The metabolic syndrome is a constellation of risk factors of metabolic origin that are accompanied by increased risk for cardiovascular disease and type 2 diabetes. These risk factors are atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. The two major underlying risk factors for the metabolic syndrome are obesity and insulin resistance; exacerbating factors are physical inactivity, advancing age, and endocrine and genetic factors. The condition is progressive, beginning with borderline risk factors that eventually progress to categorical risk factors. In many patients, the metabolic syndrome culminates in type 2 diabetes, which further increases risk for cardiovascular disease. Primary treatment of the metabolic syndrome is lifestyle therapy—weight loss, increased physical activity, and anti-atherogenic diet. But as the condition progresses, drug therapies directed toward the individual risk factors might be required. Ultimately, it might be possible to develop drugs that will simultaneously modify all of the risk factors. At present such drugs are in development but so far have not reached the level of clinical practice. (J Am Coll Cardiol 2006;47:1093–100) © 2006 by the American College of Cardiology Foundation

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced the metabolic syndrome as a risk partner to elevated low-density lipoprotein (LDL)-cholesterol in cholesterol guidelines (1,2). This step was in response to the increasing prevalence of obesity and its metabolic complications in the U.S. The term metabolic syndrome was applied to the clustering of risk factors that often accompany obesity and associate with increased risk for both atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes. One advantage of identifying this particular cluster of risk factors is that it should bring together the fields of cardiovascular disease and diabetes for a concerted and unified effort to reduce risk for both conditions simultaneously. Moreover, cardiovascular disease is the foremost killer of patients with diabetes, which is of interest to both fields (3).

RISK FACTOR CLUSTERING AND PATHOGENESIS OF THE METABOLIC SYNDROME

The risk factors of the metabolic syndrome are of metabolic origin and consist of atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state (1,2,4–6). Atherogenic dyslipidemia comprises elevations of lipoproteins containing apolipoprotein B, elevated triglycerides, increased small particles of LDL, and low levels of high-density lipoproteins (HDL). Elevated plasma glucose falls in the range of either pre-diabetes or diabetes. A prothrombotic state signifies anomalies in procoagulant factors (i.e., increases in fibrinogen and factor VII), anti-fibrinolytic factors (i.e., increases in plasminogen activator inhibitor-1), platelet aberrations, and endothelial dysfunction. A proinflammatory state is characterized by elevations of circulating cytokines and acute phase reactants (e.g., C-reactive protein).

The pathogenesis of the metabolic syndrome is multifactorial (1,2,4–6). The major underlying risk factors are obesity and insulin resistance. Risk associated with obesity is best identified by increased waist circumference (abdominal obesity). Insulin resistance can be secondary to obesity but can have genetic components as well. Several factors further exacerbate the syndrome: physical inactivity, advancing age, endocrine dysfunction, and genetic aberrations affecting individual risk factors. The increasing prevalence of metabolic syndrome in the U.S. and worldwide, however, seems to be driven largely by more obesity exacerbated by sedentary lifestyles (7).

EVOLUTION OF THE METABOLIC SYNDROME CONCEPT AND THE NAME

Our understanding of the metabolic syndrome stems from two types of research. Epidemiological studies establish strong association of obesity with ASCVD (8,9) and type 2 diabetes (10). Some of the increased risk for cardiovascular disease is due to well-established, obesity induced risk factors, (i.e., plasma cholesterol, elevated blood pressure, and diabetes) (11). These risk factors have been called the metabolic complications of obesity (12,13). Cardiovascular
epidemiologists generally have not referred to this clustering as a syndrome.

