrome patients without ASCVD or diabetes, Framingham risk scoring should be performed to estimate 10-year risk for coronary heart disease (CHD). This assessment triages patients into 3 risk categories based on 10-year risk for CHD: high risk (10-year risk >20%), moderately high risk (10-year risk 10% to 20%), or lower to moderate risk (10-year risk <10%).

Thus, detecting metabolic syndrome is only one part of overall risk assessment for cardiovascular disease. The metabolic syndrome per se is not an adequate tool to estimate 10-year risk for CHD. Although patients with the metabolic syndrome are at higher lifetime risk, in the absence of diabetes they do not necessarily have a high 10-year risk. Estimating 10-year risk entails key risk factors beyond those of the syndrome, ie, age, sex, smoking, and total cholesterol. Moreover, risk factors of the metabolic syndrome are not graded for severity as are the risk factors contained in Framingham scoring. Framingham investigators find little or no increase in predictive power for CHD by adding abdominal obesity, triglycerides, or fasting glucose to their 10-year risk algorithm. These factors come into play in the longer term.

Whether adding still other factors—apoB, small LDL, CRP, and insulin levels—will enhance shorter-term prediction of ASCVD has not been rigorously tested in multivariable models.

**Type 2 Diabetes Mellitus**

In individuals with diabetes, the coexistence of other metabolic syndrome factors denotes a higher risk for future development of ASCVD. Compared with other metabolic risk factors, IFG (fasting glucose 100 to 125 mg/dL) carries the greatest predictive power for diabetes. A closely related measure is IGT, defined as a 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL observed during a standard oral glucose tolerance test (OGTT). The ADA has introduced the term “prediabetes” to apply to individuals with either IFG or IGT. Some investigators recommend OGTT for normoglycemic subjects who have the metabolic syndrome to detect IGT or occult diabetes. IGT in fact exceeds IFG in frequency; it consequently uncovers more individuals at increased risk for diabetes. In part to reduce the need for OGTT in routine practice, the ADA recently reduced the threshold for IFG to 100 mg/dL; from its previous 110 mg/dL. People who have fasting glucose in the range of 100 to 110 mg/dL are now said to have IFG; many such people would have IGT if tested by OGTT. OGTT nonetheless remains an option in normoglycemic individuals who appear to be at elevated risk for developing diabetes. In fact, performing OGTT in people with IFG will identify some individuals who already have type 2 diabetes mellitus. Intensive lifestyle management of individuals with IFG (or IGT) will delay conversion to type 2 diabetes mellitus.

**Management of Underlying Risk Factors**

Although many people may be genetically susceptible to the metabolic syndrome, rarely does it become clinically manifested in the absence of some degree of obesity and physical inactivity. Consequently, therapies to mitigate these underlying risk factors constitute first-line intervention. If cigarette smoking, another risk factor for ASCVD, is present, then it likewise deserves intensive cessation effort. The reason to modify underlying risk factors is to prevent or delay onset of ASCVD; and if type 2 diabetes mellitus is not already present, a concomitant goal is to prevent it as well.

**Abdominal Obesity**

Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome. Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity and the use of principles of behavior change. The first aim of weight loss is to achieve a decline of about 7% to 10% from baseline total body weight during a period of 6 to 12 months. This will require decreasing caloric intake by 500 to 1000 calories per day. Greater physical activity helps to enhance caloric deficit. Achieving the recommended amount of weight loss will reduce the severity of most or all of the metabolic risk factors. Maintenance of a lower weight is just as important; this requires long-term follow-up and monitoring.

Currently available weight-loss drugs possess limited utility in the management of obesity. Nevertheless, in some patients they may be helpful. Bariatric surgery is being used increasingly in the United States for severe obesity. Individuals at high risk for the complications of obesity may benefit. Weight-loss surgery is not without risk, however. Selection of patients must be made with a team of healthcare professionals who are qualified to make appropriate clinical judgments about the pros and cons of this approach.

