

# Insulin Resistance, Cardiovascular Disease, and the Metabolic Syndrome

## How well do the emperor's clothes fit?

The recent report of the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (1) identified as cardiovascular disease (CVD) risk factors what they referred to as a “constellation of lipid and nonlipid risk factors of metabolic origin,” indicated that “this syndrome is closely related to insulin resistance,” and proposed diagnostic criteria for what they designated as “the metabolic syndrome.” Since the publication of these criteria, studies have been published defining the prevalence of the metabolic syndrome in various populations (2) and the degree to which a positive diagnosis of the metabolic syndrome predicts CVD risk (3). However, the possibility that a substantial number of individuals who do not satisfy the ATP III criteria might be sufficiently insulin resistant to be at significant increased CVD risk has not been considered and neither has the ability of the ATP III criteria to identify insulin-resistant individuals been evaluated. These issues were both addressed by Liao et al. (4) in this issue of *Diabetes Care*, and their results indicate that the “ATP III criteria have low sensitivity for identifying insulin resistance with dyslipidemia in nondiabetic subjects who are at increased risk for cardiovascular disease and diabetes.”

The study by Liao et al., performed in 74 apparently healthy, nondiabetic volunteers, found that 12.2% of their population met ATP III criteria for the metabolic syndrome, a value considerably lower than that previously reported (2). However, the prevalence of the metabolic syndrome based on the Third National Health and Nutrition Examination Survey database included patients with diabetes (2), and the lower prevalence of the metabolic syndrome in the study by Liao et al. is predictable. Liao et al. quantified insulin-mediated glucose uptake (IMGU) with the euglycemic-hyperinsulinemic clamp technique and used the values obtained to calculate the sensitivity

and specificity of the ATP III criteria to identify insulin-resistant individuals. Because values of IMGU vary by at least sixfold in an apparently healthy population (5) and the values are distributed continuously, there is no objective way to classify an individual as being insulin resistant. Therefore, Liao et al. calculated the sensitivity and the specificity of the ATP III criteria for a variety of cut points. Depending on the IMGU value used, sensitivity varied from 20 to 50%. Using a somewhat arbitrary value of IMGU to define insulin resistance, they found that sensitivity decreased and specificity increased as the number of ATP III criteria were met, with the optimal balance of sensitivity (64%) and specificity (76%) reached when at least two of the criteria were met. When the 65 volunteers who did not have the metabolic syndrome were divided into insulin-resistant ( $n = 20$ ) and insulin-sensitive ( $n = 45$ ) subgroups, the insulin-resistant group was at significantly greater CVD risk, with higher fasting glucose and triglyceride concentrations, multiple adverse changes in lipoprotein metabolism by nuclear magnetic resonance subclass measures, and 20% having impaired glucose tolerance (IGT).

Parenthetically, it is worth noting that one of the ATP III criteria, impaired fasting glucose (IFG), was not present in any of the 74 subjects. This observation is consistent with the results of Tuan et al. (6), who found that only 27 of 465 subjects studied had IFG. Using a definition based on outcome data, Tuan et al. emphasized that IFG was an insensitive way to identify insulin-resistant individuals (10% sensitivity), a figure that increased approximately threefold when IGT was substituted for IFG. Similarly, when Liao et al. used IGT as a measure of abnormal glucose metabolism, the number of subjects identified increased from 0 to 12 (16.4%). Thus, IFG is not a useful way to identify either insulin-resistant individu-

als or subjects who qualify for a diagnosis of the metabolic syndrome.

The conclusion by Liao et al. that “ATP III criteria have low sensitivity for predicting insulin resistance, the primary factor in the pathogenesis of the metabolic syndrome” is consistent with the results of McLaughlin et al. (7) in their recent study of 258 overweight/obese individuals. Using the same definition of insulin resistance as Tuan et al., they found that 67 individuals who met ATP III criteria for the metabolic syndrome were also insulin resistant, resulting in a sensitivity of 52% and a specificity of 85% (values similar those of Liao et al. when they used two or more of the ATP III criteria). McLaughlin et al. also found that 87 insulin-resistant individuals were identified by simply using a fasting triglyceride concentration  $>130$  mg/dl (34%), resulting in values for sensitivity (67%) and specificity (71%) similar to the optimal values described by Liao et al. and not that different from values obtained using the more cumbersome ATP III criteria.

The consistency of the results reported by Liao et al. and McLaughlin et al. lead to the conclusion that the ATP III criteria are not particularly useful in identifying insulin-resistant individuals. On the other hand, the goal of the ATP III report was not to identify insulin resistance, but individuals at increased CVD risk. However, the results of Liao et al. also cast doubt on the utility of the criteria proposed to accomplish that goal. Comparison of the two subgroups of individuals that did not merit a diagnosis of the metabolic syndrome indicated that a number of CVD risk factors were accentuated in the subset of these individuals, who were classified as being insulin resistant. Furthermore, although waist circumference was significantly greater in patients with the metabolic syndrome, IMGU values were no different in these individuals than those in insulin-resistant subjects without the metabolic syndrome.