The naming of risk factor grouping as syndrome came largely from the diabetes field. For example, Reaven (14,15) coined the term “syndrome X” to signify a constellation of metabolic risk factors associated with insulin resistance. Reaven (14,15) contends that insulin resistance is the dominant underlying risk factor for syndrome X. In accord, others in the diabetes field have applied the name insulin resistance syndrome (16–19). They have largely viewed obesity as an exacerbating factor but without the same pathophysiological significance of insulin resistance. Among diabetologists, some have used the term metabolic syndrome as a more generic name for the aggregation of metabolic risk factors (20–22). Regardless of the prefix, the diabetes field deserves much of the credit for introducing the term syndrome to define a grouping of metabolic risk factors. The ATP III guidelines (1,2) followed suit and employed the name metabolic syndrome because it seemed to be widely used to describe risk-factor aggregation.

CLINICAL OUTCOMES OF THE METABOLIC SYNDROME: CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES

In patients with the metabolic syndrome, relative risk for ASCVD ranges from 1.5 to 3.0 depending on the stage of progression (23–34). When diabetes is not yet present, risk for progression to type 2 diabetes averages about five-fold increase compared with those without the syndrome (35–39). Once diabetes develops, cardiovascular risk increases even more (40,41). The natural history of the metabolic syndrome and its complications are described in Figure 1. Most individuals who develop the syndrome first acquire abdominal obesity without risk factors, but with time, multiple risk factors begin to appear. At the beginning, they usually are only borderline elevated; later and in many individuals they become categorically raised (42). In some, the syndrome culminates in type 2 diabetes. If ASCVD develops, cardiovascular complications—cardiac arrhythmias, heart failure, and thrombotic episodes—often ensue. Those with diabetes can further acquire a host of complications including renal failure, diabetic cardiomyopathy, and various neuropathies. When ASCVD and diabetes exist concomitantly, risk for subsequent cardiovascular morbidity is very high. Patients with metabolic syndrome can manifest a variety of other conditions that complicate their management: fatty liver, cholesterol gallstones, gout, and sleep apnea. The presence of several or all of these outcomes commonly leads to the use of multiple medications (polypharmacy). No only does polypharmacy carry the risk of adverse drug interactions but it interferes with compliance, and for many patients, imposes a prohibitive cost burden.

THE CONUNDRUM OVER CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME

In 1998, a diabetes working group of the World Health Organization (WHO) proposed a set of criteria for a clinical diagnosis of the metabolic syndrome (20). These included clinical evidence of insulin resistance, such as impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes, as necessary for the diagnosis. Two other risk factors were also needed: elevated triglycerides or low HDL, elevated blood pressure, obesity, or microalbuminuria. Shortly afterward, the European Group for Study of Insulin Resistance (EGIR) proposed similar criteria for the insulin resistance syndrome (18).

The ATP III (1,2) simplified the WHO criteria (18) by requiring three of five simple clinical measures: increased waist circumference (abdominal obesity), elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated glucose. Abdominal obesity was not made a requirement because some persons with insulin resistance can have multiple metabolic abnormalities without overt abdominal obesity. The American Heart Association and National Heart, Lung, and Blood Institute recently reaffirmed the utility of ATP III criteria, with minor modifications (4,5) (Table 1). Simultaneously the International Diabetes Federation (IDF) (43) replaced WHO criteria with those closer to ATP III. Waist circumference thresh-
Elevated triglycerides
Elevated fasting glucose
Elevated blood pressure
Reduced HDL-C

Clinical diagnosis of the syndrome.

accompanying single risk factors (45–48); risk rises geometrically instead of linearly. This phenomenon is called multiplicative risk. Second, several metabolic risk factors are not included in standard risk algorithms; but all of them seemingly impart independent risk for cardiovascular events. These are a prothrombotic state (49–51), a proinflammatory state (52,53), and elevated triglyceride (54,55). This additional risk exceeds that which can be explained by standard risk factors. Third, some of the risk attributed to established risk factors (e.g., hypertension and low HDL) probably can be accounted for by unmeasured risk factors. For example, blood pressure-lowering with drugs fails to reduce risk as much as predicted from epidemiological studies (56); a portion of the epidemiological risk attributed to hypertension likely is subsumed by unmeasured risk factors. Likewise, the robustness of low HDL to predict ASCVD risk almost certainly is due in part to the fact that it is a marker for other metabolic risk factors (57,58).