**Physical Inactivity**

Increasing physical activity assists in weight reduction; it also has beneficial effects on metabolic risk factors; and importantly, it reduces overall ASCVD risk. Current recommendations for the public call for accumulation of ≥30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all, days of the week; even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people...
### TABLE 3. Therapeutic Goals and Recommendations for Clinical Management of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Lifestyle risk factors</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td>Reduce body weight by 7% to 10% during year 1 of therapy. Continue weight loss thereafter to extend possible with goal to ultimately achieve desirable weight (BMI &lt;25 kg/m²).</td>
</tr>
<tr>
<td><strong>Physical inactivity</strong></td>
<td>Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably ~60 min) 5 d/wk, but preferably daily.</td>
</tr>
<tr>
<td><strong>Atherogenic diet</strong></td>
<td>Reduced intake of saturated fat, trans fat, and cholesterol.</td>
</tr>
<tr>
<td><strong>Metabolic risk factors</strong></td>
<td>Shorter-term prevention of CVD or treatment of type 2 diabetes mellitus</td>
</tr>
<tr>
<td><strong>Atherogenic dyslipidemia</strong></td>
<td>Primary target: elevated LDL-C (see Table 4 for details)</td>
</tr>
<tr>
<td><strong>Secondary target: elevated non-HDL-C</strong></td>
<td>Elevated LDL-C (see Table 4 for details)</td>
</tr>
<tr>
<td><strong>High-risk patients</strong>: &lt;130 mg/dL (3.4 mmol/L) optional: &lt;100 mg/dL (2.6 mmol/L) for very high-risk patients†</td>
<td>Elevated non-HDL-C</td>
</tr>
<tr>
<td><strong>Moderately high-risk patients</strong>: &lt;160 mg/dL (4.1 mmol/L)</td>
<td>Secondary target: follow strategy outlined in Table 4 to achieve goal for LDL-C. First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy. Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy. Given preference to adding fibrate or nicotinic acid in high-risk patients. Given preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients. All patients: If TG is ~500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)</td>
</tr>
<tr>
<td>**Therapeutic option: &lt;130 mg/dL (3.4 mmol/L)</td>
<td>Tertiary target: reduced HDL-C</td>
</tr>
<tr>
<td><strong>Moderate-risk patients</strong>: &lt;160 mg/dL (4.1 mmol/L)</td>
<td>No specific goal: raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia</td>
</tr>
<tr>
<td><strong>Lower-risk patients</strong>: &lt;180 mg/dL (4.5 mmol/L)</td>
<td>Reduced HDL-C</td>
</tr>
<tr>
<td><strong>Tertiary target</strong>: reduced HDL-C</td>
<td>No specific goal: raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia</td>
</tr>
<tr>
<td><strong>Elevated BP</strong></td>
<td>Elevated LDL-C</td>
</tr>
<tr>
<td><strong>Reduce BP to at least achieve BP of 140/90 mm Hg (or &lt;130/80 mm Hg if diabetes present). Reduce BP further to extent possible through lifestyle changes.</strong></td>
<td>Follow strategy outlined in Table 4 to achieve goal for LDL-C. First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy. Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy. Given preference to adding fibrate or nicotinic acid in high-risk patients. Given preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients. All patients: If TG is ~500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)</td>
</tr>
<tr>
<td><strong>Elevated glucose</strong></td>
<td>Follow strategy outlined in Table 4 to achieve goal for LDL-C. First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy. Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy. Given preference to adding fibrate or nicotinic acid in high-risk patients. Given preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients. All patients: If TG is ~500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)</td>
</tr>
<tr>
<td><strong>Prothrombotic state</strong></td>
<td>Follow strategy outlined in Table 4 to achieve goal for LDL-C. First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy. Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy. Given preference to adding fibrate or nicotinic acid in high-risk patients. Given preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients. All patients: If TG is ~500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)</td>
</tr>
<tr>
<td><strong>Proinflammatory state</strong></td>
<td>Follow strategy outlined in Table 4 to achieve goal for LDL-C. First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy. Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy. Given preference to adding fibrate or nicotinic acid in high-risk patients. Given preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients. All patients: If TG is ~500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)</td>
</tr>
</tbody>
</table>

TG indicates triglycerides; BP, blood pressure; CVD, cardiovascular disease; CHF, congestive heart failure; BMI, body mass index; IFG, impaired fasting glucose; and ASCVD, atherosclerotic cardiovascular disease.

