Does a diagnosis of metabolic syndrome have value in clinical practice?1,2

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ABSTRACT
“The metabolic syndrome” is the name for a clustering of risk factors for cardiovascular disease and type 2 diabetes that are of metabolic origin. These risk factors consist of atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. There are 2 major, interacting causes of the metabolic syndrome—obesity and endogenous metabolic susceptibility. The latter typically is manifested by insulin resistance. The metabolic syndrome is accompanied by a 2-fold increase in the risk of cardiovascular disease and a 5-fold increase in the risk of type 2 diabetes. A clinical diagnosis of the metabolic syndrome is useful because it affects therapeutic strategy in patients at higher risk. However, there are 2 views about the best therapeutic strategy for patients with the metabolic syndrome. One view holds that each of the metabolic risk factors should be singled out and treated separately. The other view holds that greater emphasis should be given to implementing therapies that will reduce all of the risk factors simultaneously. The latter approach emphasizes lifestyle therapies (weight reduction and increased exercise), which target all of the risk factors. This approach is also the foundation of other therapies for targeting multiple risk factors together by striking at the underlying causes, as in the development of drugs to promote weight reduction and to reduce insulin resistance. Treating the underlying causes does not rule out the management of individual risk factors, but it will add strength to the control of multiple risk factors. Am J Clin Nutr 2006;83:1248–51.

KEY WORDS Metabolic syndrome, cardiovascular disease, risk factors, blood pressure, diabetes

INTRODUCTION
In an accompanying article, Reaven (1) presents the argument that the concept of metabolic syndrome has little or no utility in clinical practice. Reaven expands on the case recently made by Kahn et al (2), who oppose the application of the metabolic syndrome in practice. Both Reaven and Kahn et al agree on several principles by which to manage patients who have multiple metabolic risk factors. Those listed by Reaven (1) are the following: 1) patients should not be assigned a diagnosis of metabolic syndrome, 2) any major cardiovascular disease (CVD) risk factor should elicit a search for other risk factors, and 3) all CVD risk factors should be individually and aggressively treated. Each of these principles can be examined briefly.

ASSIGNING A DIAGNOSIS OF METABOLIC SYNDROME

The term the metabolic syndrome is a shorthand notation for a clustering of CVD factors of metabolic origin (3). Perhaps a more precise but more cumbersome term would be metabolic-risk-factor clustering. The risk factors included in such a clustering are atherogenic dyslipidemia, elevated blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. Atherogenic dyslipidemia further consists of a clustering of elevated triacylglycerols, greater concentrations of small and dense LDL, and low concentrations of HDL. Most patients with atherogenic dyslipidemia also have elevations of apolipoprotein (apo) B and low concentrations of apo A-I. Evidence of several types indicates that each of the metabolic risk factors either contributes to atherogenesis or predisposes a person to major coronary events.

Although Kahn et al (2) seemingly do not like to apply the term syndrome applied to risk-factor clustering, Reaven applied the term syndrome to an aggregation of cardiovascular risk factors (4, 5). Reaven hypothesized that insulin resistance is a major cause of the aggregation that he called syndrome X. In appreciation of this hypothesis and to be more specific, others (6) have used the name insulin resistance syndrome. Presumably, Reaven would not approve of assigning patients a diagnosis of either syndrome X or insulin resistance syndrome; these terms were apparently meant as biological concepts, without clinical utility. If so, the World Health Organization (WHO) Working Group on Diabetes (7), the National Cholesterol Education Program (NCEP; 8), and the European Group for the Study of Insulin Resistance (9) misunderstood Reaven’s intention to keep the term in the theoretical realm and not to extend it to clinical practice. Recently, Grundy et al, in an update of the NCEP report (3), and the International Diabetes Federation (10) have refined the clinical criteria for making a diagnosis of metabolic syndrome in clinical practice.

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The WHO group used the widely employed term metabolic syndrome instead of insulin resistance syndrome for risk-factor clustering because of uncertainty as to whether insulin resistance is the only cause of this phenomenon (7). The WHO nonetheless made evidence of insulin resistance a requirement for a diagnosis of metabolic syndrome. The NCEP (8) also adopted that term and introduced “metabolic syndrome” into clinical guidelines for cholesterol-lowering therapy because of the recognition of the growing prevalence of risk-factor clustering in an increasingly obese population. NCEP acknowledged the important role played by insulin resistance but further noted that obesity also contributes to risk-factor clustering.