And fourth, because metabolic syndrome often progresses and culminates in type 2 diabetes, the syndrome’s long-term risk is underestimated at any one time. Thus several lines of evidence indicate that the risk accompanying the metabolic syndrome is greater than the sum of its measured components.

DIABETOLOGIST DISCONTENT WITH NAMING OF THE METABOLIC SYNDROME

The cardiovascular community generally has embraced the concept of risk-factor clustering as a syndrome, even though it originated in the diabetes field. Moreover, cardiovascular investigators have been enthusiastic about the metabolic syndrome because it accords well with the multiple-risk-factor paradigm that is widely adopted for risk management. Conversely, the name metabolic syndrome poses problems for some investigators in diabetes. The reasons can be summarized briefly (Fig. 2).

First, a group of researchers believes that insulin resistance is the dominant cause of the syndrome (14–19,59). These investigators prefer the term insulin resistance syn-
The name metabolitic syndrome leaves open a multifactorial causation, countering one view of the essential pathogenesis. According to the insulin-resistance hypothesis, even obesity elicits the metabolic risk factors through insulin resistance.

Second, the term prediabetes, which encompasses impaired fasting glucose and impaired glucose tolerance, is meant to identify an elevated risk for type 2 diabetes (60). Yet approximately 70% to 75% of individuals with prediabetes meet clinical criteria for the metabolic syndrome (61,62). According to some investigators (63–65), prediabetes carries a predictive power for ASCVD similar to that of metabolic syndrome (63–65). But this predictive potential most likely can be explained by accompanying metabolic risk factors (66). Consequently, the overlap between prediabetes and metabolic syndrome creates a tension for nomenclature within the diabetes world.

Third, both ATP III and IDF criteria (4–6) allow for a diagnosis of metabolic syndrome to be applied to patients with type 2 diabetes who manifest a clustering of risk factors characteristic of the syndrome. The ATP III indeed defines diabetes itself as a high-risk condition for ASCVD. This high risk is due largely to associated risk factors. For example, Alexander et al. (29) reported that the metabolic syndrome, as defined by ATP III, accounts for most of the increased risk for congenital heart disease accompanying type 2 diabetes. Moreover, about 86% of persons over age 50 years living in the U.S. and who have type 2 diabetes will qualify for a diagnosis of metabolic syndrome (29). Therefore, it is not surprising that the overlap between metabolic syndrome with categorical hyperglycemia and type 2 diabetes poses significant identity issues for the diabetes community. It is not entirely clear whether type 2 diabetes as a concept is strictly hyperglycemia caused by concomitant insulin resistance and decreased insulin secretion (67,68) or whether it should include the metabolic syndrome as one of its components (29).

Regarding type 2 diabetes, the conflict in nomenclature and definitions has important clinical implications. Cardiovascular risk factors in most patients with type 2 diabetes deserve greater clinical attention than they currently receive. Intensive management including drug treatment usually is required for elevated cholesterol and blood pressure, not to mention hyperglycemia; furthermore, low-dose aspirin typically is recommended for most patients with type 2 diabetes to reduce a prothrombotic state (69). Unfortunately, many physicians who treat patients with type 2 diabetes have failed to recognize the necessity to substantially lower cholesterol and blood-pressure levels and to add aspirin prophylaxis. Clinical trials clearly document benefit of intensive reduction of non-glucose risk factors—cholesterol (70–73) and blood pressure (74,75)—in patients with type 2 diabetes. This need is strongly stated in cholesterol and blood pressure guidelines (1,2,75). For this reason, it behooves diabetes agencies as well as the cardiovascular field to take an aggressive approach to management of all cardiovascular risk factors in patients with type 2 diabetes who have features of the metabolic syndrome.