†High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes TIA or stroke of carotid origin or >50% carotid stenosis.

‡Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease + any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome.

§Moderate-high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%. Factors that favor therapeutic option of non-HDL-C <100 mg/dL are those that can raise individuals to upper range of moderately high risk: multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).

$Moderate-risk patients are those with 2+ major risk factors and 10-year risk <10%.

$Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.
with the metabolic syndrome. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day, will promote weight loss or weight-loss maintenance. Preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities.77 The latter include multiple short (10- to 15-minute) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (eg, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training148; avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. Self-monitoring of physical activity can help to achieve adherence to an activity program.

Current AHA guidelines143 call for clinical assessment of risk for future ASCVD events before initiating a new exercise regimen. This includes a detailed history of physical activity. For high-risk patients (eg, those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under medical supervision. AHA guidelines further recommend exercise testing before vigorous exercise in selected patients with cardiovascular disease and other patients with symptoms or those at high risk. It is not necessary, however, that all individuals beginning an exercise program of moderate intensity that is moderately progressive undergo an exercise stress test, although this issue remains controversial.

Atherogenic and Diabetogenic Diets

Beyond weight control and reduction of total calories, the diet should be low in saturated fats, trans fats, cholesterol, sodium, and simple sugars.1,149 In addition, there should be ample intakes of fruits, vegetables, and whole grains; fish intake should be encouraged with recognition of concerns about the mercury content of some fish (see the Food and Drug Administration web site, www.cfsan.fda.gov/~dms/admeh3.html).91,150,151 Very high carbohydrate intakes can exacerbate the dyslipidemia of the metabolic syndrome. ATP III1 recommended that for individuals entering cholesterol management the diet should contain 25% to 35% of calories as total fat. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C. On the other hand, if the fat content falls below 25%, triglycerides can rise and HDL-C levels can decline152; thus, very-low-fat diets may exacerbate atherogenic dyslipidemia. To avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome, some investigators favor fat intakes in the range of 30% to 35%; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in the range of 25% to 30%.

There has long been an interest in the question of whether changing the macronutrient content of the diet can promote weight reduction. For many years, a low-fat diet was advocated because the high caloric density of fat could increase the likelihood of obesity. More recently, interest has grown in the possibility that high-protein, low-carbohydrate diets will enhance weight reduction.153 The rationale seems to be that fat and protein offer satiety that is absent with carbohydrates. That this effect of fat and protein on satiety makes the diet more effective for producing weight loss is a disputable hypothesis. Moreover, research documenting that high-fat/high-protein/low-calorie diets can achieve long-term maintenance of a lower body weight is lacking. In fact, after 1 year of consumption of low-carbohydrate diets, severely obese patients show no more weight reduction than those eating a conventional weight-loss diet.154 High-fat diets not only tend to be higher in saturated fat but they often are deficient in fruits, vegetables, and whole grains—all of which are important components in currently recommended diets. High-protein diets of any sort are not well tolerated by individuals with chronic renal disease who have markedly reduced glomerular filtration rate; excess protein enhances phosphorus load, which can cause acidosis and worsen insulin resistance.155,156 Finally, preoccupation with macronutrient composition to promote weight loss fails to identify the key factors affecting body weight. Effective weight loss requires a combination of caloric restriction, physical activity, and motivation; effective lifelong maintenance of weight loss essentially requires a balance between caloric intake and physical activity.

**Management of Metabolic Risk Factors**

Beyond lifestyle therapies directed toward underlying risk factors, attention must be given to the metabolic risk factors. If ASCVD or diabetes is present, or if the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for risk factors may be required as defined by current guidelines.1,91,134 Recommended principles of management for each of the metabolic risk factors are also considered in Table 3.

