Does the Metabolic Syndrome Exist?

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In recent years, several organizations have proposed that the metabolic syndrome be introduced into clinical practice as a multidimensional risk condition for both atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (rev. in 1). This proposal generally has been well received. Recently, however, Kahn et al. (2) questioned whether evidence for the existence and characteristics of the metabolic syndrome is sufficiently developed to support its inclusion in clinical practice. Several critical issues were broached in their article. The present commentary will attempt to briefly respond to the issues raised.

Existence of the metabolic syndrome

Five risk factors of metabolic origin (atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state) commonly cluster together (1). This aggregation is frequently observed in clinical practice, and it has been convincingly documented in prospective studies by cluster analyses (3). Risk factor clustering cannot be explained by chance occurrence alone. Thus, if the metabolic syndrome is defined as multiple risk factors that are metabolically interrelated, then the syndrome certainly exists.

Appropriateness of the term "metabolic syndrome"

The commonly observed aggregation of metabolic risk factors has gone by several different names: syndrome X, insulin resistance syndrome, pre-diabetes, metabolic syndrome, dysmetabolic syndrome, plurimetabolic syndrome, cardiometabolic syndrome, dyslipidemic hypertension, hypertriglyceridemic waist, and deadly quartet (1). No single term has been universally accepted, and terminology likely will continue to be a topic of some disagreement. Kahn et al. have misgivings regarding whether the clustering of risk factors deserves the name "syndrome," although most investigators are accepting of it. Among the various names, "metabolic syndrome" is widely used and broadly accepted in both cardiovascular and diabetes fields. It is general and does not commit to a particular pathogenesis. Consequently, it is reasonable to employ the term because of precedent and common usage. The term appears to be at least as good as any of the alternatives.

Unitary causation of the metabolic syndrome

For reasons not entirely clear, some investigators stipulate the need for a single causation for a pathological process to be termed a "syndrome" (2). This requirement hardly seems warranted. In fact, the metabolic syndrome, along with many other syndromes and diseases, is multifactorial in origin. The pathogenesis of the metabolic syndrome can be separated into underlying causes and exacerbating factors. Two tightly intertwined conditions underlie the development of the metabolic syndrome. These are obesity and insulin resistance (1). Obesity causes insulin resistance, and conversely, inherent forms of insulin resistance modify adipose tissue responses to insulin and thereby recapitulate the obese state. Mechanisms whereby each elicits metabolic risk factors are increasingly understood. For example, in obese subjects (4) and those with inherent insulin resistance (5), excess amounts of nonesterified fatty acids and a host of other adipokines are released into the circulation. These several factors cause ectopic lipid accumulation in liver and muscle and contribute to insulin resistance, dyslipidemia, and prothrombotic and proinflammatory states. When obesity occurs concomitantly with a genetic basis for insulin resistance, the metabolic syndrome is worsened. Finally, the metabolic syndrome is exacerbated by other factors: physical inactivity, advancing age, endocrine imbalance, genetic factors, and abnormalities in regulation of specific metabolic risk factors. Thus, metabolic syndrome, like most other chronic conditions (e.g., type 2 diabetes and hypertension), has a multifactorial causation; however, in fact, the pathogenesis of the metabolic syndrome is better understood than that of many other recognized medical disorders. Certainly, a multifactorial etiology does not negate the syndrome's existence.

Metabolic syndrome and risk for ASCVD and type 2 diabetes

Many recent reports document that the metabolic syndrome raises the risk for both ASCVD and type 2 diabetes (1). Average relative risks are increased about twofold for ASCVD and fivefold for type 2 diabetes compared with those for individuals without the metabolic syndrome. This higher relative risk translates into a high lifetime risk for both ASCVD and diabetes. Kahn et al. misunderstand the intention of introducing the metabolic syndrome (1). It is not meant to be a risk-assessment tool for short-term (10-year) risk to guide treatment of the major risk factors with drugs. The latter is best achieved by global risk algorithms such as that provided by the Framingham Heart Study. The metabolic syndrome is a simple clinical tool to identify people with a particular set of risk factors who are at higher long-term risk for both ASCVD and type 2 diabetes. Affected individuals deserve *1*) lifestyle intervention (weight loss, increased physical activity, and a healthy diet) and *2*) more detailed, short-term risk assessment (e.g., Framingham scoring). On the basis of the latter, risk-reducing drugs may be required for treatment of individual risk factors.

