

Diagnosis and Management of the Metabolic Syndrome

An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement

Executive Summary

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This Executive Summary is a synopsis of the full scientific statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI), which is intended to provide up to date guidance for professionals on the diagnosis and management of the metabolic syndrome in adults.

The metabolic syndrome has received increased attention in the past few years. It consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD). This constellation of *metabolic risk factors* is strongly associated with type 2 diabetes mellitus or the risk for this condition. The metabolic risk factors consist of atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B, small LDL particles, and low HDL cholesterol [HDL-C] concentrations), elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state.

At present, it is not clear whether the metabolic syndrome has a single cause, and it appears that it can be precipitated by multiple underlying risk factors. The most important of these *underlying risk factors* are abdominal obesity and insulin resistance. Other associated conditions include physical inactivity, aging, hormonal imbalance, and genetic or ethnic predisposition.

Prospective population studies show that the metabolic syndrome confers an ≈ 2 -fold increase in relative risk for ASCVD events, and in individuals without established type 2 diabetes mellitus, an ≈ 5 -fold increase in risk for developing diabetes as compared with people without the syndrome. This finding implies that the metabolic syndrome imparts a relatively high long-term risk for both

ASCVD and diabetes. In the absence of diabetes, the absolute short-term (10-year) risk for major coronary heart disease (CHD) events is not necessarily high. In the Framingham Heart Study data, the 10-year risk for CHD depends on other risk factors in addition to the metabolic syndrome components contained in Framingham scoring (ie, blood pressure, HDL-C). These other risk factors are age, sex, serum total or LDL-C, and smoking status. For individuals with the metabolic syndrome who do not have established ASCVD or type 2 diabetes mellitus, the absolute 10-year risk is best assessed by Framingham risk scoring.

Clinical Diagnosis of the Metabolic Syndrome

Several different sets of criteria have been proposed during the past decade for diagnosis of the metabolic syndrome. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed a simple set of diagnostic criteria based on common clinical measures including waist circumference, triglycerides, HDL-C, blood pressure, and fasting glucose level. The presence of defined abnormalities in any 3 of these 5 measures constitutes a diagnosis of the metabolic syndrome. The ATP III criteria for the metabolic syndrome have been widely used in both clinical practice and epidemiological studies. The criteria also have the advantage of avoiding emphasis on a single cause. In the absence of compelling scientific reasons for change, the AHA and NHLBI affirm the overall utility and validity of the ATP III criteria and propose that they continue to be used with minor modifications and clarifications (Table 1). These modifications and clarifications include allow-

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TABLE 1. Diagnostic Criteria for Metabolic Syndrome

Measure (Any 3 of 5 Criteria Constitute Diagnosis of Metabolic Syndrome)	Categorical Cut Points
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated TG	≥150 mg/dL (1.7 mmol/L) or Drug treatment for elevated TG‡
Reduced HDL-C	<40 mg/dL (0.9 mmol/L) in men <50 mg/dL (1.1 mmol/L) in women or Drug treatment for reduced HDL-C‡
Elevated BP	≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP or Drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL or Drug treatment for elevated glucose

TG indicates triglycerides; BP, blood pressure. All other abbreviations as in text.

*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at end of normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking 1 of these drugs presumed to have high TG and low HDL.

ing for adjustment of waist circumference to lower thresholds when individuals or ethnic groups are prone to insulin resistance; allowing triglycerides, HDL-C levels, and blood pressure to be counted as abnormal when a person is taking drug treatment for these factors; clarifying that the definition of elevated blood pressure is a level that exceeds the threshold for either systolic or diastolic pressure; and reducing the threshold for counting elevated fasting glucose from ≥110 mg/dL to ≥100 mg/dL, in accordance with the American Diabetes Association's (ADA's) revised definition of impaired fasting glucose (IFG).