**Atherogenic Dyslipidemia**

As noted before, this condition consists of abnormal levels of triglycerides and apoB, small LDL particles, and low HDL-C. According to ATP III,1 atherogenic dyslipidemia can become a target for lipid-lowering therapy after the goal for LDL-C has been attained. In other words, as long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other lipid risk factors are secondary. The LDL-C goals depend on estimates of absolute risk. Table 4 reviews LDL-C goals that are consistent with recommendations of ATP III1 and its recent update.157 In patients with atherogenic dyslipidemia in whom serum triglyceride levels are \( \geq 200 \) mg/dL, non-HDL-C becomes the next target of treatment after the LDL-C goal is reached (Table 3). A related and potential secondary target is an elevated total apoB158; this measure denotes the number of atherogenic lipoproteins in circulation.85–89 Some investigators hold that total apoB is superior to non-HDL-C as a target of lipid-lowering therapy.89,159,160 ATP III nonetheless identified non-HDL-C rather than total apoB as a secondary target (after LDL-C) because accurate measurement of non-HDL-C is more readily available in clinical practice. Goals for non-HDL-C parallel those for LDL-C except that the former are 30 mg/dL higher (Table 3).

When triglycerides are \( \geq 500 \) mg/dL, triglyceride-lowering drugs should be considered to prevent the development of acute pancreatitis.1 To achieve non-HDL-C goals at triglyc-
erides <500 mg/dL, triglyceride-lowering drugs may be useful in combination with LDL-lowering therapy. Beyond lowering of non-HDL-C, a tertiary aim in patients with atherogenic dyslipidemia is to raise HDL-C when it is reduced. No specific goal of therapy is recommended for low HDL-C, but HDL-C should be raised to the extent possible after attaining goals for LDL-C and non-HDL-C.

If non-HDL-C remains elevated after the LDL-C goal is reached (Table 4), at least 2 therapeutic options are available. First, intensification of LDL lowering often also reduces non-HDL-C, a tertiary aim in patients with the metabolic syndrome. Second, a triglyceride-lowering drug can be added to LDL-lowering therapy. Both fibrates and nicotinic acid lower non-HDL-C by a similar percentage; moreover, statins reduce non-HDL-C. For example, statins lower both LDL-C and HDL-C, but HDL-C should be raised to the extent possible to minimize risks for myopathy or hepatic effects.

### Elevated Blood Pressure

When overt hypertension is present without diabetes or chronic kidney disease, the goal for antihypertensive therapy is a blood pressure of <140/90 mm Hg. In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg. Beyond these specific treatment goals, lifestyle changes deserve increased emphasis in people with the metabolic syndrome; the goals here are to reduce blood pressure as much as possible even in the absence of overt hypertension and to obtain other metabolic benefits of lifestyle change. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies: weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits and vegetables and low-fat dairy products, in accord with the Dietary Approaches to Stop Hypertension (DASH) diet. If hypertension cannot be adequately controlled by lifestyle

