

A Practical “ABCDE” Approach to the Metabolic Syndrome

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The metabolic syndrome comprises a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus that are due to abdominal obesity and insulin resistance. This increasingly important proinflammatory condition remains both underrecognized and undertreated. To aid physicians in their approach to the metabolic syndrome, we assessed and synthesized the literature on cardiovascular risk assessment and early intervention for risk reduction. We performed a comprehensive search of MEDLINE and the Cochrane database for peer-reviewed clinical studies published from January 1, 1988, to December 31, 2007, augmented by consultation with content experts. We used the search terms *metabolic syndrome, abdominal obesity, waist circumference, insulin resistance, cardiovascular disease, prediabetes, diabetes, treatment, prevention, aspirin, hypertension, cholesterol, atherogenic dyslipidemia, lifestyle therapy, diet, and exercise*. Criteria used for study review were controlled study design, English language, relevance to clinicians, and validity based on experimental design and appropriateness of conclusions. Although growing evidence supports early intervention in patients with the metabolic syndrome, many physicians do not recognize the risk associated with this condition and fail to initiate early treatment. A comprehensive management plan can be assembled through an “ABCDE” approach: “A” for assessment of cardiovascular risk and aspirin therapy, “B” for blood pressure control, “C” for cholesterol management, “D” for diabetes prevention and diet therapy, and “E” for exercise therapy. This ABCDE approach provides a practical and systematic framework for encouraging metabolic syndrome recognition and for implementing a comprehensive, evidence-based management plan for the reduction of cardiovascular risk.

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ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; CI = confidence interval; DREAM = Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; GL = glycemic load; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; PPAR = peroxisome proliferator-activated receptor; VLDL-C = very low-density lipoprotein cholesterol

Increased caloric intake, increased consumption of refined carbohydrates, and physical inactivity have led to an explosion in the incidence of abdominal obesity and an emerging epidemic of insulin resistance. Abdominal obesity has tripled in the United States during the past 4 decades,¹ currently affecting half of all adults.² More than one quarter of the US population has the metabolic syndrome,³ and the incidence is increasing.⁴

The metabolic syndrome is a multiplex risk factor for type 2 diabetes mellitus and cardiovascular disease that reflects the clustering of individual risk factors due to abdominal obesity and insulin resistance. This multiplex comprises the following interrelated metabolic risk conditions: atherogenic dyslipidemia, glucose intolerance, hyper-

tension, proinflammatory state, and prothrombotic state⁵ (Table 1).

The metabolic syndrome is a predictor of type 2 diabetes mellitus and future cardiovascular events. The incidence of diabetes mellitus is increased at least 7-fold⁶; however, increased cardiovascular risk is present long before the development of overt diabetes.⁷ A recent meta-analysis of nearly 175,000 patients showed that the metabolic syndrome confers a relative risk of 1.54 for cardiovascular events and death after adjustment for traditional risk factors.⁸

Several groups have operationalized the metabolic syndrome, choosing risk factors and cut points that are readily measurable, correlate with insulin resistance, and can be integrated with guidelines for primary prevention of cardiovascular disease⁹⁻¹² (Table 2). Despite these available clinical definitions, the metabolic syndrome remains underdiagnosed.¹³ While debate continues as to whether this risk factor clustering represents a true syndrome,¹⁴⁻¹⁷ physicians may be missing the opportunity for early identification of a disease process and comprehensive intervention aimed at risk reduction.

Recognizing the widespread failure to address fully the risk associated with this condition, we present a practical ABCDE approach to the metabolic syndrome for primary prevention of cardiovascular events.

METHODS

We performed a comprehensive search of MEDLINE and the Cochrane database for clinical studies published from January 1, 1988, to December 31, 2007, using combinations of the following terms in their titles or abstracts: *metabolic syndrome, abdominal obesity, waist circumference, insulin resistance, cardiovascular disease, prediabetes, diabetes, treatment, prevention, aspirin, hypertension, cholesterol, atherogenic dyslipidemia, lifestyle therapy, diet, and exercise*. After screening the titles of all

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7920 identified articles, we evaluated abstracts for pertinence to the study objective, selecting more than 460 articles for full text review. Bibliographies from these references were examined, and additional studies were identified by content experts. Criteria used for study selection were controlled study design, English language, relevance to clinicians, and validity based on experimental design and appropriateness of conclusions.

MECHANISMS OF INCREASED RISK

The term *metabolic syndrome* evolved from observations that cardiovascular risk factors cluster in obese, insulin-resistant people; in its current use, it also refers to metabolically obese people of normal weight.¹⁸ The concept of the metabolic syndrome is useful because of its emphasis on underlying dysmetabolism and the attention it calls to co-existing cardiovascular risk factors.

