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EDITORIAL COMMENT

The Metabolic Syndrome*

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The "metabolic syndrome" is a cluster of risk factors for cardiovascular disease (CVD) that includes hypertension, hypertriglyceridemia, low levels of high-density lipoprotein, insulin resistance, and obesity (1). Different diagnostic criteria for this syndrome have been suggested (2,3). Recently, the National Cholesterol Education Program (NCEP) put forth a definition that required the presence of at least three of the following five criteria to make a diagnosis: high-density lipoprotein <40 mg/dl in men or <50 mg/dl in women; blood pressure >130/80 mm Hg; fasting glucose >110 mg/dl; triglycerides >150 mg/dl; and waist circumference >40 inches in men or >35 inches in women (2). An important feature of this recommendation is that each of the components is easily ascertainable.

See page 1388

The use of the NCEP definition results in an apparent epidemic. The prevalence of metabolic syndrome in the U.S. population older than 20 years is 24% and rises to >40% in patients ≥60 years of age (1). The growth in prevalence of the metabolic syndrome parallels the dramatic rise in the prevalence of obesity (4).

The grouping of known cardiovascular risk factors into a syndrome has currency only if the components are synergistic in their effect and/or they have a common etiology. Although limited, available data suggest that the elements of the syndrome interact in a way that worsens the prognosis more than would be expected from the simple addition of risk factors.

The Botina study is a large (6,645 individuals) family study conducted in Finland and Sweden that aims to identify early metabolic defects in families of type 2 diabetics (5). Isomaa et al. (6) studied 4,483 of these participants, age 35 to 70 years, and identified those with metabolic syndrome according to the definition of the World Health Organization (WHO) (3). These criteria for diagnosis are different from those put forth by the NCEP, most importantly in incorporating microalbuminuria and a measure of insulin resistance into the definition. These investigators performed a multivariate analysis that adjusted for age, gender, and the presence of each of the components of the metabolic syndrome. Even after adjustment, the diagnosis of metabolic syndrome was associated with a significant threefold increase in risk of coronary heart disease and stroke and a highly significant increase in risk of cardiovascular mortality.

Salonen (7) and Lakka et al. (8) investigated the independent prognostic impact of a diagnosis of metabolic syndrome in patients entered into the Kuopio Ischemic Heart Disease Risk Factor Study. This is a prospective population-based study of men living in eastern Finland. Lakka et al. (8) excluded men with a history of cardiovascular disease, cancer, or diabetes at baseline. Multivariate analysis was performed using the NCEP and also the WHO criteria for the diagnosis of the metabolic syndrome. With either definition, presence of the metabolic syndrome was associated with increased risk independent of known covariates, including the presence of the components of the metabolic syndrome.

The study of Scuteri et al. (9) reported in this issue of the *Journal* adds further data suggestive of synergy among the risk factors comprising the metabolic syndrome. These investigators studied the effect of the presence of the metabolic syndrome, according to NCEP criteria, on arterial stiffness in patients entered into the Baltimore Longitudinal Study on Aging. Increasing arterial stiffness, for which pulse pressure has been a frequently used surrogate, is strongly associated with adverse cardiovascular events (10–17). Arterial stiffness tends to increase with normal aging and to be accelerated by the presence of cardiovascular risk factors in a manner that depends on their duration, severity, and interaction (10). In a sense, arterial stiffness represents a subtle integration of coronary risk factors into a single quantity.

Scuteri et al. (9) examined 471 participants, determining carotid intimal-medial thickness and arterial stiffness. Regression modeling disclosed a strong association of the presence of metabolic syndrome, by NCEP criteria, with increased arterial stiffness and carotid intimal-medial thickness that was independent of cardiovascular risk covariates, including each of the components of the metabolic syndrome. Furthermore, higher order interaction terms were also associated with increased stiffness and carotid-intimal thickening, suggesting synergy among the risk factors.

Thus, the available data suggest that that the confluence of risk factors that comprise the metabolic syndrome have a synergistic negative impact on prognosis. An effective therapeutic (including preventive) attack on the metabolic syndrome could dramatically reduce the burden of cardiovascular disease, underscoring the need for a far more complete understanding of the syndrome.

Central to progress is determining how to best define the metabolic syndrome. The NCEP definition is easily ascertainable by physicians and is therefore convenient operationally. However, are all of the components that should be part of the syndrome present and are they optimally de-

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fined? For instance, a central feature of the metabolic syndrome is insulin resistance (18). However, fasting hyperglycemia is an insensitive measure of insulin resistance (19). Insulin resistance may be present before the development of overt diabetes (20), and its early detection might identify patients for therapy aimed at preventing the development of diabetes. Approaches to early prevention might benefit from including an assessment of insulin resistance such as that incorporated in the WHO definition [highest quartile of: (plasma glucose × plasma insulin)/22.5] (3,6).

Another example of the difficulty with finding the optimal definition of metabolic syndrome components is obesity. The NECP criterion is easily ascertained, but is it the best possible estimate of obesity? Adipose tissue secretes a variety of potentially atherosclerosis-inducing compounds, the adipocytokines (4). It has been suggested that the level of these compounds may be a better predictor of outcome than simple waist circumference (4).

Clearly, a balance is needed between feasibility of ascertainment and prognostic effectiveness. Perhaps the definition of metabolic syndrome should be expanded in a way that permits more diagnostic flexibility in settings where the easily ascertained components of the NCEP definition are not present. One size simply may not fit all. For instance, insulin resistance precedes the development of fasting hyperglycemia. It is at this stage that the recognition of the presence of the metabolic syndrome might prompt preventive treatment rather than waiting for the development of overt diabetes. An approach to population screening may require coarser, but more easily ascertainable, measures to be practical than the more detailed workup available in a clinic devoted to lipid disorders.

Another important question is what elements should be present in the definition of the metabolic syndrome. Certainly, the elements that synergistically increase risk and/or risk factors that share a common etiology should be incorporated. Additionally, markers in the pathophysiological pathway that result in the development of metabolic syndrome components may be useful additions. For instance, it has been demonstrated that inflammatory markers, such as C-reactive protein, are associated with increased CVD risk independent of the metabolic syndrome (18). Data suggesting that inflammation may be a cause of diabetes raise the possibility that inflammation may important as an underlying etiology of the metabolic syndrome (4,16). The incorporation of inflammatory markers may, therefore, be a useful addition to the definition of metabolic syndrome.

Careful definition of the metabolic syndrome will lead to more effective prevention and treatment strategies. Additionally, an improved understanding of the dose–response relationship of risk factor reduction to prognosis is needed to formulate more effective treatment guidelines.

Conclusions. The metabolic syndrome is a series of synergistically interacting risk factors for CVD, many or all of which may share a common etiology, at least in a substantial proportion of patients. A better understanding of how to best define this syndrome is needed, including what components should be part of the definition and how they should be measured. Also, delineation of the etiology of the syndrome, including heterogeneity of etiology, will be useful in refining prevention and treatment strategies. The daunting dimensions of the apparent risk factor epidemic represented by the metabolic syndrome, combined with the suggestion that effective prevention and treatment paradigms are likely possible, strongly motivates research on this entity.

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