Metabolic Syndrome

In search of a clinical role

The concept of a "metabolic syndrome " conferring increased risk of incident type 2 diabetes and cardiovascular disease (CVD) has been around for more than a couple of decades. Recent publication of clinical definitions has transformed the metabolic syndrome from a physiological curiosity to a major focus of research and of clinical and public health interest (1,2). The metabolic syndrome is generally considered to be the co-occurrence of obesity (particularly central obesity); elevated glucose, triglyceride, and blood pressure levels; and/or low HDL cholesterol levels, and in many cases their co-occurrence signifies underlying insulin resistance (3). The metabolic syndrome has been most widely promoted as a means to identify patients for lifestyle interventions to reduce risk factor levels and, theoretically, incident disease, particularly CVD. However, various tools already exist for the identification of apparently healthy people at elevated risk of diabetes (4–6) or CVD (7). The degree to which a clinical diagnosis of the metabolic syndrome complements or improves upon risk prediction using existing methods has not been defined.

In this issue of *Diabetes Care*, Stern et al. (8) address this question using the experience of Mexican American and non-Hispanic white participants in the San Antonio Heart Study (SAHS). After a baseline examination and 7 years of follow-up, 195 subjects subsequently developed type 2 diabetes out of 1,709 subjects without baseline diabetes (defined by diabetic hyperglycemia or self-reported use of diabetes medications) and 156 experienced a CVD event out of 2,570 subjects without baseline CVD (defined as self-reported physician diagnosis of heart attack, revascularization procedure, stroke, or CVD death by death certificate). Clinical history and metabolic risk factors measured at baseline were used to categorize subjects with the metabolic syndrome by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criteria (or World Health Organization [WHO] criteria in a secondary analysis available in an online appendix) and to calculate the probability of developing diabetes (using the Diabetes Predicting Model) or CVD (with the Framingham Risk Score). The Diabetes Predicting Model is one of the more extensively validated diabetes clinical prediction rules currently in the literature (4,9), and the present work also examines diabetes outcomes in the Mexico City Diabetes Study, providing further useful validation data for the Diabetes Predicting Model. The Framingham Risk Score is a widely available, extensively validated prediction rule for defining the probability of a coronary heart disease event in diverse populations (10). Stern et al. then used the metabolic syndrome or the prediction rules to calculate sensitivities (the probability that a set of risk factors correctly identify a subject with a subsequent event, i.e., the true-positive rate), false-positive rates, and areas under the receiver operating characteristic curve (aROC; the probability that a set of risk factors correctly discriminate subjects developing an outcome from those without an outcome, where 0.5 is chance discrimination and 1.0 is perfect discrimination). They found that in the SAHS population, the prevalence of the NCEP ATP-III–defined metabolic syndrome was 27–36%, depending on ethnicity and whether baseline diabetes or CVD were excluded. The true-positive rates of the metabolic syndrome were 66% for type 2 diabetes and 67% for CVD, and the false-positive rates were 28% for type 2 diabetes and 34% for CVD. Then, to compare the performance of the metabolic syndrome with the prediction rules, they fixed the true-positive rate for diabetes at 66% and found that the false-positive rate of the Diabetes Predicting Model was 19%. When the false-positive rate was fixed at 28%, the true-positive rate for diabetes was 76%. When they fixed the true-positive rate for CVD at 67%, they found that the false-positive rate of the Framingham Risk Score was 20%. When the false-positive rate was fixed at 34%, the true-positive rate for CVD was 81%. The aROC of the Diabetes Predicting Model was 0.819, and considering both the Diabetes Predicting Model and the metabolic syndrome together only improved the aROC to 0.824. The aROC of the Framingham Risk Score was 0.816, and considering both the Framingham Risk Score and the metabolic syndrome together gave a similar aROC (0.811). What these data mean is that the Diabetes Predicting Model more accurately identifies subjects at future risk of type 2 diabetes and the Framingham Risk Score more accurately identifies subjects at future risk of CVD than diagnosis of the NCEP ATP-III–defined metabolic syndrome. Further assigning a diagnosis of the metabolic syndrome would not tell the clinician anything more about future disease risk than they would have already known on the basis of information from the prediction rules. Stern et al. conclude that the metabolic syndrome is inferior to established rules for the prediction of either type 2 diabetes or CVD.