Advances in adipocyte biology, subclinical inflammation, and oxidative stress have added to the original mechanistic understanding of how obesity and insulin resistance contribute to the metabolic syndrome.¹⁹ Abdominal fat, as determined by measures such as waist circumference and waist:hip ratio, is highly correlated with insulin resistance, prothrombotic factors, and inflammation, as well as hypertension, dyslipidemia, and hyperglycemia.²⁰ Adipose tissue, particularly in the abdominal compartment, is a powerful endocrine organ that is the main source of free fatty acids and of several important biologically active adipokines.^{21,22}

Excessive caloric intake and insulin resistance increase free fatty acid release, further inhibiting insulin action,

TABLE 1. **Five Metabolic Risk Conditions That Constitute the Metabolic Syndrome and Their Clinical Markers^a**

Metabolic risk condition	Clinical markers
Atherogenic dyslipidemia	↑ Triglycerides, VLDL-C, non-HDL-C ↓ HDL-C, LDL-C particle size
Glucose intolerance	↑ Fasting glucose, HbA _{1c} Impaired glucose tolerance
Hypertension	Elevated blood pressure
Proinflammatory state	↑ WBC, hs-CRP, IL-6
Prothrombotic state	↑ Fibrinogen, vWF, PAI-1

^a HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; VLDL-C = very low-density lipoprotein cholesterol; vWF = von Willebrand factor; WBC = white blood cell count.

causing lipotoxicity of the β -cell and leading to formation of an atherogenic lipoprotein profile.^{21,22} Levels of adiponectin, an adipokine that normally increases insulin sensitivity and is anti-inflammatory, decrease with abdominal obesity. Interleukin 6, tumor necrosis factor α , and C-reactive protein, all of which are secreted in association with abdominal obesity, increase inflammation and further insulin resistance. Secretion of plasminogen activator inhibitor 1 by adipose tissue increases thrombosis. Leptin, a metabolic signal of energy sufficiency, is increased with obesity and can lead to hypertension as well as leptin resistance, with associated loss of feedback on appetite centers.²³ The obesity-driven dysregulation of the endocannabinoid system is associated with worsening insulin resistance, dyslipidemia, and further obesity.²⁴

TABLE 2. **Current Clinical Definitions of the Metabolic Syndrome^{a,b}**

WHO, ⁹ 1999	NCEP ATP III, ^{10,11} 2001	IDF, ¹² 2005
Insulin resistance, identified as Type 2 diabetes mellitus Impaired fasting glucose Impaired glucose tolerance Abnormal findings of hyperinsulinemic euglycemic clamp Plus any 2 of the following Hypertension $\geq 140/90$ mm Hg Plasma triglycerides Men < 35 mg/dL or Women < 39 mg/dL BMI > 30 and/or Waist:hip ratio Men > 0.9 Women > 0.85 Microalbuminuria	At least 3 of the following 5 criteria Waist circumference Men ≥ 102 cm (≥ 40 in) Women ≥ 88 cm (≥ 35 in) Triglycerides ≥ 150 mg/dL ^c HDL-C ^c Men < 40 mg/dL Women < 50 mg/dL Hypertension $\geq 130/85$ mm Hg ^c Fasting glucose ≥ 100 mg/dL	Abdominal obesity, identified as Waist circumference European men ≥ 94 cm (≥ 37 in) European women ≥ 80 cm (32 in) Ethnicity-specific values for other groups Plus any 2 of the following Triglycerides ≥ 150 mg/dL ^c HDL-C ^c Men < 40 mg/dL Women < 50 mg/dL Blood pressure $\geq 130/85$ mm Hg Fasting glucose > 100 mg/dL

^a BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; WHO = World Health Organization.

^b SI conversion factors: To convert triglyceride value to mmol/L, multiply by 0.0113; to convert HDL-C value to mmol/L, multiply by 0.0259; and to convert glucose value to mmol/L, multiply by 0.0555.

^c Or taking medication for treatment of this risk factor.

Insulin itself is thought to act as an anti-inflammatory protein, inhibiting nuclear factor κ B and stimulating inhibitor of nuclear factor κ B.¹⁹ Therefore, changes in the adipocyte that increase insulin resistance also exacerbate underlying inflammation. All these dysmetabolic changes occur more often in the proinflammatory milieu of the Western diet, and most can be reversed with dietary restriction.²⁵

DEFINITION OF THE METABOLIC SYNDROME

Clinical definitions of the metabolic syndrome use commonly measured patient data to identify people who are sufficiently insulin resistant to be at increased cardiovascular risk (Table 2). Although the World Health Organization, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and International Diabetes Federation definitions vary slightly, all identify a similar population of insulin-resistant people in need of risk modification. The conclusions of this review apply only to patients who are free of known coronary artery disease and overt diabetes mellitus and who have the metabolic syndrome by any of these definitions.

Although the risk factors that comprise the metabolic syndrome are generally recognized as important, the usefulness of the metabolic syndrome diagnosis has been the subject of substantial debate.²⁶ Much of this debate has been driven by imperfections in the clinical definitions of the metabolic syndrome and by the resulting confusion about how to apply the definitions in the clinical setting.¹⁷ Indeed, because a single pathophysiologic defect for the metabolic syndrome has not yet been identified, current definitions lack a central risk variable that must be abnormal for diagnosis. Instead, current definitions are a combination of both causes (abdominal obesity) and consequences (dysglycemia) of insulin resistance.

