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Point/Counterpoint

Metabolic Syndrome Sinkholes: What to Do When Occam's Razor Gets Blunted

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See article by Fitchett, pages 596-600 of this issue.

ABSTRACT

The real promise of the metabolic syndrome concept was the opportunity to elucidate a singular common mechanism for its component abnormalities and consequently a singular therapy. That promise has not produced. This relates to the following considerations: (1) metabolic syndrome remains a syndrome not a disease, (2) its diagnosis offers little more than what can be determined by measuring waist circumference, (3) risk assessment is not improved by the diagnosis of metabolic syndrome, (4) the diagnosis of metabolic syndrome does not impact the treatment of each component of the syndrome, and (5) there is no effective therapy for metabolic syndrome in its entirety.

RÉSUMÉ

La véritable promesse du concept de syndrome métabolique était la possibilité d'élucider le mécanisme commun particulier des anomalies de ses composantes et par conséquent mettre au point un traitement particulier. Cette promesse ne s'est pas concrétisée. Cela est fondé sur les considérations suivantes : 1) le syndrome métabolique est bien un syndrome, et non une maladie; 2) son diagnostic offre un peu plus que ce que la mesure du tour de taille permet de déterminer; 3) le diagnostic du syndrome métabolique n'améliore pas l'évaluation du risque; 4) le diagnostic du syndrome métabolique n'a pas de répercussion sur le traitement de chacune des composantes du syndrome; 5) aucun traitement efficace n'existe pour traiter globalement le syndrome métabolique.

Seek simplicity and distrust it. — Alfred North Whitehead

The Metabolic Syndrome Is a Syndrome Not a Disease

It is notable that the appreciation of the clustering of the components of the syndrome predated the isolation of insulin. However, the concept of the metabolic syndrome was really propelled into the consciousness of the cardiovascular/metabolic scientific community in 1988 by Gerry Reaven with the coining of the term "syndrome X."[1] In the 2 decades after the popularization of the concept, there was an accelerated focus of research into the mechanisms linking these phenomena—especially the appreciation of the linkage of abdominal obesity and underlying insulin resistance.

The importance of metabolic syndrome as a "hook" for the investigation of a potential unifying mechanism is unquestioned. Further, the recognition of the centrality of abdominal obesity to the manifestations of the syndrome has re-energized the field of obesity.[2] One implication of this research has been the appreciation of the importance of the assessment of waist circumference as the single best clinical index of the development of insulin resistance. Also, a raft of new discoveries —including a range of adipokines,[3] unappreciated mechanisms of sympathetic activation related to obesity,[4] and fatty acid–mediated signaling pathways—[5] can be linked to the popularization of this concept. Additionally, the discovery of the vascular effects of insulin and disordered regulation of insulin's vascular effects with obesity and hypertension occurred during the early days of the popularization of the metabolic syndrome concept.[6,7] More recently, extensive

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research in the cross talk between adipose tissue and vascular function has been considered as a mechanism linking components of metabolic syndrome.[8]

However, despite its importance as a focus of research activity, what remains is a metabolic syndrome, not a metabolic disease. This is exemplified by the various definitions that exist to describe the condition. Reaven originally included impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol.[1] He did not include obesity. The core components of our current definition have been in place since the World Health Organization definition of 1998 that added hypertension, obesity, and microalbuminuria.[9] Because of the difficulty in measuring insulin resistance by a hyperinsulinemic clamp approach, new definitions were brought forward by the National Cholesterol Education Program Adult Treatment Panel III.[10] With the American Heart Association/National Heart, Blood, and Lung Institute (AHA/NHLBI) modification of this definition in 2005, 3 of the 5 criteria of waist circumference, hypertension, hypertriglyceridemia, low HDL cholesterol, and elevated fasting glucose levels could be used to establish the definition.[11] Thus, with the AHA/NHLBI guideline, the metabolic syndrome could now be diagnosed without a measure of central obesity or insulin resistance. Notably, the widely used International Diabetes Federation definition still requires obesity (based on body mass index [BMI] or waist circumference) along with 2 of the 4 other criteria outlined.[12] However, this ambiguity in the definition of the metabolic syndrome reflects the fact that despite refining the criteria for diagnosis of the metabolic syndrome, we are no closer to defining it as a singular disease.