Metabolic syndrome and multiplicative risk

Kahn et al. specifically ask whether the risk accompanying the metabolic syn-

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Comparison of diagnostic criteria for metabolic syndrome from the International Diabetes Federation (IDF) and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI)*

IDF clinical criteria for metabolic syndrome		AHA/NHLBI diagnostic criteria for metabolic syndrome	
Measure (central obesity plus any two of five other criteria constitute a diagnosis of metabolic syndrome)	Categorical cut points	Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome)	Categorical cut points
Central obesity	Waist circumference ethnicity specific	Elevated waist circumference	General U.S. population: ≥102 cm (≥40 in) in men, ≥88 cm (≥35 in) in women; lower cut points for insulin-resistant individuals or ethnic groups (based on clinical judgment)
Raised triglycerides	>150 mg/dl (1.7 mmol/l) or on specific treatment for this lipid disorder	Elevated triglycerides	≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.29 mmol/l) in women or on specific treatment for this lipid abnormality	Reduced HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men, <50 mg/dl (1.3 mmol/l) in women
Raised blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on treatment for previously diagnosed hypertension	Elevated blood pressure	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on drug treatment for hypertension
Raised fasting glucose	Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes	Elevated fasting glucose	≥100 mg/dl (5.6 mmol/l) or on drug treatment for elevated glucose

drome is more than the sum of its parts. This question can be answered in at least four ways. First, risk factors are multiplicative, i.e., risk for ASCVD from risk factors rises geometrically, not linearly, as the number of risk factors increases (6). Therefore, total risk is more than a summation of the individual risk factors. Second, several risk factors of the metabolic syndrome are hidden in routine clinical practice; examples include insulin resistance, prothrombotic and proinflammatory states, endothelial dysfunction, and elevated apolipoprotein B. The risk conveyed by these factors therefore is not detected by the risk factors typically measured in the clinic. Third, some of the risks associated with the major risk factors of the syndrome, low HDL cholesterol and higher blood pressure, are confounded by these unmeasured risk factors. This is important because efforts to treat a low HDL cholesterol and blood pressure will not necessarily reduce the risk accompanying the hidden risk factors. And fourth, the metabolic syndrome is a progressive disorder that worsens over time. Thus, risk measured at any one time will underestimate the long-term risk resulting from the syndrome.

Clinical criteria for diagnosis of the metabolic syndrome

Kahn et al. noted that the several proposed clinical "definitions" of the metabolic syndrome create a state of confusion that interferes with using the syndrome in practice. The evolution of clinical criteria is reviewed in ref. 1. The first tentative criteria for diagnosis were proposed only in 1998. These have now evolved and been largely harmonized in the recent update of the Adult Treatment Panel III criteria for the U.S. (1) and the International Diabetes Federation criteria (7). The two are highly congruent (Table 1). Each contains five virtually identical components, three of which can confer a diagnosis. They represent a simple way to identify individuals in clinical practice who are highly likely to have most or all features of the metabolic syndrome. All people who meet either criterion deserve *1*) lifestyle intervention to reduce long-term risk for both ASCVD and diabetes and *2*) more detailed, short-term risk assessment for ASCVD to determine whether drugs are needed to treat risk factors. In diabetic subjects, oral glucose tolerance testing is an option to identify veiled diabetes or increased risk for diabetes (7).

Extension of metabolic syndrome into type 2 diabetes

There has been a reluctance on the part of some diabetologists to allow a diagnosis of metabolic syndrome to carry into type 2 diabetes (2), although this proscription is by no means universally held (1,7). Within the realm of diabetes, there appears to be ambivalence about the meaning of type 2 diabetes. Diabetes itself is defined as a fasting glucose ≥126 mg/dl or, alternatively, a 2-h postprandial glucose ≥200 mg/dl after a 75-g glucose load or symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl. Furthermore, type 2 diabetes is defined as categorical hyperglycemia that is caused by a dual defect in glucose metabolism, namely insulin resistance and decreased insulin secretion. This definition of type 2 diabetes does not include the presence of other cardiovascular disease (CVD) risk factors, but it is commonly recognized that the majority of patients with type 2 diabetes carry multiple CVD risk factors (8). A reasonable solution to this ambiguity is to maintain the accepted definition of type 2 diabetes, i.e., hyperglycemia secondary to a dual defect in glucose metabolism, and to allow to met-

abolic syndrome to be independently identified in patients with diabetes (1,7). The alternative, i.e., including multiple CVD risk factors in the definition of type 2 diabetes, seemingly has little support in the diabetes field. Despite this, many diabetologists seem to believe that a diagnosis of metabolic syndrome should not extend into the sphere of type 2 diabetes. The logic of this position is not clear.

