

# The Coming of Age of the Metabolic Syndrome

The metabolic syndrome, or insulin resistance syndrome, is present in almost one-half of older individuals and is associated with dyslipidemia (especially low HDL cholesterol, increased triglycerides, and apolipoprotein B levels), hypertension, insulin resistance/glucose intolerance/hyperglycemia, and visceral adiposity (as well as lipid deposition in other nonadipose sites) (1). Although the term "insulin resistance syndrome" has many supporters among the diabetes community, many others (especially cardiologists) favor the term "the metabolic syndrome," which will be used here.

In many countries, the prevalence of the metabolic syndrome appears to be increasing along with BMI, especially in younger individuals. Onset varies from adolescence in the most severe cases to the very elderly. Prevalence varies markedly by race/ethnicity and the environment. Those ethnic/racial groups in the U.S. living in environments with high-sugar, high-fat food and little physical activity have an extremely high prevalence of the metabolic syndrome (e.g., Pima Indians in Arizona compared with Mexico). Most individuals with type 2 diabetes have the metabolic syndrome. Although it is suspected to predate the onset of diabetes, longitudinal studies of individuals with the metabolic syndrome are needed to confirm this. It is clear that there is a step-wise increase in prevalence of the metabolic syndrome with increasing glucose intolerance/hyperglycemia. The major consequences of the metabolic syndrome are type 2 diabetes and increased cardiovascular risk. It is not known if there are any other consequences of the metabolic syndrome.

The underlying cause of the metabolic syndrome is unknown, although insulin resistance and visceral adiposity are proposed precursors. While both often occur in patients with the metabolic syndrome, the cause may be a more complex interaction of genetics/environmental milieu and could also involve the central

nervous system and/or subcellular organelles (e.g., mitochondria).

Although the association of obesity, hypertension, diabetes, and hyperuricemia was recognized in the early part of the 20th century, current definitions exclude hyperuricemia and include dyslipidemia (it was not possible to recognize dyslipidemia clinically until well into the middle of the last century, with the development of specific assays). The first publications that noted the association of hypertension, obesity, dyslipidemia, and hyperglycemia were first published in Italy in the 1960s by Crepaldi and others and subsequently by Haller and others in Germany. Reaven and Feraninni wrote landmark articles focused on this syndrome. Interest in this area has recently intensified as a result of new diagnostic criteria and the recognition of the epidemic of obesity (2,3).

Ideally, criteria for the metabolic syndrome should identify a population at high risk for atherosclerotic cardiovascular disease and the development of diabetes and be applicable in clinical practice. Practical criteria should not require use of stimulatory testing (e.g. intravenous or oral glucose tolerance tests) and should be easy to use by primary care physicians. There are at least four available definitions: World Health Organization (WHO) (1998, revised in 1999), National Cholesterol Education Program (NCEP) (2001), European Group for Study of Insulin Resistance (2002), and the American Association of Clinical Endocrinologists (2003) (2–5). Despres and his Canadian colleagues have advocated identifying these individuals using only elevated waist circumference and triglycerides ("hypertriglyceridemic waist").

The first article systematically showing the increased cardiovascular risk of the metabolic syndrome was published by Isomaa et al. (6) in 2001. More recently, researchers from the Atherosclerosis Risk in Communities and Multiple Risk Factor Intervention Trial (MRFIT) studies have also found that there appears to be an increased cardiovascular risk, al-

though not as high as that seen in individuals with coronary heart disease (CHD) or type 2 diabetes. Confirming those observations, we recently showed an increased prevalence of CHD among adults with the metabolic syndrome over 50 years using the Third National Health and Nutrition Examination Survey (NHANES III) (7). Those without the metabolic syndrome had the lowest CHD prevalence regardless of diabetes status. The metabolic syndrome without diabetes showed a higher CHD prevalence and the combination of both CHD and the metabolic syndrome had the highest prevalence of CHD (relative risk 2.1). Blood pressure, HDL cholesterol, and diabetes were significant multivariate predictors of prevalent CHD; however, after adjustment for these factors, the metabolic syndrome did not increase prevalence of CHD. Individuals with diabetes without the metabolic syndrome had no greater prevalence of CHD than those with neither. The question of whether the cardiovascular risk from diabetes without features of the metabolic syndrome is as low as seen in NHANES III remains controversial with some studies (e.g., MRFIT) showing higher risk.

Most studies comparing criteria have focused on the WHO and NCEP. Ford found that the two criteria generally identified the same individuals with discordance in a substantial minority (i.e., 15–20%) (8). Specific racial/ethnic/sex groups (e.g., African-American men) had more discordance than the overall population. The clinical implications of the differences between the criteria need to be clarified.

The study by Lorenzo et al. (9) in the current issue of *Diabetes Care* points out the value of identifying individuals with the metabolic syndrome so they can be targeted for strategies to reduce the development of type 2 diabetes. Lorenzo et al. also point out that the NCEP criteria for the metabolic syndrome seem to be better for this purpose than a modified version of the 1999 WHO criteria that excludes the 2-h glucose requirement despite the

