

GUEST EDITORIAL

## Metabolic syndrome: Fact or fiction

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Recently, the American Diabetes Association (ADA) and American Heart Association (AHA) along with the National Heart, Lung and Blood Institute (NHLBI) have all made diverging statements regarding their support of the diagnosis of the metabolic syndrome and its value (Grundy, 2005; Grundy et al., 2005; Kahn, Buse, Ferrannini, & Stern, 2005a, 2005b). The AHA and NHLBI have sworn allegiances to the syndrome, while the ADA is challenging the whole concept.

The ADA voiced several concerns that challenge the validity of the metabolic syndrome concept. One of the ADA concerns will be the focus of this discussion. The current definition of metabolic syndrome based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) includes any three of the following: central obesity, hypertension, elevated triglycerides, low HDL-C, and/or impaired fasting glucose. According to the ADA, this definition does not fit all populations (Ford, Giles, & Dietz, 2002; NCEP, 2001). This has merit because it is generally agreed that insulin resistance is a pathology underlying the metabolic syndrome (Reaven, 1988). The ATP III did not include any specific measures of insulin resistance within the current definition. Instead, the ATP III apparently assumed that an insulin-resistant individual would likely also have elevated triglycerides. Although this is true within most populations (Nieves et al., 2003), elevated triglycerides are not always an early marker of insulin resistance. For example, this does not consistently hold true among nondiabetic African Americans, especially women. Since, the Charleston Heart Study in the 1960s, it has been noted that lipid patterns differ by race.

Research has shown that nondiabetic African Americans generally do not manifest the abnormal lipid profiles commonly found in Caucasian and Hispanic populations (Conway, Yanovski, Avila, & Hubbard, 1995; Knapp, Sutherland, Keil, Rust, & Lackland, 1992; Metcalf et al., 1998). The Insulin Resistance Atherosclerosis Study found

that African Americans have significantly higher HDL-C ( $p < 0.001$ ) and lower triglyceride levels ( $p < 0.001$ ) than either Caucasians or Hispanics (Haffner et al., 1999). Other large epidemiological studies such as the Charleston Heart Study (Knapp et al.) and Atherosclerosis Risk in Communities study (Metcalf et al.) confirm racial differences in lipid profiles. High to normal levels of HDL-C and acceptable triglyceride levels in nondiabetic African Americans are perplexing in the company of the paradoxically high cardiovascular-related premature morbidity and mortality in this population, which leads to significant cardiovascular health disparities.

The finding of racial differences in patterns of dyslipidemia highlights the need for further elucidation of the mechanisms involved in race-specific development of vascular injury. The popularity of the ATP III lipid criteria as is now so commonly used within primary care settings raises concerns about the reliability of the cardiovascular risk profile it predicts, especially among nondiabetic African American women, who tend to have adequate to higher levels of HDL-C and lower triglycerides than either their Caucasian or Hispanic counterparts (Appel, 2004; Appel et al., 2005; Gower, Weinsier, Jordan, Hunter, & Desmond, 2002; Liao et al., 2004). Earlier markers of cardiovascular risk among nondiabetic African American women would more likely consist of signs of insulin resistance, hypertension, and then impaired fasting glucose. These women may not manifest the common dyslipidemias screened for in the ATP III criteria until they manifest frank type 2 diabetes mellitus. Therefore, solitary use of the ATP III criteria may mislead clinical healthcare providers causing them to underestimate the level of cardiovascular risk among African Americans, particularly the women.

Based on findings from the National Health and Nutrition Examination Survey III, Hispanic women have the highest prevalence of metabolic syndrome and African American men have the lowest. Because of this, some

clinicians feel that African Americans are not predisposed to manifest the metabolic syndrome. This is very unlikely, in light of studies that show an increased risk for type 2 diabetes and cardiovascular-related diseases imposed by metabolic syndrome. African American men and women have the highest prevalence of stroke in the United States. Similarly, African American women have one of the highest prevalences of combined obesity, hypertension, and type 2 diabetes, which all lead to cardiovascular diseases. It is difficult to accept the notion that a population with such significant morbidity and mortality from components of the metabolic syndrome and its sequelae of type 2 diabetes and cardiovascular-related diseases simply do not manifest the syndrome.

Results from the Jackson Heart Study recently released and announced to the press at the 2005 AHA meeting in Dallas confirmed that 37% of 5000 African American participants had the metabolic syndrome (Gardner, 2005). Insulin resistance may be one of the earliest components of the syndrome to be manifested when the individual is still euglycemic (Reaven, 1988). Unfortunately, the current ATP III definition likely identifies the syndrome later rather than earlier by failing to consider the underlying and important pathology of insulin resistance. The metabolic syndrome was identified among participants of the Jackson Heart Study primarily by the presence of central obesity, hypertension, and impaired fasting glucose (Gardner). Impaired fasting glucose is a late sign of insulin resistance, which may take up to a decade to be fully manifested.

What then is the answer? One suggestion is to incorporate other markers of insulin resistance that have already been identified into the NCEP ATP III's metabolic syndrome definition (Appel, Jones, & Kennedy-Malone, 2004). For example, the American Association of Clinical Endocrinologists (ACE) recommended using acanthosis nigricans as an early marker of insulin resistance (ACE, 2003; Einhorn, 2003). Acanthosis nigricans is a velvety plaque that when present is easily seen on skin at the back of the neck and is most prominent among individuals with darker skin pigmentation (i.e., African Americans and some Hispanics) (Burke, Hale, Hazuda, & Stern, 1999). Unfortunately, the World Health Organization's very sophisticated measures of insulin resistance proved impractical in clinical settings (Balakau & Charles, 1999). Another method to determine the presence of insulin resistance is by calculating Homeostatic Models of Assessment (HOMA) insulin resistance, considered to be the most accurate measure of insulin resistance when used in a euglycemic individual (Appel, 2005; Matthews et al., 1985; Monzillo & Hamdy, 2003). Used early in the trajectory of risk development, HOMA calculations may alert the provider to the patient's increased risk for the metabolic syndrome and its deleterious sequelae.

No matter which definition practitioners embrace, they will have to decide how to best apply the concept of the metabolic syndrome in their practice. The question may need to be answered by each of us: Is it a whole syndrome that we need to treat or simply the sum of its parts? There is no doubt that both sides of this academic debate have merits, and examining these issues will lead to the best definition. Until the dust settles, each provider will have to weigh the evidence to decide how best to determine early patient cardiometabolic risk identification. Despite the controversy, one thing is certain. Further research is needed to determine how racial and gender differences contribute to differences in cardiovascular outcomes in order for us to eventually solve health-related disparities.

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