### Table 4. Elevated LDL-C: Primary Target of Lipid-Lowering Therapy in People at Risk for ASCVD

<table>
<thead>
<tr>
<th>Goals of Therapy</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk patients*: &lt;100 mg/dL (2.6 mmol/L) for very high-risk patients‡ in this category, optional goal &lt;70 mg/dL</td>
<td>High-risk patients: lifestyle therapies† plus LDL-C-lowering drug to achieve recommended goal if baseline LDL-C &gt;100 mg/dL, initiate LDL-lowering drug therapy if on-treatment LDL-C ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination) if baseline LDL-C &lt;100 mg/dL, initiate LDL-lowering therapy based on clinical judgment (ie, assessment that patient is at very high risk)</td>
</tr>
<tr>
<td>Moderately high-risk patients§: &lt;130 mg/dL (3.4 mmol/L) (for higher-risk patients) in this category, optional goal is &lt;100 mg/dL (2.6 mmol/L)</td>
<td>Moderately high-risk patients: lifestyle therapies + LDL-lowering drug if necessary to achieve recommended goal when LDL-C ≥130 mg/dL (3.4 mmol/L) after lifestyle therapies if baseline LDL-C is 100 to 129 mg/dL, LDL-lowering therapy can be introduced if patient’s risk is assessed to be in upper ranges of this risk category</td>
</tr>
<tr>
<td>Moderate-risk patients¶: &lt;130 mg/dL (3.4 mmol/L)</td>
<td>Moderate-risk patients: lifestyle therapies + LDL-C-lowering drug if necessary to achieve recommended goal when LDL-C ≥100 mg/dL (4.1 mmol/L) after lifestyle therapies</td>
</tr>
<tr>
<td>Lower-risk patients#: &lt;160 mg/dL (4.9 mmol/L)</td>
<td>Lower-risk patients: lifestyle therapies + LDL-C-lowering drug if necessary to achieve recommended goal when LDL-C ≥190 mg/dL (5.1 mmol/L) after lifestyle therapies (for LDL-C 160 to 189 mg/dL, LDL-lowering drug is optional)</td>
</tr>
</tbody>
</table>

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack or stroke of carotid origin or >50% carotid stenosis.
†Lifestyle therapies include weight reduction, increased physical activity, and antithrombotic diet (see Table 3 for details).
‡Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease + any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and multiple risk factors of metabolic syndrome.
§Moderately high-risk patients are those with 2 or more CVD risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).
¶Moderate-risk patients are those with 2–3 major risk factors and 10-year risk 10%–20%.
†Moderate-risk patients are those with 2–3 major risk factors and 10-year risk 10%–20%.
‡Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.

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therapies, antihypertensive drugs usually are necessary to prevent long-term adverse effects, eg, myocardial infarction, stroke, and chronic kidney disease.91 The benefits of therapy extend to patients with type 2 diabetes mellitus whose blood pressure is above goal level, and presumably to hypertensive patients with the metabolic syndrome. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present.170 Indeed, inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) may lower risk for diabetes itself.171 ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have left ventricular dysfunction.172 Debate persists about the latter strategy. The results of a large clinical trial173 raised the possibility that use of diuretics in patients with IFG or IGT may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events.91,173 Most investigators in the hypertension field believe that the potential benefit of low-dose diuretics in combination antihypertensive therapy outweighs their risk.

Elevated Fasting Glucose
In the metabolic syndrome diagnosis, elevated fasting glucose ($\geq 100$ mg/dL) includes both IFG and type 2 diabetes mellitus. In metabolic syndrome patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of type 2 diabetes mellitus.145,174 In addition, metformin,145 thiazolidinediones,175,176 and acarbose177 will lower risk for type 2 diabetes mellitus in people with IFG or IGT. Except for a preliminary trial with acarbose,178 no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risk for cardiovascular events. Moreover, neither metformin nor thiazolidinediones are recommended in this statement solely for the purpose of preventing diabetes because their cost-effectiveness and long-term safety have not been documented.

For patients with established type 2 diabetes mellitus, clinical trials confirm a reduction in cardiovascular risk from treatment of dyslipidemia161–163,179–181 and hypertension.91 Glycemic control to a hemoglobin A1c of $<7\%$ reduces microvascular complications and may decrease risk for macrovascular disease as well.182

Prothrombotic State
People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. These abnormalities, however, are not routinely detected in clinical practice. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antithrombotic agents. These agents, especially aspirin, are recommended in patients with established ASCVD provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is an attractive therapeutic option to lower vascular events.183

Proinflammatory State
People with the metabolic syndrome frequently have a proinflammatory state as shown by elevated cytokines (eg, tumor necrosis factor-$\alpha$ and interleukin-6) and acute-phase reactants (eg, CRP, fibrinogen).96,184 Measurement of CRP is the simplest way to identify a proinflammatory state in clinical practice. CRP levels $>3$ mg/L can be taken to define such a state in a person without other detectable causes.95 If CRP is measured, the finding of an elevated level supports the need for lifestyle changes. The latter, particularly weight reduction, will reduce CRP levels and presumably will mitigate the underlying inflammatory stimulus.185 No drugs that act exclusively through this mechanism are available for reducing cardiovascular risk. However, several drugs used to