**THE METABOLIC SYNDROME IS NOT A RELIABLE RISK ASSESSMENT TOOL FOR SHORT-TERM RISK**

The metabolic syndrome carries increased long-term risk both for ASCVD and diabetes as well as higher short-term risk. The ATP III (1,2) introduced the syndrome primarily to augment the clinical management of obese persons who have progressed to the stage of multiple risk factors (Fig. 1). Importantly, the metabolic syndrome is not a reliable tool for global risk assessment for ASCVD in the short term (e.g., 10-year risk). It does not include all of the risk factors contained in standard risk-prediction algorithms (e.g., age, gender, total cholesterol, smoking status). Thus, 10-year risk assessment is best carried out with algorithms such as Framingham risk scoring (1,2). Even so individuals with the metabolic syndrome live on a higher trajectory of long-term risk for both ASCVD and type 2 diabetes. Consequently, the progressive nature of the syndrome should be recognized (Fig. 1).

But even risk algorithms based on established risk factors are limited in predictive power for individuals. More effective prediction tools are needed. One promising technique is identification of atherosclerotic burden through noninvasive imaging (76,77). The finding of significant atherosclerotic burden in patients who otherwise would not be identified as being at high risk could trigger more intensive interventions such as cholesterol-lowering drugs and low-dose aspirin. Patients with the metabolic syndrome might be particularly good candidates for atherosclerosis imaging. To date, however, the potential of this strategy has not been fully developed.

All patients with the metabolic syndrome deserve global risk assessment, whether by risk-factor algorithms or by atherosclerosis imaging; its essential purpose is to identify candidates for drug therapies for prevention. But once a person is found to have the syndrome, lifestyle therapies should be introduced, reinforced, and monitored. Drug therapy is a secondary consideration that should be guided by global risk assessment.

**LIFESTYLE MODIFICATION IS THE PRIMARY THERAPY OF THE METABOLIC SYNDROME**

The ATP III (1,2) embedded the metabolic syndrome into cholesterol guidelines to reinforce clinical lifestyle therapies. These therapies consist of weight reduction, increased physical activity, and an anti-atherogenic diet; smoking cessation in addition is mandatory. Lifestyle intervention unfortunately is often neglected in routine practice. It has the potential to reduce the severity of all metabolic risk factors at every stage of progression as well as to slow their progression (8) (Fig. 1). Drug therapies of established risk factors alone are not sufficient to completely reverse risk associated with the syndrome (i.e., risk for either ASCVD
or diabetes). Clinical trials consistently show a substantial residue of risk that cannot be reversed with drugs (56,72). Lifestyle modifications are one way to cut into this residual risk. In addition, institution of lifestyle therapies early in the syndrome can delay risk-factor progress and the need for drug therapies. Beyond reducing risk for cardiovascular disease, weight reduction and increased physical activity slows progression to type 2 diabetes in individuals with the metabolic syndrome (78,79). Thus the combined effect of drug therapies can delay risk-factor progress and the need for lifestyle therapies early in the syndrome.

**HAS THE PHARMACEUTICAL INDUSTRY USURPED THE METABOLIC SYNDROME?**

When ATP III guidelines were crafted to include the metabolic syndrome, the pharmaceutical industry recognized it as a potential target of drug therapy. The idea of reducing multiple risk factors with a single drug or a drug combination obviously is attractive and needed. It is curious that one criticism leveled against the metabolic-syndrome concept is that the pharmaceutical industry has tried to take advantage of it to promote or develop new drugs. New drug development need not detract from the priority given to lifestyle modification. Moreover, the challenge for developing a new drug that will substantially reduce multiple risk factors is formidable. Some in industry might have hoped that the scientific community would agree on a single criterion for the syndrome and, if so, that regulatory agencies would accept this criterion so that a new drug could be registered for the metabolic syndrome. This hope is unrealistic, not because of the lack of a single criterion, but because regulatory agencies are unlikely to allow registration for new targets in the cardiovascular field without clinical end-point trials.

