The 2 major definitions of the metabolic syndrome (MetS) are based on disparate views as to the etiology of this diagnostic category. Proponents of the Adult Treatment Panel III (ATP 3) version (1) consider this entity to be “truly is a syndrome,” a grouping of atherosclerotic cardiovascular disease risk factors that probably has more than one cause. In contrast, adherents to the International Diabetes Federation (IDF) definition feel that there is a specific cause of their version of the MetS (2), stating that “central obesity is an early step in the etiological cascade leading to the full metabolic syndrome.”

I believe the view expressed by the proponents of the ATP III version of the MetS that there is no single “cause” of the components is true at the most simplistic level, but misleading, whereas the notion that abdominal obesity is the “cause” of these components, as expressed by the adherents to the IDF version, can be challenged.

ONE OR MULTIPLE CAUSES OF THE MetS?
The fundamental question is whether there is one root cause that can explain the clustering of the components that comprise the various metabolic conditions thought to indicate the presence of the MetS, not whether any individual component can have more than one cause. It is obvious that any of these individual metabolic abnormalities, e.g., glucose intolerance, high triglyceride (TG) or low HDL cholesterol (HDL-C) concentration, and high blood pressure, can have more than one cause. For example, hypertriglyceridemia can result from a deficiency of lipoprotein lipase and hypertension from renal artery stenosis. Ample evidence exists, however, that insulin resistance and compensatory hyperinsulinemia increase the risk of all of these individual metabolic abnormalities, and I know of no other mechanistic explanation that fulfills that role. The substantial evidence in support of this view cannot be summarized in the context of this presentation, and perhaps the single publication that makes the point most clearly is that of Zavaroni et al. (3). These authors surveyed 732 factory workers and identified 247 individuals who were without known disease or a family history of diabetes, had normal physical examination results, and had a body mass index (BMI) < 27.0 kg/m², blood pressure < 160/90 mm Hg, no drug consumption, and oral glucose tolerance test results within reference intervals. The plasma insulin response during the glucose tolerance test of 32 of these individuals was found to be >2 SDs higher than the mean of the 247 index subjects, and these individuals were defined as being hyperinsulinemic, a finding considered to be a surrogate marker of insulin resistance (IR). A control group of insulin sensitive (IS) individuals consisted of another 32 of the 247 study participants whose insulin concentrations during the glucose tolerance test were within 1 SD of the index subjects, and who were of similar age, sex, and BMI of each individual in the IR group. The IR and IS groups were identical in age (39 years), sex distribution (22 men and 10 women), and BMI (24.7 kg/m²), and did not differ in alcohol consumption, smoking history, or work or leisure-time activity. In addition to hyperinsulinemia, the IR group exhibited some glucose intolerance, with significantly higher TG concentrations and systolic and diastolic blood pressures and lower HDL-C concentrations. Multiple regression analysis indicated that the insulin response was an independent predictor of each of the metabolic variables. Zavaroni et al. hypothesized that “a cluster of risk factors for coronary artery disease would be found in persons with normal glucose tolerance who were insulin resistant and hyperinsulinemic.” These authors concluded that their results “support the hypothesis and provide a database that permits us to speculate that insulin resistance and hyperinsulinemia have central and etiologic roles in the development of a series of events leading to an increased risk of coronary artery disease.” These same “events” serve as the components of the ATP III and IDF definitions of the MetS.
HOW CENTRAL IS CENTRAL OBESITY?

Both the ATP III and the IDF have indicated that abdominal obesity, as quantified by measuring waist circumference (WC), is of greater clinical and diagnostic importance than BMI, an estimate of overall obesity. The IDF has gone one step further, and concluded that abdominal obesity is the fundamental abnormality responsible for the development of the components that comprise the MetS (2). Substantial evidence exists that challenges these views as to the unique importance of abdominal obesity, and the results of 2 recently published reports are worth noting in this regard.

The International Day for the Evaluation of Abdominal Obesity (IDEA) was a study supported by Sanofi-Aventis to define the association of BMI and WC with CVD and diabetes in 69,409 men and 98,750 women, in 63 countries around the world. The investigators were provided with strict criteria for measuring WC, i.e., in the standing position, midway between the lowest rib and the iliac crest, but apparently such rigor was not applied in the determination of BMI, which was assessed in individuals who were clothed or unclothed, with shoes on or shoes off, etc. The participants were divided into 11 groups based on their geographic regions, and the results were presented as the odds ratios (ORs) for the association of CVD or diabetes with a 1-SD increase in BMI or WC. The authors concluded that “BMI and particularly WC were both strongly linked to CVD and especially to diabetes mellitus,” and that “routine measurements of WC—a convenient and inexpensive measure in primary care—provides a clinical marker for risk of CVD and diabetes mellitus in all regions of the world.” If the question of the convenience and reliability of measures of WC is ignored, closer inspection of the actual data might lead a reader to a somewhat more tempered conclusion as to the relative clinical utility of measurements of BMI vs WC. At the minimum, it appears to this reader that there were no substantive differences between the ORs for BMI vs WC in association with disease state in any of the 11 regions. For example, the overall ORs for the association between WC and BMI and CVD in men were 1.36 (1.33–1.39) and 1.32 (1.29–1.35), respectively, and for women similar values were 1.40 (1.37–1.43) and 1.38 (1.35–1.41). Because the difference between the ORs of the 2 indices were ≤3%, it does not seem unreasonable to suggest that the 2 estimates provided comparable clinical information. The differences between BMI and WC and the association with diabetes are somewhat greater, but in this case the “superiority” of WC was ≤9%. In light of care taken to ensure that measurements of WC were standardized, coupled with the apparent lack of concern as to the conditions for assessing height and weight and the similarity of the association between the 2 estimates of obesity and disease state, it might be concluded that it really does not matter a great deal what index of obesity is used to assess disease association.

If the results of the IDEA study raise questions regarding the unique association between WC and CVD and diabetes mellitus compared to the relationship between these clinical syndromes and BMI, the results of the recent study by Lee and associates (5) pose a serious challenge to the statement of Alberti, et al. (2) that “central obesity is an early step in the aetiological cascade leading to the full metabolic syndrome.” The study by Lee et al. included 4334 participants, including individuals of Chinese, Malay, and Asian Indian ancestry. The criteria for identifying the MetS were those outlined in (1) and (2), with the exception of the use of ethnic-specific criteria for an abnormal WC, as proposed by the IDF. The prevalence of the MetS in this population was 26.2%, with 17.7% of these individuals having an abnormal WC. Consequently, 8.5%, or one-third of those with the MetS, did not have an abnormal WC, and in these individuals at least 3 of the 4 remaining criteria were abnormal; glucose intolerance, increased blood pressure, and either a high TG or a low HDL-C concentration occurred in the absence of abdominal obesity. Furthermore, other than the degree of obesity, no differences were observed in any CVD risk factors in individuals with MetS, with or without abdominal obesity, or in the risk of developing CVD in these 2 groups. The observation that these 4 components clustered together so relatively frequently in the absence of an abnormal WC, and the similarity of the 2 groups in regard to CVD risk factors and risk of developing CVD, calls into question the view that abdominal obesity is the fundamental cause of either the metabolic abnormalities subsumed under the rubric of the MetS, or the development of CVD in these individuals.

Conclusions

The papers cited in this report (a) reinforce the notion that a cluster of related abnormalities exists that increases risk of CVD, (b) indicate that these events can occur independently of abdominal obesity, and (c) suggest that a defect in insulin action provides the most reasonable explanation to account for this phenomenon.

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References