<table>
<thead>
<tr>
<th>TABLE 5. Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research</th>
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<tbody>
<tr>
<td><strong>Abnormal body fat distribution</strong></td>
</tr>
<tr>
<td>General body fat distribution (dual-energy x-ray absorptiometry [DXA])</td>
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<tr>
<td>Central fat distribution (CT/MRI)</td>
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<tr>
<td>Adipose tissue biomarkers: leptin, adiponectin</td>
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<tr>
<td>Liver fat content (magnetic resonance spectroscopy)</td>
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<tr>
<td>Myocellular fat (magnetic resonance spectroscopy)</td>
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<tr>
<td><strong>Atherogenic dyslipidemia</strong></td>
</tr>
<tr>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>Small LDL particles</td>
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<tr>
<td>Triglycerides/HDL-C ratios</td>
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<tr>
<td><strong>Dysglycemia</strong></td>
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<tr>
<td>Fasting glucose</td>
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<tr>
<td>OGTT</td>
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<tr>
<td><strong>Insulin resistance (other than elevated fasting glucose)</strong></td>
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<tr>
<td>Fasting insulin/proinsulin levels</td>
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<tr>
<td>Homeostasis model assessment for insulin resistance (HOMA-IR)</td>
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<tr>
<td>Insulin resistance by Bergman Minimal Model</td>
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<tr>
<td>Elevated free fatty acids (fasting and during OGTT)</td>
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<tr>
<td><strong>Vascular dysregulation (beyond elevated blood pressure)</strong></td>
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<tr>
<td>Measurement of endothelial dysfunction</td>
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<tr>
<td>Microalbuminuria</td>
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<tr>
<td>Chronic renal disease</td>
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<tr>
<td><strong>Proinflammatory state</strong></td>
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<tr>
<td>Elevated high-sensitivity CRP</td>
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<tr>
<td>Elevated inflammatory cytokines (eg, interleukin-6)</td>
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<tr>
<td>Low levels of adiponectin</td>
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<tr>
<td><strong>Prothrombotic state</strong></td>
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<tr>
<td>Fibrolytic factors (plasminogen activator inhibitor-1, etc)</td>
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<tr>
<td>Clotting factors (fibrinogen, etc)</td>
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<tr>
<td><strong>Hormonal factors</strong></td>
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<tr>
<td>Corticosteroid axis</td>
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<td>Polycystic ovary syndrome</td>
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</tbody>
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treat other metabolic risk factors have been reported to reduce CRP levels (eg, statins, nicotinic acid, fibrates, ACE inhibitors, thiazolidinediones). At present, these drugs cannot be recommended specifically to reduce a proinflammatory state independent of their indications for other risk factors.

**Future Research**

This statement recognizes several issues related to the metabolic syndrome that require additional research for clarification. Foremost is the need for improved strategies to achieve and sustain long-term weight reduction and increased physical activity. Moreover, a lack of understanding of the genetic and metabolic contributions to the causation of the syndrome stands in the way of developing new therapeutic approaches. The need exists, therefore, for additional basic and clinical research designed to better understand pathophysiology from the standpoint of genetics, molecular biology, and cellular signaling. At present, tools to assess short-term risk for ASCVD and diabetes in patients with the metabolic syndrome need significant improvement. Although statins and other LDL-lowering drugs effectively reduce the risk for ASCVD, adequate therapies for remaining dyslipidemias either are not available or have not yet been proved to reduce risk in combination with LDL-lowering drugs. Insulin resistance is an attractive target for prevention of ASCVD; clinical trials to date, however, have not been carried out to confirm ASCVD risk reduction from decreasing insulin resistance per se. The emerging relationship between a proinflammatory state and the development of both ASCVD and diabetes deserves much additional investigation. Finally, the cost-effectiveness of various drugs, both alone and in combination therapies, requires more extensive evaluation.

