

Obesity, Risk Factors, and Predicting Cardiovascular Events

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A PubMed search in March 2005 with the key word “metabolic syndrome” yielded >10 000 references. Past labels for this disorder include “syndrome X,” “deadly quartet,” and “cardiovascular dysmetabolic syndrome.”¹⁻³ What is driving the current increased interest in the metabolic syndrome? Possibly the impetus comes from the dramatic increases in obesity in the United States and other developed countries.⁴ This pandemic has been blamed variously on fast food, high-fat foods, low-fat foods, overreliance on the automobile, television, the Internet, homes in which both parents work, unsafe streets, the disappearance of physical education from the K-12 school curriculum, neighborhoods unsuitable for walking, and some or all of the above. An extensive and consistent body of evidence predicts that accompanying this increase in obesity will be increases in insulin resistance/diabetes, hypertension, hypertriglyceridemia, and decreased HDL cholesterol, as well as unfavorable changes in endothelial function and a host of inflammatory, thrombotic, and fibrinolytic factors. Thus, there is, indeed, reason for concern.

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In this issue of *Circulation*, Tankó and colleagues⁵ attempt a simplification of the National Cholesterol Education Program-Adult Treatment Panel III definition of metabolic syndrome (MS-NCEP) in postmenopausal women. They report that the combination of an enlarged waist and “elevated” triglycerides (EWET; enlarged waist, elevated triglycerides), as compared with the MS-NCEP, was equally prevalent, somewhat more predictive of cardiovascular disease (CVD) death, and somewhat more predictive of abdominal aortic calcium (AAC) progression. Their argument is carefully researched and presented but may strike the reader as counterintuitive. Why should a definition that uses only 2 criteria be a better predictor than the MS-NCEP, which requires at least 3 of 5 known atherogenic risk factors? The answer lies in the cutpoints for abnormality, the inclusion/exclusion nature of the 2 definitions, and the strength of the individual predictive components. First, the MS-NCEP uses a triglycerides cutpoint of 1.69 mmol/L (150 mg/dL), whereas the EWET cutpoint is lower, 1.45 mmol/L (128 mg/dL), and

the risk associated with triglycerides appears to reach at least to the 1.45-mmol/L level.⁶ Thus, more women appropriately qualify as having elevated triglycerides in EWET. Second, the EWET definition requires that a woman have both a large waist circumference and elevated triglycerides, whereas women meeting the MS-NCEP definition may have normal values for any 2 of the following: waist, triglycerides, blood pressure, insulin resistance, and HDL cholesterol. Finally, the strongest predictor of outcome in this study was triglycerides, and in fact, enlarged waist was not significantly related to CVD mortality in multivariate analysis, a finding concordant with our results for CVD morbidity from a large national US sample.⁷ This does not mean that enlarged waist is not a CVD risk factor, but rather that the biological effect is mediated by correlated risk factors.⁷ There is a growing consensus about the importance of triglycerides, particularly in women, and we have shown in the same national US sample that triglyceride level was the single most predictive component of the MS-NCEP for CVD in multivariate analysis.⁷

What the EWET definition really does is include all of the women with the highest risk component, triglycerides, whereas the MS-NCEP does not. This also likely explains why EWET showed a stronger relationship to AAC progression than did the MS-NCEP. The authors also report a strong association between any baseline AAC and CVD mortality, with an adjusted hazard ratio of 6.4. This is concordant with earlier studies, which similarly measured AAC with a lateral abdominal plain film.^{8,9} Several current studies are precisely quantifying AAC deposits with CT scans, and preliminary data indicate AAC may be a particularly useful “subclinical” measure. There is much interest in the idea that CVD risk equations can be improved by considering subclinical CVD measures or “newer” risk factors, such as inflammatory markers.¹⁰⁻¹² The goal would be a parsimonious and ideally inexpensive set of markers that would explain a large proportion of the variance in CVD events.

In paying such close attention to the MS-NCEP (a natural tendency, given the ongoing obesity epidemic), it is important to realize that the CVD risk factors that define the MS-NCEP and the EWET are not newly recognized. More than a half-century of prospective epidemiological research has identified several modifiable independent CVD risk factors, including cigarette smoking, hypertension, insulin resistance/diabetes, and dyslipidemia, with the best single marker of dyslipidemic risk being the total cholesterol to HDL cholesterol ratio.¹³ Our concern with the obesity epidemic rightly focuses our attention on the risk factors linked to obesity, which cluster in the MS-NCEP, but nothing we have learned in studying the MS-NCEP changes what we learned in earlier epidemiological studies. For example, in the study by Tankó et al,⁵ the 2 significant predictors of CVD mortality in their cohort other than triglycerides were low HDL cholesterol and

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hypertension, and again, enlarged waist was not predictive. The EWET ignores low HDL cholesterol and hypertension, although many women with EWET will of course have them because these risk factors are correlated.¹⁴ Thus, the findings of this study support an extensive body of literature showing that elevated triglycerides, low HDL cholesterol, and hypertension pose independent risks for CVD mortality in postmenopausal women. Cigarette smoking was presumably a risk factor as well, although hazard ratios for this variable were not presented.

Tankó et al⁵ summarize by stating they believe that “EWET comprises a simple diagnostic tool” and “further evaluation of EWET as a universally applicable screening tool . . . is warranted.” I believe the authors’ data support a different conclusion: that abnormal triglycerides, HDL cholesterol, and blood pressure should be measured, along with other independent CVD risk factors, to provide the best estimate of CVD risk. Indeed, why would you not consider HDL cholesterol if you were planning to measure triglycerides? Why would you not consider the important and routinely available blood pressure? The authors further conclude, with admirable scientific caution, “intervention studies are awaited to test the hypothesis that decreases in waist circumference and serum levels of triglycerides confer beneficial effect in terms of reducing cardiovascular risk in postmenopausal women.” This begs the question: How much more data do we really need? I think little doubt remains that weight loss in the obese patient will have a favorable impact on CVD risk.¹⁵ As for triglycerides intervention per se, one clinical trial showed that the benefit from drug therapy was related to a change in triglycerides but not cholesterol,¹⁶ and at least 3 other trials showed that the benefit of drug therapy was largely confined to subjects with high triglycerides, accompanied by low HDL cholesterol, because of its inverse correlation with triglycerides.^{17–19}

Methods to reduce obesity and improve obesity-related risk factors have not changed much throughout the course of history; they involve reduced calorie consumption or increased physical activity, and ideally both in the typical patient. Dietary weight loss and accompanying CVD risk factor reduction are direct results of reduced calorie intake and are largely unrelated to the composition of the diet used,²⁰ although individual components of diet, such as fruit, omega-3 polyunsaturated fats, and fiber, may provide additional health benefits. Of course, not all risk factors accompany obesity, and some individuals have “obesity-related” risk factors without being obese. Although pharmacological therapy will remain a mainstay of treatment, significant improvement in CVD risk factors is possible with lifestyle changes alone. Curbing the obesity epidemic at an individual and a societal level is as daunting a challenge as it is worthy a goal.

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