Current clinical definitions of the metabolic syndrome do not include all features of the disease, leaving out prothrombotic and proinflammatory markers. Moreover, current definitions are weakened by the somewhat arbitrary dichotomization of risk variables. To be sure, the metabolic syndrome should be considered a continuum of risk. However, as will be discussed, the metabolic syndrome is not intended to be a comprehensive risk-scoring equation, but rather a tool to identify people at increased lifetime risk of developing diabetes mellitus and cardiovascular disease because of abdominal obesity and insulin resistance.

CARDIOVASCULAR RISK PREDICTION

A diagnosis of metabolic syndrome allows early identification of patients with excessive adipose tissue and insulin resistance; as such, it can be considered a tool for the

selection of patients who may have an increased *lifetime* risk of *cardiovascular disease*. Although the diagnosis should not be confused with a precise risk-scoring instrument, current definitions of the metabolic syndrome may identify a population of patients at greater cardiovascular risk than predicted by traditional risk factors alone.²⁷⁻³¹

For example, a middle-aged woman with abdominal obesity, atherogenic dyslipidemia, and a fasting glucose of 110 mg/dL (to convert to mmol/L, multiply by 0.0555) is classified as low risk in the Framingham model. Yet there is ample evidence that abdominal obesity,³² elevated triglyceride levels,³³ the small dense high-density lipoprotein cholesterol (HDL-C)/low-density lipoprotein cholesterol (LDL-C) phenotype,³⁴ insulin resistance,³⁵ and impaired fasting glucose³⁶ are all risk factors for coronary artery disease. Indeed, patients with the metabolic syndrome considered low-risk by Framingham often show a substantial burden of subclinical atherosclerosis and may have event rates characteristic of those in higher-risk groups.³⁷⁻³⁹

In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, men classified as having low cardiovascular risk (10-year risk, <5%) by the European Systematic Coronary Risk Evaluation (SCORE) model who had the metabolic syndrome experienced nearly 3 times as many fatal cardiovascular events as those without the syndrome.⁴⁰ A comparable increased event rate among patients with the metabolic syndrome and low calculated risk was seen in a pooled analysis of 2 large lipid-lowering trials.⁴¹ Although it is less clear if the metabolic syndrome improves risk prediction across an entire high-risk population,^{42,43} there appears to be a benefit in discriminating increased risk among otherwise lower-risk groups.

The metabolic syndrome therefore represents risk not accounted for by traditional models and a missed opportunity for aggressive lifestyle and medical management. Clinical diagnosis of the metabolic syndrome can be used as a complementary tool for “correcting” the risk calculated by instruments such as the Framingham risk score. Precedence for advancing a calculated risk score comes from the 2003 American College of Cardiology (ACC) Bethesda conference on atherosclerosis imaging, which endorsed an expanded intermediate risk category (10-year risk, 6%-20%) when coronary calcium imaging predicts increased risk not fully captured by the Framingham risk equation.⁴⁴

Similarly, a practical approach to accounting for the unmeasured risk due to the metabolic syndrome would be to reclassify patients with the syndrome and a calculated Framingham 10-year event rate between 6% and 10% as intermediate risk, equivalent to patients without the meta-

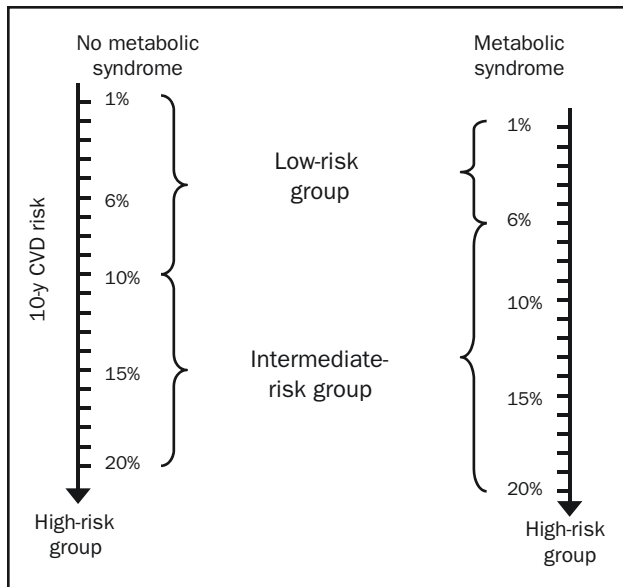


FIGURE. Proposed reclassification of cardiovascular disease (CVD) risk categories for patients with the metabolic syndrome. An augmented intermediate risk group (from 10%-20% to 6%-20% 10-year risk) adjusts for the unaccounted risk present with the metabolic syndrome.

bolic syndrome and a calculated Framingham 10-year risk of 10% to 20% (Figure). Physicians can then use these adjusted risk estimates to guide more aggressive lifestyle

changes, lower blood pressure goals, and intervene earlier with aspirin and LDL-C-lowering drugs.