Recently, the International Diabetes Federation (IDF) has proposed a set of clinical criteria that are similar to those of the updated ATP III criteria. In fact, thresholds are identical for triglycerides, HDL-C, blood pressure, and plasma glucose. The major difference is that the IDF proposed that waist circumference thresholds be adjusted for different ethnic groups. This suggestion is consistent with emerging information on the variable relationship between waist circumference and metabolic

risk factors in different populations. The updated AHA/NHLBI diagnostic criteria maintain ATP III waist circumference thresholds for Americans, except that a lower threshold can be invoked for individuals who are especially prone to insulin resistance, particularly Asian Americans. Abdominal obesity is highly correlated with and easier to measure than other indicators of insulin resistance. The IDF therefore concluded that abdominal obesity incorporates both concepts of obesity and insulin resistance as being the 2 major underlying risk factors of the metabolic syndrome; thus, they made increased waist circumference a required element for diagnosing the metabolic syndrome. Another major reason for this recommendation was to make possible rapid identification of individuals who are likely candidates for the metabolic syndrome. In the updated ATP III classification, increased waist circumference is not deemed a necessity if 3 other risk factor criteria are present. Despite these minor differences in criteria for diagnosis, in the US population, updated ATP III and IDF criteria identify essentially the same individuals as having the metabolic syndrome. Moreover, recommendations for the clinical management of the metabolic syndrome are virtually identical in updated ATP III and IDF reports.

Clinical Management of the Metabolic Syndrome

The primary goal of clinical management of the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. A closely related goal is to decrease the risk for type 2 diabetes mellitus in those patients who do not yet manifest clinical diabetes. Management of the metabolic syndrome should be carried out in the context of global cardiovascular disease-prevention efforts. For reduction of ASCVD events, the first-line therapy is to reduce the major risk factors: stop cigarette smoking and reduce LDL-C, blood pressure, and glucose levels to the recommended goals. Choice and intensity of risk factor reduction therapy depend in part on the absolute risk of patients. Patients with established ASCVD and diabetes are at high risk in the short-term (within 10 years) and deserve intensive intervention. The level of short-term risk for individuals without these conditions depends on the mix and severity of risk factors used in Framingham risk scoring; hence, even in individuals with the metabolic syndrome, 10-year risk assessment depends on Framingham scoring. For patients who manifest the metabolic syndrome, long-term risk also is elevated regardless of the Framingham score. Thus, long-term risk must be considered a high priority for clinical management of people with the metabolic syndrome.

For management of long-term as well as short-term risk, lifestyle therapies are first-line interventions to reduce the metabolic risk factors. The major lifestyle interventions include weight loss in overweight or obese subjects, increased physical activity, and modification of an atherogenic diet (Table 2). These changes will produce a reduction in all of the metabolic risk factors simultaneously. In the long run, the greatest benefit for those with the metabolic syndrome will be derived from effective lifestyle intervention.

For individuals at higher 10-year risk, consideration must be given to specific therapies for the metabolic risk factors (see Table 3). A person's 10-year risk status will determine the intensity of therapy for each risk factor and, particularly, whether

TABLE 2. Treatment of Lifestyle Risk Factors for Long-Term Prevention of ASCVD or Prevention/Treatment of Type 2 Diabetes

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Abdominal obesity Goal: Reduce body weight by 7%–10% during first year of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI <25 kg/m ²)	Consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of ≈7%–10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity Goal: Regular moderate-intensity physical activity; at least 30 min of continuous/intermittent (preferably 60 min) 5 d/wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or exercise test, to guide prescription. Encourage 30–60 min moderate-intensity aerobic activity (eg, brisk walking), preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, household work). Higher exercise times achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet Goal: Reduced intakes of saturated fat, <i>trans</i> fat, cholesterol	Recommendations: Saturated fat <7% of total calories; reduce <i>trans</i> fat; dietary cholesterol <200 mg/d; total fat 25%–35% of total calories. Most dietary fat should be unsaturated, simple sugars should be limited.

BMI indicates body mass index; CVD, cardiovascular disease; and CHF, congestive heart failure.

drug therapy should be employed. No specific drugs are currently recommended for people with the metabolic syndrome independent of those agents most appropriate for specific, abnormal risk factors. Recommendations for drug therapy are based on current guidelines for each risk factor that are established by the AHA, NHLBI, and ADA. The following sections summarize the recommended approaches to the management of each of the risk factors of the metabolic syndrome.