Even in individuals without type 2 diabetes, there is an overlap between metabolic syndrome and the condition called pre-diabetes. Again, the latter is defined by the American Diabetes Association strictly in terms of dysglycemic parameters. On the other hand, many people with categorical pre-diabetes carry multiple risk factors characteristic of the metabolic syndrome (9). Kahn et al. quoted Hunt et al. (10), who reported that impaired fasting glucose, a form of pre-diabetes, is present and associates with CVD and all-cause mortality in a general population, at least as well as either the metabolic syndrome or any of its components. However, it is most unlikely that pre-diabetes is a cause of CVD to the same extent as metabolic syndrome. As a risk factor for CVD, pre-diabetes appears to be largely a marker for the atherogenic metabolic syndrome (9). By the same token, treatment of pre-diabetes with drugs to lower glucose, e.g., metformin or thiazolidinediones, almost certainly will not reduce risk for CVD nearly as much as favorable modification of all of the metabolic risk factors. For these reasons, by the American Diabetes Association's definition, pre-diabetes is not a robust substitute for metabolic syndrome as a therapeutic target to prevent CVD.

Role of metabolic syndrome for clinical practice

Kahn et al. question whether the concept of the metabolic syndrome has matured enough to be introduced into clinical practice. However, there are several reasons why physicians, other health professionals, and patients can benefit from using this concept in practice. First, and perhaps most importantly, recognizing the metabolic syndrome will help to focus attention on the need for lifestyle therapies to reduce all metabolic risk factors concurrently. Lifestyle therapies are a neglected part of present-day clinical management of risk. Second, the syndrome identifies patients who are at increased risk for both CVD and type 2 diabetes. This will reinforce the need for lifestyle modification to prevent both conditions. Third, increased awareness of the possibility of metabolic syndrome changes medical perspective from a single–risk factor paradigm to one of multiple risk factors. In this regard, the presence of the syndrome calls for more refined risk assessment for both CVD and diabetes. For CVD risk, Framingham risk scoring is indicated; for diabetes risk, some authorities recommend glucose tolerance testing in those without diabetes (7). Finally, patients with the syndrome deserve long-term follow-up in clinical practice, including regular physician appointments and, ideally, medical nutrition therapy, behavior modification, and exercise training.

Therapeutic strategy

One approach to treatment of the metabolic syndrome is to individually and separately treat the major risk factors (elevated LDL cholesterol, hypertension, and hyperglycemia) according to current guidelines, regardless of whether the syndrome is present (2). This approach, even when necessary in higher-risk patients, tends to minimize the benefit of reducing all of the metabolic risk factors simultaneously through lifestyle intervention. Furthermore, focusing only on the major risk factors neglects the benefit of treating other metabolic risk factors (low HDL cholesterol, elevated triglycerides, and a prothrombotic state) with drugs already shown to reduce risk (1). Finally, exclusive attention to the major risk factors fails to acknowledge that the field is rapidly evolving such that new drugs to simultaneously treat multiple risk factors likely will become available in the future. One must ask whether it is necessary for these drugs to become available before the metabolic syndrome can come into being. This is analogous to saying that hypercholesterolemia did not exist before the introduction of statins.

More research is needed

Kahn et al. propose that the field needs to wait for new research before introducing the metabolic syndrome into clinical practice. Everyone favors acquisition of new knowledge. But what new knowledge must become available to trigger release of the metabolic syndrome into clinical practice? Should it be a more detailed understanding of all of the pathogenic steps linking obesity and insulin resistance to the metabolic syndrome? Should it be improved tools for risk assessment for determining long-term risk or short-term risk for ASCVD and type 2 diabetes? Should it be in the form of new drugs that simultaneously treat multiple risk factors? Or, should we wait for all national and international organizations in the cardiovascular and diabetes fields to get together and formulate more precise criteria for the diagnosis of the syndrome? Many experts in both the CVD and diabetes fields (1,7) hold the position that the questions posed by Kahn et al. have been answered sufficiently for clinical management of the metabolic syndrome to proceed. New discoveries will be welcomed and can be incorporated into clinical practice.

Summary and conclusions

The fundamental questions raised by Kahn et al. are *1*) whether the well-established clustering of metabolic risk factors underlying both CVD and type 2 diabetes deserve to be called a "syndrome" and, *2*) even if the metabolic syndrome can be accepted as a concept, whether the concept has matured enough to be introduced into medical practice. The first is a matter of semantics and is controversial because of differences in perspectives and biases of cardiovascular and diabetes communities and individual investigators. Yet the term metabolic syndrome seems to be as good for describing the proven clustering of metabolic risk factors as any alternative. The second question is more substantial and requires considerations of the growing importance of obesity in causation of CVD and diabetes, the need for more intensive lifestyle intervention in clinical risk management, and the necessity for identification of patients in whom multiple risk factors convey greater risk than otherwise recognized by a single–risk factor strategy for CVD and diabetes prevention. There appears to be growing support for moving clinical practice away from the single–risk factor strategy to one that focuses on multiple risk factors, of which the metabolic syndrome is a prime example.

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