ABCDE APPROACH

In 2001, our center proposed an “ABC” approach to the implementation of ACC/American Heart Association (AHA) primary prevention guidelines,⁴⁵ and we have since adopted an “ABCDE” approach to secondary prevention⁴⁶ and the treatment of non-ST-segment elevation acute coronary syndromes.⁴⁷ This review adapts this practical approach to the metabolic syndrome (Table 3).

ASSESSMENT

The first step in treatment is recognition of the condition. Clinical definitions of the metabolic syndrome vary only slightly (Table 2), with little evidence to suggest that one is superior to another.

Treatment of the metabolic syndrome requires a multidisciplinary approach, including physicians and health educators skilled in nursing, nutrition, and exercise physiology. Therefore, a formal diagnosis recorded in the medical record may improve clinical communication. The *International Classification of Diseases, Ninth Revision* code is 277.7.

After diagnosis, all patients should have their 10-year risk calculated using a traditional scoring tool, such as the

TABLE 3. **ABCDE Approach for Treating the Metabolic Syndrome^{a,b}**

A	Assessment	Make metabolic syndrome diagnosis, <i>ICD-9</i> code 277.7 Calculate Framingham risk score
	Aspirin	All patients with >6% 10-y Framingham risk
B	Blood pressure control	Goal blood pressure is <130/80 mm Hg if intermediate risk (≥6% 10-y risk) First-line therapy: ACEI or ARB β-Blockers, thiazide diuretics may increase risk of diabetes
C	Cholesterol management	
	First target: LDL-C	Statins to achieve LDL-C <100 mg/dL in high-risk, <130 mg/dL in intermediate-risk (≥6% 10-y risk) patients per the NCEP ATP III
	Second target: non-HDL-C	Statin intensification Fenofibrate to achieve target non-HDL-C <130 mg/dL in high-risk, <160 mg/dL in intermediate-risk patients per NCEP ATP III
	Third target: HDL-C	Consider omega-3 fatty acids Long-acting niacin, although insufficient evidence for wide use of niacin at this time due to concern for increased glucose intolerance
D	Diabetes prevention	Intensive lifestyle modification for all patients; pharmacotherapy is second line Metformin Consider pioglitazone
	Diet	Weight loss Mediterranean diet: increase omega-3 fatty acids, fruits, vegetables, fiber, nuts Low glycemic load diet
E	Exercise	Daily vigorous activity Recommend use of pedometer with goal >10,000 steps/d

^a ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL-C = high-density lipoprotein cholesterol; *ICD-9* = *International Classification of Diseases, Ninth Revision*; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

^b SI conversion factors: To convert LDL-C, HDL-C, and non-HDL-C values to mmol/L, multiply by 0.0259.

Framingham risk score. We propose that patients with the metabolic syndrome and a 10-year risk of a hard coronary artery disease event (myocardial infarction, cardiovascular death) of 5% or less should be considered low risk; those with a 6% to 20% 10-year risk, intermediate risk; and those with more than a 20% risk, high risk (Figure).

ASPIRIN

Patients with the metabolic syndrome are at increased risk of thrombosis because of increased platelet aggregation, increased fibrinogen, increased vitamin K–dependent clotting factors, and decreased fibrinolysis via increased levels of plasminogen activator inhibitor 1.⁴⁸ Aspirin decreases platelet aggregation and effectively reduces the risk of initial thrombotic events.

The benefits of aspirin must be weighed against the risks of bleeding.⁴⁹ The ACC/AHA gives a class I recommendation for 75 to 162 mg of aspirin for primary prevention in men with intermediate risk,⁵⁰ a class IIa recommendation for women aged 65 years and older with intermediate risk, and a class IIb recommendation for women younger than 65 years with intermediate risk.⁵¹ The Third US Preventive Services Task Force recommends aspirin for all those with a 10-year risk greater than 6%.⁵² A recent systematic review indicates that aspirin doses of 75 to 81 mg are noninferior to higher doses and have fewer bleeding risks.⁵³

Therefore, to treat the increased thrombogenicity and cardiovascular risk seen with the metabolic syndrome, we think that all patients in the augmented intermediate-risk category (calculated 10-year risk, 6%-20%) and all high-risk patients with the metabolic syndrome should be treated with 75 to 81 mg/d of aspirin in the absence of contraindications.

BLOOD PRESSURE

Blood pressure with the metabolic syndrome may be increased because of reduced bioavailability of nitric oxide secondary to obesity-induced oxidative stress, increased sodium reabsorption secondary to increased angiotensinogen production by adipocytes, and increased sympathetic activity secondary to hyperinsulinemia, as well as the vasoconstrictive effects of fatty acids and other adipokines.⁵⁴

New AHA guidelines recommend a goal of less than 130/80 mm Hg for all patients with known coronary artery disease or with a 10-year cardiovascular risk of 10% or greater.⁵⁵ Although data are insufficient to set specific blood pressure goals for patients with the metabolic syndrome, it is reasonable, given the increased risk of cardiovascular events, to aim for a blood pressure of less than 130/80 mm Hg in patients with the metabolic syndrome who have an augmented intermediate risk (10-year risk, $\geq 6\%$).