Atherogenic Dyslipidemia

Recommendations for treatment of atherogenic dyslipidemia are based on NCEP guidelines. A few comments can be made to amplify the goals of therapy listed in Table 3 for the 3 cholesterol targets LDL-C, non-HDL-C, and HDL-C. These targets still hold for people with atherogenic dyslipidemia. The primary target of lipid-lowering therapy is LDL-C. The level of LDL-C should be reduced to that recommended by NCEP guidelines as determined by risk category. Four categories of absolute 10-year risk for CHD are identified for cholesterol-lowering therapy: high-risk (>20%), moderately high risk (10% to 20% with ≥2 risk factors), moderate risk (<10% with ≥2 risk factors), and lower risk (<10% with 0 to 1 risk factor). LDL-C goals for each risk category are listed in Table 3. If TG levels are ≥200 mg/dL, non-HDL-C is a secondary target of treatment after the LDL-C goal is achieved; the non-HDL-C goal is 30 mg/dL higher than that specified for LDL-C. If TG are ≥500 mg/dL, reduction of TG to <500 mg/dL takes primacy over LDL reduction as the primary goal because of the immediate need to reduce risk for acute pancreatitis. After LDL-C and non-HDL-C goals are achieved, a tertiary target is HDL-C. No goals for raising HDL-C are specified, but an effort should be made to raise HDL-C to the extent possible with standard therapies.

For patients with atherogenic dyslipidemia who enter clinical cholesterol management, lifestyle intervention should be employed as the basic therapy. In addition, however, for some individuals, lipid-lowering drugs may be required to achieve goals, depending on 10-year risk estimates. For LDL-C reduc-

tion, the standard LDL-lowering drugs are statins, ezetimibe, and bile acid sequestrants. Other drugs that can produce moderate reductions of LDL-C are nicotinic acid and fibrates; these 2 agents are considered to be secondary drugs to lower non-HDL-C and to raise HDL-C after LDL-C goals are achieved. Caution must be exercised in using fibrates (particularly gemfibrozil) with statins because of the accentuated risk for severe myopathy. The fibrates or nicotinic acid are a first-line therapy for patients with severe hypertriglyceridemia for the purpose of preventing acute pancreatitis.

Elevated Blood Pressure

Basic guidelines for blood pressure management are presented in the 7th Report of the Joint National Commission (JNC 7). For individuals with blood pressure in the range of “prehypertension” (blood pressure 120 to 139/80 to 90 mm Hg), lifestyle changes designed to maximize the lowering of blood pressure should be used. At higher pressures (≥140/90 mm Hg), drug therapies should be considered according to current hypertension guidelines. When either diabetes or chronic renal disease is present, reducing the blood pressure to <130/80 mm Hg, with drugs if necessary, is recommended.

Elevated Plasma Glucose

As shown by recent clinical trials, when IFG is present as one component of the metabolic syndrome, progression to type 2 diabetes mellitus can be delayed or prevented by instituting lifestyle changes, especially weight reduction and increased physical activity. At present, drug therapies to reduce plasma glucose or insulin resistance are not recommended for patients with IFG. Once diabetes develops, drug therapy often is needed to achieve the recommended ADA goal for hemoglobin A1c of <7%. In addition to lifestyle therapies, serious consideration should be given to drug therapies for managing atherogenic dyslipidemia and hypertension in patients with type 2 diabetes mellitus; the efficacy of these therapies for reducing risk for ASCVD has been amply demonstrated in clinical trials.

TABLE 3. Therapy of Metabolic Risk Factors for Prevention of ASCVD or Treatment of Type 2 Diabetes

