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EDITORIAL

Is There an Obesity Paradox in Cardiogenic Shock?

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Obesity has reached epidemic levels in the United States and in much of the Westernized world.[1–3] The majority of the US population is now either overweight or obese (75%), and 42% meet the current body mass index criteria (BMI ≥30 kg/m^2) for obesity, with 9% meeting criteria for severe, class III obesity (formerly called morbid obesity with a BMI ≥40 kg/m^2 or a BMI of 35 kg/m^2 or higher and experiencing obesity-related health conditions).[1] Obesity adversely influences cardiovascular diseases (CVD) by its intersection with major CVD risk factors, including worsening of arterial pressure and glucose intolerance, thus leading to metabolic syndrome and diabetes and worsening lipids, especially triglyceride levels. Not only is obesity associated with worsening inflammation, but it also increases the prevalence of hypertension and coronary heart disease, all of which conspire to cause heart failure (HF). Thus, obesity increases the risk of HF, especially HF with preserved ejection fraction (EF) more so than HF with reduced EF. As reviewed elsewhere[3,4] obesity is associated with development of atrial fibrillation, worsened renal function, venous thromboembolism, and respiratory illness, all of which alone and together can worsen HF prognosis.

See Article by Kwon et al.

Despite the increased health risks associated with obesity, considerable focus has centered on the "obesity paradox" (wherein individuals with overweight or obesity and CVD have a better short- and medium-term prognosis than do leaner patients with the same degree of disease) among patients with CVD, end-stage renal disease, pulmonary diseases (including chronic obstructive pulmonary disease), and complications from infections.[2,3,5–8] Particularly, an obesity paradox has been noted with both HF with reduced EF and HF with preserved EF, manifest by a lower overall and CVD-mortality in people who are overweight or mildly obese, whereas hospitalizations seem to be increased as obesity progresses to severe.[9,10] In advanced stages of HF and especially in states of therapy for such a condition such as use of left ventricular assist devices or heart transplantation, the presence of obesity perpetuates complications and worsens survival.[11,12] Similarly, an obesity paradox has not been demonstrated in cardiogenic shock. Recently, Sreenivasan and colleagues[13] did not find an obesity paradox in a large US population of cardiogenic shock (CS) compared with those who were nonobese, and moderate and severe obesity had progressively higher mortality.[13,14]

In this issue of the *Journal of the American Heart Association (JAHA)*, Kwon and colleagues[15] studied 1227 patients with CS from a South Korean registry and classified patients as obese (BMI ≥25 kg/m^2 based

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on the Asian-Pacific criteria) and nonobese. In-hospital mortality was considerably higher in the men who were not obese compared with their counterparts who were obese, whereas BMI was not significantly associated with mortality in women. In their multivariate-adjusted model, mortality was 37% lower in the men who were obese, but obesity did not affect mortality in women, with evidence of significant interaction (*P* value for the association between BMI and sex 0.023). The results in the present study by Kwon et al.[15] appear to differ from the recent publications,[13,14] which did not find an obesity paradox in CS. There are significant methodological differences between prior evaluations and the Kwon study that may shed light on these observations.

First, Kwon and colleagues[15] used the Asian-Pacific BMI criteria for obesity (BMI ≥25 kg/m^2), and their average BMI in the obese group was only in the 27 to 28 range with very few (n=50) patients with a BMI ≥30 kg/m^2. The Asian-Pacific cut-point for obesity is different because at lower levels of BMI, Asian people have greater body fat and risk of cardiometabolic disease compared with the US and European populations at a similar level of BMI.[16,17] There are differences among the various Asian populations in cardiometabolic risk, including metabolic syndrome and risk of diabetes at various BMI levels, making it difficult to generalize these results to populations outside of Korea, especially if the Asian people or Asian descendants live in different countries with different environmental factor exposures. Next, the Kwon study[15] curiously found an obesity paradox only in men who were obese, who appeared to be vastly different as a group, including lower age and greater prevalence of ischemic etiology of CS that may be associated with better prognosis (than those with HF and CS) in some studies. In general, CS in the setting of a coronary heart disease event may be associated with recovery and stabilization more often (perhaps facilitated by revascularization) than in situations of severe decompensated HF. They also demonstrated markedly lower levels of N-terminal pro-brain natriuretic peptide expression; a marker associated with prognosis. Although their multivariate analysis corrected for age, it is unclear if they fully accounted for the markedly different NT-pro brain natriuretic peptide levels. Furthermore, obese men in this study had lower rates of renal replacement therapy, and more hypertension, potentially allowing for greater exposure to guideline-directed medical therapies. They were also the least likely to require mechanical ventilation, all suggesting that they may have been a less sick group by virtue of their presentation and not necessarily their obese status. The lack of knowledge in terms of how much pressor support was required in the group of men with obesity versus others is a significant limitation that cannot allow for control in the level of sickness and separation with the innate biology of obesity and its effects. Thus, there is doubt if the authors conclusively established the presence of an obesity paradox in this analysis. Even if we posit that a difference does indeed exist between patients with CS who are obese and not obese, it remains uncertain why this would be so in the state of CS, which is, after all, driven in prognosis as a metabolic complication with inflammatory states similar to the adverse consequences of obesity.[18] Perhaps one could consider that the patients with obesity have more reserve in coping with gut-derived endotoxemia, via translocation, a factor that is modulated via lipids.[19]

In summary, the strength of the present study is that this is a nested cohort of patients with homogeneous race and ethnicity, but its main weakness lies in the fact that the sickness at presentation may have accounted for the observed differences, and it is difficult if not impossible for statistical configuration to account for such confounding. Further, adipocytokine adiponectin is inversely associated with BMI, and in healthy subjects, low adiponectin is a predictor of mortality.[20] Whether there are biological differences in Asian populations between these various facets of metabolic reserve may deserve further scientific inquiry but until then, the presence of an obesity paradox in states of CS remains largely speculative.

ARTICLE INFORMATION

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