Sorting Through the Relations Among Metabolic Syndrome, Insulin Resistance, and Endothelial Dysfunction

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The metabolic syndrome (MS) is a clustering of risk factors that includes abdominal obesity, dyslipidemia, hypertension, and hyperglycemia.[1] The presence of the MS is associated with an increased risk for developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[2,3] The utility of the MS has recently been questioned, because published research is inconclusive as to whether the MS confers a risk burden greater than the sum of its component factors.[4] It is clear, however, that the component risk factors included in the MS represent a common link between CVD and T2DM. Endothelial dysfunction and insulin resistance are associated with CVD and T2DM and are also associated with the MS. The relations among endothelial dysfunction, insulin resistance, and the MS are complex, and only a few studies have addressed these relations in a large sample of subjects free of CVD and T2DM.

In this issue of the *Journal*, Hamburg et al[5] report on the associations among the MS, insulin resistance, and brachial artery endothelial function in a large sample of 2,123 Framingham Offspring Cohort participants. The main objective of the study was to evaluate the relation of the MS as a single entity, and broken down into individual components, with endothelial dysfunction and insulin resistance. Subjects with previous CVD or T2DM were excluded from the analysis. The MS was defined using guidelines based on the National Cholesterol Education Program Adult Treatment Panel III.[1] Endothelial function was measured by flow-mediated dilatation and reactive hyperemic blood flow in the brachial artery. Insulin resistance was estimated using homeostasis model assessment.

Similar to previously reported national prevalence estimates,[6] the investigators found that 36% of the subjects had the MS. The presence of the MS was associated with decreased endothelial function. In addition, increasing number of MS components was correlated with progressively worse endothelial function. When the presence of the MS was adjusted for its component factors expressed as continuous variables, its association with flow-mediated dilatation was severely weakened yet remained statistically significant ($p = 0.0496$). However, a clear reduction in reactive hyperemia was still present ($p = 0.009$). Insulin resistance by homeostasis model assessment was inversely associated with endothelial function, but this relation dissolved when corrected for MS components. Hamburg et al[5] conclude that the collective burden of the component factors that make up the MS, not the presence of the condition per se, explains the association with endothelial dysfunction. The investigators further speculate that components of the MS may mediate the association between insulin resistance and endothelial dysfunction or, alternatively, that insulin resistance may be the underlying mechanism leading to the MS and endothelial dysfunction.

Although the relation between the presence of the MS and endothelial dysfunction was weakened after adjustment for the component factors of the MS, clear differences remained, especially for reactive hyperemia. Whether these differences are clinically meaningful is debatable, but they cannot be ignored. The jury is still out as to whether the MS confers increased cardiometabolic risk beyond its component factors, but the issue remains that subjects with this clustering of risk factors have a significant decrease in endothelial function that should be addressed to reduce the progression to CVD. Brachial artery flow-mediated dilatation is an independent predictor of future cardiovascular events and is considered a surrogate measure of nitric oxide bioavailability within the artery wall.[7,8] Possibly a seminal event in the atherosclerotic process, one could argue that endothelial dysfunction should be a therapeutic target for the prevention of CVD, particularly in subjects with the MS. Therefore, 1 factor to consider when choosing the specific therapies for individual components of the syndrome might be the potential impact on endothelial function.

The study by Hamburg et al[5] represents an important step toward better understanding the complex relations among the MS, insulin resistance, and endothelial dysfunction. The current data suggest that most, but not all, of the risk is explained by the cumulative burden of each individual factor, leaving the door open to the possibility that the unique convergence of risk factors that constitute the MS may confer additive risk. The large sample size from a community-based cohort and the use of well-validated and robust measures of endothelial function make the present study a welcome addition to the available research. Future studies that include detailed measures of body fat distribution and adipokines and more direct measures of insulin resistance would further strengthen the available research in this area and would extend our understanding of the potential mechanisms that link these precursors of CVD and T2DM.

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