Measures of Obesity and Outcomes After Myocardial Infarction

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Overweight and obesity have become increasingly common; worldwide, at least 1.1 billion adults are overweight and 312 million are obese, when overweight and obesity are defined conventionally as having a body mass index (BMI) of >25 kg/m² and >30 kg/m², respectively. In the general population, overweight and obesity are associated with increased risk of developing cardiovascular disease, and thus it is not surprising that in cohorts of patients with prevalent ischemic heart disease or acute coronary events, well over 50% are overweight or obese. Despite the association between obesity and cardiovascular risk in the general population, a multitude of studies have described an inverse correlation between BMI and mortality in patients with coronary artery disease (CAD), including post-coronary revascularization patients and those with acute myocardial infarction (MI); the association between elevated BMI and improved survival has been termed the obesity paradox.

In this issue of Circulation, Zeller et al further investigate the obesity paradox in a cohort of 2229 consecutive patients presenting with acute MI in the Côte d’Or region of France. In assessing the impact of obesity on mortality after MI, the group uses both BMI, a traditional index of obesity, as well as waist circumference, an alternate anthropometric index that is more specific for abdominal obesity. Approximately one-half of the subjects in the study were overweight (BMI 25 to 29.9 kg/m²) and one-half had increased waist circumference, which was defined as >102 cm in men and >88 cm in women. Left ventricular ejection fraction, type of MI, and acute treatment strategy did not generally differ by BMI or waist circumference values. Of note, BMI was inversely correlated with age and plasma N-terminal pro B-type natriuretic peptide, whereas waist circumference was positively correlated with age and did not correlate with N-terminal pro B-type natriuretic peptide.

Consistent with prior studies, survival analysis showed that the risk of death decreased with increasing BMI tertile. In a waist-matched analysis of 832 subjects, BMI was a significant predictor of mortality, with markedly increased mortality in the low- versus high-BMI groups. However, after adjustment for age, sex, N-terminal pro B-type natriuretic peptide, and additional covariates, BMI was no longer a significant predictor of mortality in this acute MI cohort. Furthermore, waist circumference also had no effect on mortality, although multivariate analyses were not reported. The authors proceeded to stratify the cohort by both BMI and waist-circumference tertile, and identified a subgroup, namely, those with low BMI (<28 kg/m²) and high waist circumference (>104 cm in women and >105 cm in men), that was at particularly high risk for 1-year mortality.

Does the study by Zeller et al dispel the myth of an obesity paradox in patients with CAD or MI, as described by previous investigators? Although an inverse relationship between BMI and mortality did not persist after multivariable risk adjustment, this study did not demonstrate the traditional and expected relationship between obesity and increased cardiovascular risk in this acute MI population. Neither high BMI nor high waist circumference conferred increased short- or intermediate-term mortality risk. And thus the question remains: Why is obesity, which is a strong predictor of cardiovascular morbidity and mortality in the general population, not associated with detrimental effects in populations with CAD and acute MI?

BMI, defined as weight (in kilograms) divided by height (in meters squared), has been considered the gold standard for identifying patients with obesity at increased health risk, and guidelines for healthy weight by the National Institutes of Health have been based on BMI. Waist circumference, a perimeter of the abdomen variably measured at the midpoint between the lowest rib and the iliac crest, the umbilicus, or the minimum or maximum waist perimeter, is not widely used in routine clinical practice. In the general population, both BMI and waist circumference are strongly correlated with total body fat and total subcutaneous adipose tissue; however, waist circumference is a much stronger predictor of total intraabdominal adipose tissue than BMI. Intra-abdominal adipose tissue has been closely associated with features of the metabolic syndrome. BMI in CAD is not only highly correlated with total percentage of body fat, but also highly correlated with total lean body mass. In the general population, elevations of both BMI and waist circumference are associated with incidence of cardiovascular events, but several studies have shown a high waist circumference or waist-hip ratio to be a stronger predictor than increased BMI for both cardiovascular events and prevalent atherosclerosis.