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Atherogenic dyslipidemia	
Primary target: LDL-C Reduce LDL-C levels to ATP III goals (see Therapeutic Recommendations).	For elevated LDL-C: Give priority to reduction of LDL-C over other lipid parameters. Achieve LDL-C goals based on patient's risk category. LDL-C goals for different risk categories are High risk*: <100 mg/dL (optional <70 mg/dL for high-risk patients†) Moderately high risk‡: <130 mg/dL (optional <100 mg/dL) Moderate risk§: <130 mg/dL Lower risk : <160 mg/dL
Secondary target: Non-HDL-C If TG ≥200 mg/dL, reduce non-HDL-C to ATP III goals (after attaining LDL-C goals; see Therapeutic Recommendations).	If TG ≥200 mg/dL, goal for non-HDL-C for each risk category is 30 mg/dL higher than for LDL-C. If TG ≥200 mg/dL after achieving LDL-C goal, consider additional therapies to attain non-HDL-C goal.
Tertiary target: HDL-C If HDL-C <40 mg/dL in men or <50 mg/dL in women after attaining non-HDL-C goal, raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia.	For reduced HDL-C: If HDL-C is low after achieving non-HDL-C, either lifestyle therapy can be intensified or drug therapy can be used for raising HDL-C levels, depending on patient's risk category.
Elevated BP	
Reduce BP to at least achieve BP of <140/90 mm Hg (or <130/80 mm Hg if diabetes is present). Reduce BP further to extent possible through lifestyle changes.	For BP ≥120/80 mm Hg: Initiate or maintain lifestyle modification via weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products in all patients with metabolic syndrome. For BP ≥140/90 mm Hg (or ≥130/80 mm Hg if diabetes is present), add BP medication as needed to achieve goal BP.
Elevated glucose	
For IFG, delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A _{1c} <7.0%.	For IFG, encourage weight reduction and increased physical activity. For type 2 diabetes, lifestyle therapy and pharmacotherapy, if necessary, should be used to achieve near-normal HbA _{1c} (<7%). Modify other risk factors and behaviors (eg, abdominal obesity, physical inactivity, elevated BP, lipid abnormalities).
Prothrombotic state	
Reduce thrombotic and fibrinolytic risk factors	For high-risk patients, initiate and continue low-dose aspirin therapy; in patients with ASCVD, consider clopidogrel if aspirin is contraindicated. For moderately high-risk patients, consider low-dose aspirin prophylaxis.
Proinflammatory state	
	Recommendations: No specific therapies beyond lifestyle therapies

TG indicates triglycerides; BP, blood pressure; CHD, coronary heart disease; IFG, impaired fasting glucose; and ASCVD, atherosclerotic cardiovascular disease. All other abbreviations as in text.

*High-risk patients have established atherosclerotic CVD, diabetes, or 10-year risk for CHD >20%. For cerebrovascular disease, high-risk conditions include TIA or stroke of carotid origin or >50% carotid stenosis.

†Very high-risk patients are likely to have major CVD events during next few years; diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established CHD + multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome.

‡Moderately high-risk patients have 10-year risk for CHD of 10%–20%. Factors favoring therapeutic option of non-HDL-C <100 mg/dL are those that can elevate patients 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 have ≥2 major risk factors and 10-year risk <10%.

||Lower-risk patients have 0–1 major risk factor and 10-year risk <10%.

Prothrombotic and Proinflammatory States

Most individuals with the metabolic syndrome exhibit a prothrombotic state characterized by elevations of plasminogen activator inhibitor-1 and fibrinogen. Although there are no specific therapies available to treat these abnormalities, the use of low-dose aspirin can be recommended for patients with the metabolic syndrome who have a 10-year risk for CHD ≥10%, those with overt type 2 diabetes mellitus or ASCVD, or others in the high-risk category. In patients with ASCVD in whom aspirin is contraindicated, consideration should be given to use of clopidogrel. In addition, the metabolic syndrome frequently is

accompanied by a proinflammatory state, characterized by elevations of C-reactive protein. At present, no specific drug therapies are available that specifically target a proinflammatory state; nevertheless, several of the drugs used to treat other metabolic risk factors will also reduce C-reactive protein levels.

Conclusions

This AHA/NHLBI update on the metabolic syndrome reaches several conclusions. The writing group found the ATP III criteria for clinical diagnosis of the metabolic syndrome to be a robust and clinically useful tool. This scientific statement

recommends that the ATP III diagnostic criteria be maintained with minor modifications. It is recognized that the metabolic syndrome is a complex disorder, with no single factor as the cause. Nevertheless, its prevalence rises with increasing obesity, particularly abdominal obesity. The presence of the syndrome is associated with increased long-term risk for both ASCVD and type 2 diabetes mellitus, and thus requires attention in clinical practice. Lifestyle interventions deserve prime consideration for risk reduction across a lifetime; these interventions include weight control, increased physical activity, and a diet designed to reduce the risk for ASCVD. In patients with the metabolic syndrome found to be at a relatively high 10-year risk for ASCVD, drug therapy of

both major and metabolic risk factors can contribute to risk reduction. Drug therapies should be used according to current recommendations for individual risk factors. At the present time, drug therapy is not recommended specifically to reduce risk for type 2 diabetes mellitus independent of treatments to prevent ASCVD. Additional research is required both to better understand the underlying pathophysiology of the metabolic syndrome and to identify new targets for therapy.

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TABLE 4. Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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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.