β -Blockers should be avoided as initial agents in patients with the metabolic syndrome without known cardio-

vascular disease on the basis of data from several clinical trials indicating worsening glucose intolerance and decreased efficacy.⁵⁶ The new British National Institute for Health and Clinical Excellence (NICE) guidelines state that traditional types of β -blockers are associated with an “unacceptable risk of provoking type 2 diabetes,”⁵⁷ and have removed these drugs as potential first-line blood pressure agents. New AHA guidelines have also removed these drugs as options for initial therapy in the primary prevention population.⁵⁵

Higher doses of thiazide diuretics may also increase the risk of diabetes. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), chlorthalidone was shown to have the same efficacy for mortality reduction as other antihypertensive agents but led to a significant increase in glucose intolerance.⁵⁸ Patients taking a combination of a β -blocker and a thiazide are at higher risk of diabetes. Indeed, current clinical guidelines specifically advise against this combination in patients with impaired glucose tolerance.⁵⁷

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) do not worsen glucose intolerance and may improve glycemia. A predefined substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial first suggested this salutary effect. This study examined 5720 patients without diabetes and with known vascular disease, showing that patients with features of the metabolic syndrome who received the ACEI ramipril had a 34% reduction in new diabetes in the 4.5 years of follow-up compared with placebo (3.6% vs 5.4%; $P < .001$).⁵⁹

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial showed similar diabetes reduction with an ARB compared with placebo.⁶⁰ Reductions in diabetes have also been observed in secondary analyses of large head-to-head trials comparing ARBs with β -blockers⁶¹ and ARBs with calcium channel blockers.⁶² Although the recent Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial failed to show a significant reduction in the incidence of diabetes among glucose-intolerant patients randomized to ramipril (18.1% vs 19.5%; $P = .15$), glucose values were more likely to return to the euglycemic range in these patients (hazard ratio, 1.16; $P = .001$).⁶³

We suggest that ACEIs and ARBs be used for initial treatment of hypertension with the metabolic syndrome because they have been consistently shown to improve glycemic control, whereas evidence suggests that other common antihypertensive agents do not improve or may even worsen glucose intolerance. Data are insufficient to recommend specific combination therapies in patients requiring additional agents for blood pressure control.

CHOLESTEROL

Low-Density Lipoprotein Cholesterol. Although not part of the metabolic syndrome, LDL-C has an integral role in the pathophysiology of atherosclerosis, and targeting LDL-C remains an important component of any strategy to reduce cardiovascular risk. Cholesterol synthesis can be blocked by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), leading to a reduction in LDL-C concentration and the total number of atherogenic apolipoprotein B-containing particles. Several clinical trials support the effectiveness of statins in reducing cardiovascular risk in patients with risk factors characteristic of the metabolic syndrome.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a primary prevention trial of 6605 patients with moderately elevated LDL-C and low HDL-C.⁶⁴ Almost half of all participants (46%) had the metabolic syndrome. In this trial, lovastatin reduced first major coronary events by 37% (183 vs 116 first events; 95% confidence interval [CI], 0.50-0.79) during an average 5.2 years of follow-up, with patients with the metabolic syndrome receiving the greatest benefit.

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) enrolled 10,305 participants with average levels of LDL-C (133 mg/dL) (to convert to mmol/L, multiply by 0.0259), hypertension, and 3 or more other risk factors, most of which were characteristic of the metabolic syndrome.⁶⁵ Because of the relatively low baseline LDL-C levels, many of these patients would not have been candidates for LDL-lowering therapy using the Framingham risk score and current guidelines. Nonetheless, the study was stopped early after a mean of 3.3 years of follow-up, with atorvastatin lowering the primary end point of nonfatal myocardial infarction and fatal coronary heart disease by 36% (154 vs 100 events; 95% CI, 0.50-0.83).

Similar to NCEP ATP III guidelines, statin therapy should be considered in all patients with the metabolic syndrome and an augmented intermediate 10-year cardiovascular risk (10-year risk, $\geq 6\%$) if LDL-C remains above goal after intensive lifestyle intervention. Patients at intermediate risk should have a goal of less than 130 mg/dL with an optional goal of less than 100 mg/dL, and patients at high risk should have LDL-C lowered to less than 100 mg/dL.

Atherogenic Dyslipidemia. Low-density lipoprotein cholesterol has long been considered the principal lipoprotein determinant of atherosclerosis, particularly small, dense LDL particles that more efficiently transport cholesterol into the vessel wall and have greater susceptibility for oxidation. Although LDL-C is a potent risk factor for cardiovascular disease, more than half of all events occur in patients with "normal" LDL-C levels. In the setting of

elevated triglycerides, other lipoproteins become important determinants of atherosclerosis.