Despite the cardiovascular risks associated with overweight and obesity that are observed in the general popula-

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tion, patients with CAD, several chronic disease states including heart failure, and end-stage renal disease on maintenance hemodialysis, as well as elderly populations have exhibited a reversal of the traditional obesity epidemiology.\textsuperscript{17,18} Potential hypotheses to explain the paradoxical association between obesity and improved outcomes have been set forth. Chronically ill patients with high BMI and its associated increased fat and lean mass may have a greater metabolic reserve that protects them from the inflammation and cachexia that characterize chronic catabolic diseases such as heart failure and hemodialysis. Inflammatory cytokine activation is observed not only in heart failure and hemodialysis, but also in acute MI.\textsuperscript{19–21} As the authors mention, elevated BMI may be associated with a more favorable neurohormonal profile, such as reduced levels of B-type natriuretic peptide, which is a strong predictor of mortality in both acute MI and heart failure. Alternatively, the advantages associated with obesity may be attributable to a selection bias, whereby only the healthiest obese patients are surviving long enough to present to the hospital with acute MI or a diagnosis of heart failure. Obese subjects may be more likely to be treated with guideline-recommended therapies, as described previously.\textsuperscript{6} In the present study, higher BMI in men (but not women) was associated with greater likelihood of receiving angiotensin-converting enzyme inhibitors and \( \beta \)-blockers, although revascularization was similar among the groups. Residual confounding and intrinsic limitations of observational studies may also contribute to this observed relationship.

The authors are to be commended for evaluating the obesity paradox in CAD from the viewpoint of waist circumference, an index of abdominal adiposity; most previous investigations have focused on the prognostic importance of BMI, a quantification of obesity more reflective of total body fat as well as lean mass. One previous study of acute MI found high BMI to be protective but increased waist circumference to be associated with neutral to slightly increased risk.\textsuperscript{22} Additional strengths of the study include the careful methodology in measuring waist circumference and BMI at multiple study sites, the large, well-characterized sample population, and the well-designed statistical analyses. One inevitable (given the laws in France) shortfall of the present study is the lack of race and/or ethnicity data on the subjects. Because waist-circumference cutoffs associated with increased cardiovascular risk differ by race and ethnicity, the lack of race or ethnicity data introduces the potential for bias or type II error.\textsuperscript{23} Additional limitations to the study include the absence of more direct adiposity quantification such as dual-energy x-ray absorptiometry or computed tomography, and the absence of measurements of cytokines or adipokines, which present future avenues of investigation.

Although Zeller et al\textsuperscript{9} do not find BMI or waist circumference alone to reliably predict outcomes in acute MI, the study helps to shed light on the importance of body weight and body composition in this population. In the waist circumference-BMI stratified analysis, the only subgroup identified to be at increased 1-year mortality risk were those within both the 2 lowest BMI tertiles and the highest waist-circumference tertile; the markedly increased risk observed with the presence of both low BMI and high waist circumference raises the possibility that it is the combination of decreased muscle mass and increased abdominal adiposity, which may be termed \textit{sarcopenic obesity}, that elevates mortality risk in those with CAD. Sarcopenic obesity, characterized by low muscle strength and mass combined with increased fat mass, has clearly been defined as a risk factor for inflammatory cytokine activation, metabolic syndrome, and mortality in the elderly (another obesity-paradox population). It has also been suggested that the inflammatory cytokines produced by visceral fat may contribute to catabolism and loss of lean muscle mass.\textsuperscript{24,25} Thus, determining central body fat and loss of muscle mass may be relatively more important than BMI in patients with established CAD.

Additional understanding of the risks associated with low BMI and high waist circumference in CAD will stem from further characterization of risk, including accurate quantification of body composition and fat distribution, measurement of inflammatory biomarkers, and investigation of dietary and physical activity habits. Zeller et al\textsuperscript{9} recommend “aggressive lifestyle and therapeutic interventions for secondary prevention” after MI in subjects with high waist circumference but normal BMI. What are the potential novel therapeutic interventions for this high-risk subgroup? Regular physical activity, a standard component of secondary prevention in CAD, may be particularly relevant and efficacious in patients with low muscle mass and abdominal obesity. In addition to reducing visceral adipose tissue, exercise in the elderly has been shown to help prevent sarcopenia and to aid muscle growth, and in heart failure exercise has been shown to have local antiinflammatory and anticycatabolic effects on skeletal muscle.\textsuperscript{26–28} Other avenues of research include high-protein nutritional interventions and other mechanisms to target inflammation.

The study by Zeller et al\textsuperscript{9} contributes to our understanding of obesity and body composition in CAD. Unlike the traditional epidemiological associations between obesity and cardiovascular risk that are observed in multiple studies of the general population, elevation of BMI or waist circumference in CAD does not translate to increased risk. In CAD, a more thorough assessment of body composition and body habitus may have greater prognostic relevance, and a focus on BMI as a risk factor to be modified by weight loss may be irrelevant or even harmful. To expand and improve our therapeutic interventions after MI, further clarification and characterization of favorable versus unfavorable body composition, beyond traditional definitions of obesity, are needed.

\textbf{Disclosures}

None.

\textbf{References}


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