The metabolic syndrome can be clinically manifested in a variety of ways. A sizable number of metabolic changes thus occur in people with clinical evidence of the syndrome. Identification of these changes should provide a broader picture of the metabolic status of an affected individual. They may also give insights into pathogenesis. At present, many of these factors cannot be readily identified in routine clinical practice. Nevertheless, several factors appear to overlap with alternative measures of the same underlying or metabolic risk factor. For example, there are several ways to estimate body fat distribution. In addition, multiple tests for insulin resistance have been proposed; each examines a different aspect of the insulin resistance phenomenon. The IDF report lists many of these factors as important targets for research even when they are not used for routine clinical diagnosis. Table 5 presents a list of research targets similar to those proposed by the IDF. Epidemiological, metabolic, and genetic studies directed to a broad profile of parameters related to the metabolic syndrome should provide new insights into the responsible pathways. It is not expected that these measures will be used in routine clinical practice because the incremental value of measurement is uncertain. Their study at present is expected to be mainly for research, ie, metabolic and epidemiological studies.

**Conclusions**

In summary, the following points should be emphasized:

1. The metabolic syndrome is a term for a constellation of endogenous risk factors that increase the risk of developing both ASCVD and type 2 diabetes mellitus.
2. The syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups.
3. In the United States, the syndrome is strongly associated with the presence of abdominal obesity.
4. The metabolic syndrome is a secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary targets for risk reduction.
5. Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome. If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated.
6. To date, there is insufficient evidence for primary use of drugs that target the underlying causes of the metabolic syndrome.
7. Considerable additional research is needed to better refine the most appropriate therapies for individuals with the metabolic syndrome.
<table>
<thead>
<tr>
<th>Writing Group Member</th>
<th>Employment</th>
<th>Research Grant</th>
<th>Other Research Support</th>
<th>Speakers Bureau/ Honoraria</th>
<th>Ownership Interest</th>
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<tr>
<td>James I. Cleeman</td>
<td>National Heart, Lung, and Blood Institute</td>
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<td>Fernando Costa</td>
<td>American Heart Association</td>
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<td>Stephen R. Daniels</td>
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<td>Karen A. Donato</td>
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<td>John A. Spertus</td>
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.
TABLE 7. Reviewer Disclosures

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<td>George Alberti</td>
<td>University of Newcastle Upon Tyne</td>
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<td>AstraZeneca; GlaxoSmithKline; Novartis</td>
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<td>John Brunzell</td>
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<td>Harold Franch</td>
<td>Emory University; Atlanta VA Medical Center</td>
<td>National Institutes of Health; Department of Veterans Affairs</td>
<td>AHA Kidney Foundation</td>
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<td>Daniel Porte, Jr.</td>
<td>Independent consultant</td>
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<td>Paul Thompson</td>
<td>Hartford Hospital</td>
<td>Otsuka; Merck; Pfizer; AstraZeneca; Schering-Plough; KOS</td>
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References


Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation. 2001;104:3046–3051.


Keywords: AHA/NHLBI Scientific Statements ■ metabolic syndrome ■ cardiovascular disease ■ obesity ■ diabetes ■ lifestyle therapy
In the version of “Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement” that published online ahead of print on September 12, 2005 (DOI: 10.1161/CIRCULATIONAHA.105.169404), the following changes have been made to Table 2:

1. The value for categorical cut points in elevated waist circumference for men should have added “(≥40 inches)” after “102 cm.”
2. The value for categorical cut points in elevated waist circumference for women should have added “(≥35 inches)” after “88 cm.”
3. The conversion of mg/dL to mmol/L for reduced HDL-C is incorrect. The correct value for men should be 1.03 mmol/L and the correct value for women should be 1.3 mmol/L.
4. In the footnotes, the values for marginally increased waist circumference should read “(eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women).”

These changes were incorporated into the version of the article printed in the October 25, 2005, issue (Circulation. 2005;112:2735–2752) and the current online version of the article. (If needed, the original version of the article posted online on September 12, 2005, is available by selecting the “Previous Version of This Article” link.)

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