Atherogenic dyslipidemia, which includes fasting and postprandial hypertriglyceridemia, elevated levels of very low-density lipoprotein cholesterol (VLDL-C), low HDL-C levels, and an atherogenic small dense LDL profile, is associated with the metabolic syndrome and likely accounts for much of the residual risk after LDL-C lowering. Several other lipoprotein measures, including the apolipoprotein B:apolipoprotein A-I ratio, correlate well with insulin resistance and lipid abnormalities in the metabolic syndrome but are less routinely measured.⁶⁶ Although combination lipid-lowering therapy targeting atherogenic dyslipidemia may result in additional cardiovascular risk reduction in these patients, definitive trial data are currently lacking. On a routine lipid profile, atherogenic dyslipidemia can be most easily quantified using 2 measures: (1) non-HDL-C (total cholesterol – HDL-C); and (2) HDL-C.

Non-High-Density Lipoprotein Cholesterol. In epidemiologic studies, non-HDL-C predicts cardiovascular disease better than LDL-C, particularly when triglycerides are high.⁶⁷ Non-HDL-C offers the benefit of being an aggregate measure that includes the concentrations of *all* apolipoprotein B-containing lipoproteins currently thought to contribute to atherosclerosis. Indeed, non-HDL-C includes LDL and lipoprotein(a), as well as triglyceride-rich lipoproteins, such as VLDL, intermediate-density lipoprotein, and chylomicron remnants. Not surprisingly, as triglycerides increase, non-HDL-C correlates with apolipoprotein B much better than does LDL-C.⁶⁸

Very low-density lipoprotein cholesterol, the chief contributor to non-HDL-C levels after LDL-C, is a triglyceride-rich apolipoprotein B-containing particle that is particularly sensitive to increases in abdominal obesity, insulin resistance, free fatty acid flux to the liver, and the resultant hypertriglyceridemia. Because VLDL-C is the principal carrier of plasma triglycerides, routine triglyceride measurements can be considered surrogate measures for VLDL-C concentration.

Triglyceride and non-HDL-C levels can be lowered with fibrate drugs, which are agonists of the peroxisome proliferator-activated receptor (PPAR) α transcriptional factor. Fibrates also modestly raise HDL-C and increase the size of LDL particles via pathways downstream of PPAR- α .⁶⁹ Trials have shown that gemfibrozil therapy may reduce initial and subsequent cardiovascular events.

The Helsinki Heart Study randomized 4081 men with non-HDL-C of 200 mg/dL (to convert to mmol/L, multiply by 0.0259) or more to the fibrate gemfibrozil or placebo.⁷⁰ Gemfibrozil reduced the primary end point of first nonfatal

myocardial infarction or cardiac death by 34% (2.7% vs 4.1%; $P < .02$), with a larger 66% reduction in patients with triglyceride levels of 200 mg/dL (to convert to mmol/L, multiply by 0.0113) or more and HDL-C levels of less than 42 mg/dL (to convert to mmol/L, multiply by 0.0259).⁷¹ A similar result was seen in the Bezafibrate Infarction Prevention (BIP) study, with a 42% reduction in fatal and nonfatal cardiac events in patients with triglyceride levels of 200 mg/dL or more and HDL-C levels of less than 35 mg/dL ($P = .02$).⁷²

More recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 patients with type 2 diabetes mellitus to micronized fenofibrate or placebo.⁷³ This study showed a nonsignificant reduction in first myocardial infarction or death from coronary heart disease (5.2% vs 5.9%; $P = .16$). However, fenofibrate use resulted in a significant 24% reduction in nonfatal myocardial infarction ($P = .01$) and a significant 21% reduction in revascularization ($P = .004$); post hoc analyses adjusting for statin use revealed a 19% reduction in coronary heart disease events ($P = .01$).

When used in combination with statin therapy, fibrates provide incremental improvements in triglyceride, LDL-C, apolipoprotein B, and HDL-C levels.⁷⁴ However, the benefits of combination therapy must be weighed against the elevated risk of myalgias, myositis, and rhabdomyolysis. This risk may be reduced by combining statins with fenofibrate, which does not affect statin pharmacokinetics, rather than with gemfibrozil.⁷⁵

Currently, no completed clinical trial has shown reduced cardiovascular events with combination statin-fibrate therapy. This approach is currently under study with fenofibrate in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which will be completed in 2009.⁷⁶

Omega-3 fatty acids are useful in the treatment of hypertriglyceridemia. In large doses, these fatty acids reduce hepatic secretion of triglyceride-rich lipoproteins. Lovaza, an omega-3 fatty acid supplement, has received an Food and Drug Administration indication for treatment of primary hypertriglyceridemia. Omega-3 fatty acid therapy has also been shown to provide additional triglyceride reduction in statin-treated individuals.⁷⁷

In summary, patients with the metabolic syndrome are likely to have elevated triglyceride levels and thus elevated non-HDL-C levels. In accordance with NCEP ATP III guidelines, non-HDL-C should be a secondary goal of treatment. Non-HDL-C targets are 30 mg/dL higher than the corresponding LDL-C goal for a given risk group.¹⁰ Given the increased risk conferred by atherogenic dyslipidemia, it is appropriate to consider fibrate therapy and/or omega-3 fatty acid therapy to achieve

non-HDL-C goals after lifestyle modification and intensification of statin therapy.