Reaven and Kahn et al part company when it comes to the pathogenesis of metabolic-risk-factor clustering. Reaven (4, 5) seemingly holds that all of these factors increase insulin resistance; if so, they presumably account for most of the metabolic susceptibility that gives rise to the clustering of risk factors characteristic of the metabolic syndrome. Kahn et al (2) claim that the causes of clustering are not well understood and likely are many and diverse. Neither Reaven nor Kahn et al, however, emphasized obesity as a major cause of risk-factor aggregation. The NCEP (8) and, particularly, the IDF (10) have taken the position that obesity (especially abdominal obesity) is a dominant factor behind the multiplication of risk factors. According to the NCEP, the onset of obesity elicits a clustering of risk factors in persons who are metabolically susceptible (Figure 1; 3). Metabolic susceptibility has many contributing factors, including genetic forms of insulin resistance, increased abdominal fat, ethnic and racial influences, physical inactivity, advancing age, endocrine dysfunction, and genetic diversity. According to Reaven (4, 5), all of these factors increase insulin resistance, which in turn accounts for most of the metabolic susceptibility that gives rise to the clustering of risk factors characteristic of the metabolic syndrome.

Kahn et al (2) particularly oppose extending the concept of the metabolic syndrome to patients with type 2 diabetes, although =85% of hyperglycemic persons aged ≥50 y have metabolic-risk-factor clustering (11). It is doubtful that either Kahn et al or Reaven would object to diagnosing patients with type 2 diabetes, even though logic would require that, if a diagnosis of metabolic syndrome is rejected, so should be the use of the term type 2 diabetes in patients with risk-factor clustering. The concordance of the 2 conditions is striking (10). A key point is that simultaneous aggregation of risk factors in patients with elevated glucose concentrations is not coincidental but results from a common pathogenesis. Reaven deserves significant credit for focusing attention on a common etiologic basis for both risk-factor clustering and hyperglycemia in patients with type 2 diabetes.

Furthermore, in addition to assigning a diagnosis of diabetes, these investigators (1, 2) presumably have no qualms about applying the labels of hypertension, dyslipidemia, or obesity to patients. Therefore, the concern about informing patients that they have a clustering of these risk factors—i.e., the metabolic syndrome—is difficult to understand. This diagnosis signifying a risk-factor clustering would seem to convey more of a sense of urgency for intervention than would the presence of only a single risk factor.

**EVALUATION FOR MULTIPLE RISK FACTORS**

According to Reaven (1), when any major CVD risk factor is present, the patient should be evaluated for other risk factors. Thus, a physician must be aware of the concept of risk-factor clustering to understand the rationale for this statement. Of course, it could be said that, when any major CVD risk factor is present, the patient should be evaluated for the presence of other conditions, e.g., cancer and rheumatoid arthritis. When a physician evaluates a patient, all diagnostic possibilities are in play. So why focus on the presence of other risk factors? Obviously, the answer is that metabolic risk factors commonly occur together, and that fact is one of the main arguments for educating physicians about the metabolic syndrome so as to heighten their awareness of the phenomenon of risk-factor clustering. Such an increased awareness will lead to a more comprehensive approach to risk reduction.

At the same time, an understanding of the metabolic syndrome will help physicians to recognize that patients with a clustering of measured risk factors usually have several metabolic risk factors that are hidden from view, e.g., a prothrombotic state, a proinflammatory state, and multiple lipoprotein abnormalities, including elevations of apo B (3). The simple, recently proposed criteria for clinical recognition of the metabolic syndrome (3, 10) can be likened to an iceberg. These criteria are not meant to “define” the metabolic syndrome, as many people seem to believe, but, rather, to provide a simple means of recognizing the patient in whom much of the risk is submerged in a tangle of metabolic derangement. It seems fruitless to dissect surface configuration of an iceberg when most of the danger lies below. On the other hand, for captain of a ship at sea, seeing the tip of the iceberg can be lifesaving. The same is true for a finding of the aggregation of metabolic signs such as high triglyceridemia, low HDL, impaired fasting glucose, and mildly elevated blood pressure in a patient with an increased waist circumference. In such a patient, there is much more in the way of metabolic danger than meets the eye.

Several investigators have noted that the signals of the metabolic syndrome suggested by the WHO group (7), the NCEP (3,
TREATING ALL CARDIOVASCULAR DISEASE RISK FACTORS INDIVIDUALLY AND AGGRESSIVELY

Treatment of all CVD risk factors individually and aggressively must be a statement of principle and not one to be taken literally. There are many putative CVD risk factors, and treatment guidelines have been developed for only a limited number, namely, those that meet the criteria for being independent risk factors with proven evidence of treatment benefit. It can be assumed that this statement is meant to apply to smoking cessation, elevated LDL, hypertension, diabetes, and a prothrombotic state. Whether it is efficacious to treat elevations of triacylglycerols, reduced HDL, and a proinflammatory state either aggressively (with drugs) or at all has not been ascertained through controlled clinical trials. Moreover, the word aggressively carries the risk of being misunderstood. For example, some people believe that, because patients with established coronary heart disease will benefit from a reduction in LDL cholesterol to < 70 mg/dL (13, 14), all persons with any increase in LDL concentrations should be treated until they reach that concentration, regardless of their risk status. But that approach is currently not recommended, because of safety and cost considerations (15). It would be preferable to say that risk factors should be treated to achieve the goals of therapy developed through evidence-based medicine. It can also be questioned whether risk factors should always be treated individually. One concern about this prescription is that it may lead to the aggressive use of medications at the expense of lifestyle therapies—particularly, weight reduction and increased physical activity. These lifestyle therapies do not treat each risk factor individually but rather target multiple risk factors at once. Although lifestyle therapy may not modify any given risk factor as much as will a particular drug, its benefit lies in the fact that it produces moderate reduction in all metabolic risk factors (16). The primary reason that the NCEP introduced the metabolic syndrome into its clinical guidelines was to emphasize the importance of lifestyle therapy in clinical practice (8). Should effective weight-reduction drugs become available in the future, they would augment the benefit that can be obtained by treating multiple risk factors simultaneously—not treating them individually.