At present, the only drugs approved for treatment of risk factors are those that target the individual risk factors: lipid-lowering drugs, antihypertensive agents, hypoglycemic drugs, anti–platelet drugs, and weight-loss agents. For the use of these drugs in persons with the metabolic syndrome, a physician should follow current treatment guidelines of the NCEP (1,2), the Sixth Joint National Commission for blood pressure treatment (75), the American Diabetes Association (69,80), the American Heart Association/ American College of Cardiology (81,82), and the National Institutes of Health Obesity Initiative (8). Pharmacological therapies for the two underlying risk factors for the syndrome—obesity and insulin resistance—are under development, albeit in the early stages. They nonetheless hold promise for adding benefit for delaying progression of the condition. Candidate drugs for treatment of the metabolic syndrome as a whole and to reduce risk for ASCVD and/or diabetes are weight-reduction drugs, peroxisome proliferator–activated receptor (PPAR)-alpha agonists (fibrates), PPAR-gamma agonists (thiazolidinediones [TZDs]), and dual PPAR agonists.

Two weight-loss drugs—sibutramine and orlistat—are already approved by the Food and Drug Administration. These improve all of the metabolic syndrome risk factors but produce only a moderate weight loss (83,84). A new and promising weight-loss drug is a selective cannabinoid receptor-1 (CB1) antagonist called rimonabant. Endocannabinoids, which activate G-protein–coupled CB1 in hypothalamus and limbic forebrain, accentuate hyperphagia (85). Rimonabant suppresses endogenous activation of the endocannabinoid system (86). The drug causes a 5% to 10% weight loss up to two years (87) and might have systemic actions that independently reduce risk factors for the metabolic syndrome (88,89).

Clinical trials suggest that fibrates will independently reduce risk for ASCVD through treatment of atherogenic dyslipidemia, possibly because of their anti-inflammatory properties (2). The TZDs lessen insulin resistance and modestly improve the various metabolic risk factors. A recent clinical trial found a strong trend toward decreasing cardiovascular outcomes with one TZD, pioglitazone (90). Dual PPAR agonists combine PPAR-alpha and PPAR-gamma agonism in a single agent and thus have favorable effects on several metabolic risk factors (91,92). In spite of promise, all of these drugs have outcome hurdles to mount before they can be approved for routine use in patients with the metabolic syndrome.

**CONCLUSIONS**

The metabolic syndrome consists of a clustering of risk factors of metabolic origin that together are associated with higher risk for ASCVD and diabetes. The syndrome occurs in approximately one-fourth of American adults. It is accompanied by insulin resistance but its increasing prevalence is due largely to escalating obesity. Simple clinical criteria are available to identify persons most likely to have the syndrome. These individuals typically have several metabolic risk factors that are not measured in clinical practice; thus the syndrome as a whole conveys a greater risk for ASCVD and diabetes than revealed by usual clinical measures. Moreover, the syndrome is a progressive condition that worsens with advancing age and increasing obesity. It often culminates in type 2 diabetes, which carries a particularly high risk for both cardiovascular events and other complications. The metabolic syndrome itself is not a robust risk assessment tool for estimating absolute 10-year risk; but its presence calls for more extensive short-term risk assessment, either by risk-factor scoring or imaging for subclinical atherosclerosis. The primary intervention is lifestyle therapy, particularly weight reduction and increased exercise. Lifestyle therapies will dampen the syndrome and slow its progression at every stage but particularly in its early phases. Drug therapies should be based on global risk assessment and should follow current treatment guidelines for each of the risk factors. But new drugs under development promise to better treat the syndrome as a whole. The
metabolic syndrome should serve to bring cardiovascular and diabetes fields together in a joint effort to reduce both ASCVD and diabetes. At present this joint action is being hampered by the issue of how to integrate the metabolic syndrome into concepts of insulin resistance, prediabetes, and type 2 diabetes, all of which are important to the diabetes field. Nonetheless, the common clustering of metabolic risk factors in obese persons is a fact of American medicine; and it deserves increased attention for clinical management of affected patients.

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