High-Density Lipoprotein Cholesterol. High-density lipoprotein cholesterol is critical for reverse cholesterol transport, and increased levels have a protective effect against atherosclerosis. Levels of HDL-C, which are inversely correlated with abdominal obesity and insulin resistance, can be improved with lifestyle modification.

Niacin inhibits hepatic uptake of apolipoprotein A-I and thus increases plasma pre- β HDL-C levels. It is the most efficacious agent for raising HDL-C levels, leading to 20% to 35% increases in plasma, while also reducing triglycerides. Niacin has been shown to reduce secondary cardiovascular events in the Coronary Drug Project.⁷⁷ In combination with a statin, the drug seems to slow atherosclerosis progression.^{78,79} Use of higher doses of niacin (>1500 mg/d) in patients with the metabolic syndrome has been limited by data indicating mild worsening of glucose tolerance.^{80,81} The ongoing Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial, which combines niacin with simvastatin for the treatment of atherogenic dyslipidemia, will help clarify the risks and benefits of niacin for patients with the metabolic syndrome.⁸²

Niacin can be considered adjunctive therapy for patients with the metabolic syndrome who have low HDL-C or high triglyceride levels despite maximal lifestyle modification and therapy with statins and/or fibrates. At this time, safety in patients with glucose intolerance is not clearly established.

DIABETES PREVENTION

Dysglycemia results when the pancreas fails to produce adequate compensatory hyperinsulinemia for the degree of insulin resistance. Vascular damage can be evident long before a patient is overtly hyperglycemic. Clinical trial data indicate that early treatment of abnormal glucose metabolism with aggressive lifestyle therapy can delay or prevent frank diabetes. Currently, the use of pharmacotherapy for this indication is controversial.

The Diabetes Prevention Program randomized 3234 high-risk patients without diabetes who had elevated fasting and postload plasma glucose concentrations to placebo, metformin (850 mg twice daily), or an intensive lifestyle modification program with specific weight loss and exercise goals.⁸³ During 2.8 years of follow-up, the incidence of diabetes was 11 cases per 100 person-years in the placebo group vs 7.8 cases per 100 person-years in patients receiving metformin. An even greater decrease was noted in the lifestyle group with 4.8 cases per 100 person-years, corresponding to a 58% reduction (95% CI, 0.48-0.66)

compared with placebo. Multiple cost-benefit analyses have confirmed the feasibility of implementing such an intervention in higher-risk patients, such as those with the metabolic syndrome.⁸⁴

The thiazolidinedione class of drugs are agonists of the PPAR- γ transcription factor and have pleiotropic effects, including improved insulin sensitivity, pancreatic β -cell preservation, improved HDL-C levels, decreased triglyceride levels, and increased LDL particle size.⁸⁵ Troglitazone, the first thiazolidinedione, was shown to reduce cases of new-onset diabetes but was withdrawn from the market because of hepatotoxicity.⁸⁶ In the DREAM trial, 5269 patients with abnormal glucose levels were randomized to rosiglitazone or placebo and followed up for a median of 3 years.⁸⁷ Patients who received rosiglitazone were 62% less likely (10.6% vs 25.0%; $P<.001$) to develop diabetes.

Despite the reduction in diabetes, the safety profile of rosiglitazone is not completely clear. In secondary analyses of several clinical trials, rosiglitazone increased cardiovascular events.⁸⁸ However, the only prospective study specifically examining rosiglitazone and cardiovascular events found it to be no more associated with cardiovascular events than were other common hypoglycemic agents.⁸⁹ In contrast, data from a meta-analysis and a recent large clinical trial suggest a neutral or possible modest salutary effect of pioglitazone on cardiovascular disease.^{90,91} Data from the ongoing Pioglitazone in the Prevention of Diabetes (PIPOD)⁹² and Actos Now for Prevention of Type 2 Diabetes (ACT-NOW)⁹³ will help determine if pioglitazone is indeed safe and effective for the prevention of diabetes.

Physicians should therefore concentrate on lifestyle interventions for the prevention of diabetes. Pharmacotherapy with metformin or pioglitazone may be considered if further glucose control is required. Fasting glucose levels should be measured periodically throughout treatment to monitor for progression to overt diabetes mellitus.

DIET

Weight loss has been shown to reduce oxidative stress²⁵ and to improve each of the components of the metabolic syndrome.⁹⁴ Unfortunately, emphasis on low-fat diets during the past half-century has led to a proportional increase in refined carbohydrate intake, contributing to insulin resistance, the metabolic syndrome, and diabetes.⁹⁵ Many readily available refined carbohydrates lead to more rapid increases and decreases in blood sugar levels, and this high glycemic load (GL) produces more insulin resistance.

Epidemiologic evidence from 2 large studies has linked high-GL diets with cardiovascular events, noting a greater effect on obese women.^{96,97} Similar conclusions were reached in a recent clinical trial by Ebbeling et al.⁹⁸ In that study, 73 obese young adults were randomized to a low-GL

diet or a low-fat diet. Patients in the low-GL group had greater increases in HDL-C levels ($P=.002$) and greater reductions in triglyceride levels ($P=.02$) at 6 months. Despite equivalent caloric intake and physical activity, the insulin-resistant patients in the low-GL group lost significantly more weight at 18 months ($P=.004$), suggesting specific benefit of the low-GL diet in hyperinsulinemic patients with the metabolic syndrome.