In the case of dyslipidemia, it is not clear whether the prescription to treat each risk factor individually is meant to apply to each of the atherogenic lipoprotein subfractions—triaclyglycerol-rich lipoproteins, LDL, and low HDL—separately or, rather, to the subfractions in the aggregate. Some drugs, such as nicotinic acid and fibrates, affect multiple lipoprotein risk factors simultaneously, whereas others mainly target LDL. The recommendation to treat each risk factor separately provides little guidance as to how best to treat the complex dyslipidemia of the metabolic syndrome.

HDL is a lipoprotein with a particularly complex connection to the metabolic syndrome. Patients with metabolic-risk-factor clustering usually have low HDL (3), which is designated a major risk factor for CVD on the basis of its power to predict CVD events. On the other hand, it is not known whether a therapeutic increase in HDL due to the administration of drugs will reduce the risk of CVD. That possibility will have to be tested in clinical trials that uniquely raise HDL concentrations. Thus, it may be premature to prescribe aggressive treatment of low HDL in patients with risk-factor clustering.

With respect to hypertension, there are 2 schools of thought about therapy. One holds that lowering blood pressure per se is the exclusive goal of therapy in hypertensive patients. Others hold that some anti-hypertensive agents can affect multiple metabolic systems and, hence, that the choice and priority of drug therapies should depend on a hypertensive patient’s overall metabolic state. Among the anti-hypertensive agents, thiazide diuretics and β-blockers have been shown to have adverse metabolic effects, whereas angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may have beneficial metabolic effects (17). Thus, it may be increasingly important to take a patient’s metabolic status into account when making decisions about anti-hypertensive drugs.

With respect to diabetes, several hypoglycemic agents have generalized metabolic effects; thus, it is not possible to restrict their use to an individual risk factor, namely, hyperglycemia. Among these drugs are metformin, sulfonylureas, thiazolidinediones, and insulin itself. Although these drugs may be approved by the Food and Drug Administration for a single indication, because of the complex pathways involved in the risk-factor clustering, that approval does not mean that they act exclusively on a single risk factor. Thus, treatment of hyperglycemia may improve the metabolic syndrome as a whole whether that result is intended or not. As more is learned about the actions of hypoglycemic agents, it is likely that widespread metabolic changes will be uncovered.

The future holds the promise of drugs that will affect multiple metabolic risk factors simultaneously. Even now, such drugs are under investigation. In the early stages of development are dual and pan-peroxisome proliferator–activator receptor agonists that affect energy metabolism in liver, muscle, and adipose tissue (18). Whether the current generation of drugs of this type will prove to be safe is uncertain, but they are a prototype for future drugs. It has been noted as well that some angiotensin receptor blockers have peroxisome proliferator–activator receptor–γ agonism; drugs of that type could be used to simultaneously treat elevations of blood pressure and glucose (19). Several efforts are being made to combine drugs into single capsules that simultaneously treat multiple risk factors. The FDA is open to this approach. One goal of combination drugs is that they will help to reduce the burden of polypharmacy that plagues patients with advanced risk-factor clustering.
It is understandable why Kahn et al, whose publication (2) is a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes, are reluctant to support the metabolic syndrome concept. These organizations naturally fear a dilution of the focus on type 2 diabetes, which closely resembles the metabolic syndrome. They would be expected to prefer the single-risk-factor approach because of their investment in and commitment to diabetes. It is more difficult, however, to understand why Reaven joins with these organizations. He has contributed so much to our understanding of the phenomenon of clustering of CVD risk factors. Yet, whether he approves or not, his concepts already have been widely accepted by clinicians who desire to apply them in their clinical practice. One of the reasons that the extension of the metabolic syndrome concept to clinical guidelines by WHO and NCEP was so well received by the medical world was that it was an idea whose time has come. Reaven did much to lay the foundation for this acceptance. Now it can be expected that the concept will be increasingly influential in both research and clinical practice. Moreover, whereas single-disorder organizations and subspecialties may find it difficult to embrace risk-factor clustering as a new prevention paradigm, its reality makes a move in this direction virtually inevitable.

The author has been a speaker or served as a consultant for Merck/Schering-Plough, GlaxoSmithKline, Pfizer, Kos, Bristol-Myers Squibb, Sanofi Aventis, Abbott, AstraZeneca, Sankyo, and Lilly.

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