A Diagnosis of Metabolic Syndrome Does Not Change the Approach to Risk Factor Screening

One advantage of early identification of a disease is to mitigate further unnecessary laboratory testing or prompt screening for other risk factors. The diagnosis of metabolic syndrome is predominantly biochemical (HDL cholesterol, triglycerides, and glucose-to-insulin ratio) and physiological (blood pressure). However, making the diagnosis of the metabolic syndrome biochemically provides little additional diagnostic benefit beyond the recognition of its component risk factors (ie, dyslipidemia and hypertension). In the 2012 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines, it is recommended that the presence of metabolic syndrome prompt clinicians to screen for lipid levels.[13] However, the presence of any of the individual risk factors also prompts such action. In addition, blood pressure screening is not dependent on a diagnosis of metabolic syndrome. Further, the added value of any of these tests beyond the assessment of waist circumference has been questioned. We know that visceral fat content is highly correlated with blood pressure, insulin resistance, triglyceride levels, and HDL cholesterol levels. The concept of the hypertriglyceridemic waist has been advocated as well.[2] However, the presence of high triglyceride levels and waist circumference provides as strong information about visceral fat and prognosis as does metabolic syndrome, which does not seem to add much to either of these more simple measures.

The Diagnosis of Metabolic Syndrome Does Not Improve the Precision of Cardiovascular/ Atherosclerosis Risk Assessment

The designation of an entity as a syndrome should provide useful information with which to discriminate risk for those with and those without the condition. However, with respect to metabolic syndrome, it is unclear that this is the case. It is clear that individuals with the metabolic syndrome have an increased cardiovascular risk compared with those without the condition. Interestingly, this appears to be independent of the degree of insulin resistance. However, there is no clear evidence that a diagnosis of metabolic syndrome is associated with an adverse prognosis independent of the adverse prognosis associated with the individual components. Thus, there is no apparent synergy of risk with the aggregation of components of the metabolic syndrome. As such, the metabolic syndrome as an entity is not part of the risk engine assessment for the Framingham Risk Score or those risk engines used in Europe or the United States. The individual component of blood pressure is in these models, but glucose levels, triglyceride levels, BMI, and waist circumference are not. Measures of atherogenic lipoproteins such as low-density lipoprotein (LDL) cholesterol, apolipoprotein B, or non-HDL cholesterol are instead used for risk assessment. This is because the individual components of total cholesterol (or LDL cholesterol) and blood pressure are statistically important factors in the overall risk assessment. However, the aggregate entity of the metabolic syndrome is not. Finally, although the metabolic syndrome is certainly a risk factor for the development of type II diabetes, this is driven mainly by the presence of impaired glucose tolerance as a defined component of the syndrome.

Pharmacologic Treatment of the Individual Components of the Metabolic Syndrome Is Independent of a Diagnosis of Metabolic Syndrome

Currently, there is no single drug to treat metabolic syndrome. Further, the pharmacologic management of the components of the metabolic syndrome—ie, dyslipidemia, insulin resistance/diabetes, and hypertension—is based solely on the treatment of each singular component of the syndrome. Additionally, there is no "hard" evidence that appreciation of whether or not a patient has the metabolic syndrome has any significant impact on management of any of the individual components of the syndrome. For example, in patients with diabetes, blood glucose control and choice of hypoglycemic agent is not predicated on the presence or absence of hypertension. In hypertension, some of the first-line agents (ie, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) have been shown to improve insulin sensitivity.[14] Further, β-blockers and diuretics have been shown to worsen insulin resistance or dyslipidemia components (or both) of the metabolic syndrome.[15] However, there has never been any convincing evidence that these considerations have an impact on the therapeutic benefit of these drugs either in lowering blood pressure or, more importantly, in reducing the risk of hypertension-related cardiovascular complications. The treatment of dyslipidemia is similarly not impacted by a