Inflammation is an integral part of the metabolic syndrome that is made worse by the proinflammatory macronutrient profile of the Western diet.⁹⁹ Strong data suggest that diets rich in omega-3 fatty acids and other unsaturated fats, natural antioxidants in fruits and vegetables, and fiber in nuts and whole grains provide specific benefit for patients with the metabolic syndrome.

The Mediterranean diet, based on the macronutrient profile of Mediterranean cultures, is rich in anti-inflammatory agents and antioxidants and was shown to reduce incidence of myocardial infarctions in the Lyon Diet Heart Study.¹⁰⁰ Adherence to a Mediterranean diet has been directly associated with lower total and cardiovascular mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) study,¹⁰¹ as well as decreased incidence of the metabolic syndrome in the large Seguimiento University of Navarra (SUN) cohort.¹⁰²

Recently, Esposito et al¹⁰³ randomized 180 patients with the metabolic syndrome to the Mediterranean diet or a traditional heart-healthy low-fat diet. After 2 years, greater reductions in both insulin resistance and proinflammatory cytokines were observed in the Mediterranean diet group—56% of patients in the Mediterranean diet group had the metabolic syndrome at the end of the study vs 87% of those in the low-fat group ($P<.001$).

Recent clinical trial evidence points to supplementation with omega-3 fatty acids as a promising approach for the prevention of major coronary events, even in patients with adequate consumption of these oils.¹⁰⁴ These fatty acids decrease thrombosis, decrease oxidative stress, and decrease inflammation. In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), statin-treated patients consuming an extra 1800 mg of eicosapentaenoic acid experienced a 19% relative reduction in major coronary events during a 5-year follow-up (2.8% vs 3.5%; $P=.011$), despite identical LDL-C concentrations.¹⁰⁵

Rimonabant, an endocannabinoid inhibitor available in Europe but not in the United States, is an emerging therapy that encourages weight loss. In the Rimonabant In Obesity (RIO) trials, rimonabant was shown to improve cardiovascular risk factors.¹⁰⁶ In the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—the Intravascular Ultrasound Study (STRADIVARIUS), rimonabant slowed the progression of atherosclerosis.¹⁰⁷

We conclude that a Mediterranean diet rich in omega-3 fatty acids, fruits, vegetables, and fiber that provides a low overall GL is appropriate for patients with the metabolic syndrome. Supplementation with omega-3 fatty acids is an emerging treatment modality and should be strongly considered in patients unable to consume goal amounts of omega-3 fatty acids. Additionally, referral to a nutritionist should be strongly considered for long-term reinforcement and follow-up.

EXERCISE

Cardiorespiratory fitness is associated with improved cardiovascular risk factors, increased insulin sensitivity,¹⁰⁸ decreased incidence of the metabolic syndrome,¹⁰⁹ and decreased cardiovascular mortality independently of measures of obesity.^{110,111} Exercise is the primary determinant of fitness and of course is also effective for reducing fatness (obesity).¹¹²

Physical activity appears to have an even greater effect on patients with the cluster of abnormalities associated with insulin resistance. In a subgroup analysis of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, levels of HDL-C increased with exercise only in patients with abdominal obesity and lipid components of the metabolic syndrome.¹¹³

A healthy exercise program can comprise many different activities. Simple, daily, vigorous walking can significantly improve cardiac risk factors and glucose metabolism.¹¹⁴ A recent meta-analysis suggested that regular use of pedometers can motivate patients to increase their physical activity if daily goals are set.¹¹⁵ A specific step goal such as 10,000 steps/d is associated with a significant increase in physical activity, decreased body mass index, and decreased systolic blood pressure.¹¹⁵

Despite changing guidelines, the optimal “dose” of exercise is unknown. Recent data from the Dose-Response to Exercise in Women Aged 45-75 Years (DREW) study reveals that there is a graded, dose-response improvement across levels of exercise training.¹¹⁶ Patients exercising as little as 4 kcal/kg per week experienced significant increase in fitness and reduction in waist circumference compared with the no-exercise control group. Patients in the 12 kcal/kg per week group showed the greatest improvements.

These findings suggest that current guidelines are somewhat arbitrary and that, with regard to exercise and the metabolic syndrome, “a little is good, more is better.”¹¹⁷ Physicians may find pedometers a useful tool for motivating patients and monitoring their exercise habits.

CONCLUSION

An underrecognized and undertreated condition caused by abdominal obesity and insulin resistance, the metabolic

syndrome predisposes people to the development of cardiovascular disease and diabetes. A clinical diagnosis of metabolic syndrome can be used as a tool to identify patients in need of comprehensive cardiovascular risk reduction therapy. A simple ABCDE approach is both easily accessible and comprehensive and can assist physicians by encouraging identification of patients with the metabolic syndrome and encouraging appropriate initiation and maintenance of treatment.

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