

Critical Questions About the Metabolic Syndrome

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In this issue of *Circulation*, Hanley et al¹ show that the metabolic syndrome, whether defined according to criteria of the National Cholesterol Education Program,² the International Diabetes Federation,³ or the World Health Organization,⁴ predicts the development of diabetes. The new finding of Hanley et al is that the International Diabetes Federation criteria, including central obesity as a critical feature of the metabolic syndrome, predicts diabetes as well as the other definitions, at least in the cohort studied. Thus, clinicians could define metabolic syndrome in any of the above 3 ways and thereby identify many patients at heightened risk of diabetes. Although diabetes and its prediction are of interest to clinicians in a variety of medical specialties and this article provides useful and valid information on this topic, the report by Hanley et al¹ leaves aside issues of cardiovascular disease (CVD) origin, pathogenesis, and risk that arguably have constituted the major impetus for heightened attention to the metabolic syndrome over the past 5 years.

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Despite recognition of the presence of clustering of metabolic and cardiovascular risk factors for many years,⁵ the term "metabolic syndrome" appeared relatively uncommonly in the medical literature until the 2001 report of the National Cholesterol Education Program (NCEP), which described the syndrome as a means of identifying more patients as candidates for lipid-altering therapies and other CVD risk factor treatments.² I conducted a PubMed search spanning from 1991 through August 2005 for articles containing the title phrase "metabolic syndrome" and found a total of 776 references cited. Before 2001, fewer than 30 articles appeared with the phrase "metabolic syndrome" in the title in any year, whereas in 2004, there were 263 such entries, and there were nearly that many already published between January and August of 2005, which projects to about 360 for the entire year. Without question, the metabolic syndrome is currently a focus of much research and clinical interest. A full summary of what is known and unknown about the metabolic syndrome is beyond the scope of this editorial; however, several excellent recent reviews are available on these issues.^{6–10} Several key facts are agreed on by consensus committees^{6,7}

and by experts writing as individuals,⁹ and these can be summarized as follows:

1. Metabolic syndrome describes a constellation of clinical characteristics that are associated with an increase in the risk of developing both atherosclerotic CVD and type 2 diabetes.
2. The "syndrome" is not a discrete entity caused by a single factor. There is considerable variation in the components found among different individuals, and this variation is even greater among different racial and ethnic groups.
3. The metabolic syndrome is not a primary target for reducing cardiovascular events. Rather, standard CVD risk factors present in patients with metabolic syndrome, including cigarette smoking, elevated levels of LDL cholesterol, and blood pressure, are primary targets for CVD risk reduction in patients with metabolic syndrome.
4. Consensus groups^{6,7} agree that considerable additional research is needed on various aspects of the metabolic syndrome to define more clearly its clinical importance, its underlying cause or causes, and whether there are treatments specific to the syndrome itself rather than its clustered and associated CVD risk factors.

More important than all other unanswered questions about the metabolic syndrome, I suggest that there are 3 critical questions that must be answered as soon as possible because, in my view, the answers will determine whether the metabolic syndrome should continue to receive the attention of clinicians and researchers that it has in the past few years. The first question is whether consideration of the metabolic syndrome, by whichever definition one chooses to use, provides a better understanding than we currently have of the cause or pathogenesis of atherosclerotic cardiovascular disease. To date, new concepts about atherosclerosis have not emerged, although the metabolic syndrome has raised interest in factors already considered to be involved, or possibly involved, in the cause or pathogenesis of atherosclerosis such as inflammation, insulin resistance, or central obesity. Given the burgeoning worldwide obesity epidemic, the metabolic syndrome has given greater attention to overweight and obesity as CVD precursors than has been the case previously. However, because no new mechanistic concepts have emerged, physicians currently are advised to identify metabolic syndrome as a marker of increased risk of diabetes or CVD, but treatments are nevertheless directed at components of the syndrome or other standard CVD risk factors rather than the syndrome itself. Without an etiological or pathogenic reason to identify metabolic syndrome, clinicians can rightfully choose now only to focus on the components or the associated major risk factors.

The second critical question is whether using the metabolic syndrome as a construct improves prediction of future risk of CVD compared with various alternatives. The NCEP report² suggests the use of a global risk score, using the Framingham

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Risk Equation, as a reasonable means of identifying those at heightened risk of CVD. Various reports (as summarized in References 6 and 10 through 12) have addressed whether the metabolic syndrome is a better means of detecting those at risk of CVD than is the Framingham Risk Score. Repeatedly,^{11,12} the answer to this question has been “no.” Thus, rather than stress the use of the metabolic syndrome for CVD risk detection, why not endorse the Framingham score and encourage its use more enthusiastically? A related question is that because the metabolic syndrome contains traits that are not included in the Framingham score, do the components of the syndrome predict CVD better than either the Framingham score or the “syndrome” itself? As summarized by Kahn et al⁶ recently, at least 5 studies have addressed these questions in various populations, and they noted that the syndrome itself conveys no greater information than the sum of the components for CVD prediction. Therefore, unless a new answer is found to this question in future research, the lack of improved risk prediction poses another reason for the metabolic syndrome to be set aside while focusing only on the individual parts.

The third question should be extremely important to both clinicians and patients and yet appears to have received no attention at all to date. Does identification of the metabolic syndrome improve patient outcomes compared with other available ways of identifying and treating CVD risk? Should clinicians endeavor to measure waist circumference, make the effort to aggregate the metabolic syndrome risk factors together for clinical risk assessment, or rather use competing alternatives such as a global CVD risk score? Studies of patient outcomes are sorely needed in which patients are classified according to metabolic syndrome criteria versus alternative modes of risk identification, treated according to guidelines, and then evaluated for improved risk factor control or (better yet) lowered CVD event rates. Given that clinicians have many competing ways to assess CVD risk,² it is appropriate to expect that evidence-based research findings will inform selection of 1 approach over another rather than merely imploring clinicians to determine risk by >1 approach.

In conclusion, although there is a great deal of interest in the metabolic syndrome by clinicians, researchers, and health policy agencies and although many articles are being published on this topic, important and key areas of uncertainty remain. In my opinion, these 3 critical questions require urgent attention if the construct of the metabolic syndrome is to continue to be a focus of clinical practice or medical research. A similar challenge has been recently issued by Kahn et al⁶ on behalf of the American Diabetes Association and the European Association for the Study of Diabetes.

Given the challenge of these key questions, research efforts should be focused on answering these questions as soon as possible.

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