These data contribute valuable quantitative information that might temper the gathering enthusiasm for widespread use of the metabolic syndrome as a focus of screening for metabolic risk modification (11,12), and in many ways, the SAHS results are not surprising. As Stern et al. discuss, the metabolic syndrome would be expected a priori to be inferior to the Diabetes Predicting Model for prediction of diabetes because the metabolic syndrome does not consider a family history of diabetes, one of the most potent known diabetes risk factors. Likewise, the metabolic syndrome would be expected to be inferior to the Framingham Risk Score for prediction of CVD because the metabolic syndrome does not consider age, sex, smoking, or total cholesterol levels, all potent CVD risk factors. Further, because of collinearity in regression models containing metabolic syndrome and either of the prediction rules (here collinearity means, in effect, that the same variable

[e.g., blood pressure] is being introduced twice in the same model), it is to be expected that the aROC would not improve much over models including only the metabolic syndrome or one of the prediction rules alone. It may be self-evident that the value of a set of risk factors as a prediction tool depends entirely on what one desires to predict. Stern et al.'s results clearly suggest that for the most accurate clinical classification of future risk for diabetes, the clinician should use the Diabetes Predicting Model and, for CVD, the Framingham Risk Score.

Despite these findings, I am not sure we are quite ready to write off the metabolic syndrome as a condition unworthy of clinical attention. First, the NCEP ATP-III–defined metabolic syndrome is very readily diagnosed on the basis of a simple, standard clinical exam, whereas calculation of rule-based probabilities generally requires a computer with risk-prediction equations preprogrammed into the interface or available via the Web. Although these prediction rules provide the most sophisticated estimates of future disease risk, effectiveness data have thus far been quite discouraging about whether computerized clinical decision support can make meaningful changes in clinical care or patient outcomes (13). While outcomes data are thus far not available, it is reasonable to think that if a clinician identifies a patient as having the metabolic syndrome on the basis of a standard exam and takes action to reduce risk factor levels, then outcomes are likely to be improved to the same extent as if a more refined estimate of future disease probability had been made. Indeed, Stern et al. show that about two-thirds of SAHS subjects who eventually developed diabetes or CVD had metabolic syndrome at baseline. If a family history of diabetes, smoking, or elevated total cholesterol levels were also considered (data very likely to be collected at the same exam as the traits of the metabolic syndrome), then these might be combined with a diagnosis of metabolic syndrome to further increase concern for risk of future disease outcomes, as well as to provide additional foci for specific interventions. Unfortunately, Stern et al. do not provide data on the performance of the metabolic syndrome when these few, additional, disease-specific risk factors are also accounted for. This consideration raises the idea that perhaps the current NCEP ATP-III definition of the metabolic syndrome is not yet quite optimized for full clinical usefulness. However, there is little evidence to suggest that smoking or total cholesterol levels are intimately related to the other features of the syndrome, although genetic factors (marked by familial diabetes) may be related (14). Perhaps addition of a surrogate measure of insulin resistance might help refine the definition. Stern et al. show that the WHO metabolic syndrome definition, which requires insulin resistance as part of the definition, performs somewhat better than the NCEP ATP-III definition, which does not. In addition, other data show that the NCEP ATP-III metabolic syndrome criteria miss many subjects with measurable insulin resistance (15) and that considering insulin resistance in the criteria increases detection of the CVD risk associated with the metabolic syndrome (16) and may be required for the metabolic syndrome to indicate increased risk of diabetes (17). Others have proposed to add markers of subclinical inflammation to the syndrome criteria (18). Thus, the clinical role of the metabolic syndrome remains ill defined, in part because its current definition (at least by NCEP ATP-III criteria) may not account for the full spectrum of its underlying abnormalities or future disease risk.

A fundamental tenet of the metabolic syndrome is that it is a condition conferring increased risk for both type 2 diabetes and CVD. These data from the SAHS strongly underscore this characteristic of the metabolic syndrome. While Stern et al. do not show whether the Diabetes Prediction Model is a good predictor of CVD or the Framingham Risk Score of diabetes, they do show that that the metabolic syndrome is a reasonable all-purpose predictor of both outcomes. Another fundamental tenet is that traits of the metabolic syndrome are all highly intercorrelated; a patient with one or two traits is likely to have others as well. Although Stern et al. do not show the data, it is likely that many subjects with high predicted risk by either of the prediction rules also have the metabolic syndrome. Thus, any way one views it, a patient with obesity; elevated glucose, triglyceride, and blood pressure levels; and/or low HDL cholesterol levels is a patient likely to benefit from risk-factor–reduction interventions. A family history of diabetes, smoking, or elevated total cholesterol levels only raises the degree of concern for future disease. Because a focus on obesity in particular is likely to give the greatest payoff in terms of global risk-factor reduction (19), another way to think about the problem is that a patient with obesity and any other metabolic or familial risk factors could have their diabetes or CVD more carefully defined using existing prediction rules and should be the focus of specific, aggressive, clinical risk-factor reduction. Perhaps this is the most useful current role of the metabolic syndrome: it offers a simple public health concept and an easily identified starting point for clinical interventions known to reduce risk for the growing scourge of obesity-related type 2 diabetes, CVD, and perhaps even cancer (20).

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