

EDITORIAL COMMENT

Impact of Obesity on Outcomes in Myocardial Infarction

Combating the “Obesity Paradox”*

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Overweight and obesity are increasing in epidemic proportions both in the United States and throughout the world (1). Alarming, the proportion of patients with severe and morbid obesity is increasing even more so than are overweight and obesity per se. Almost all of the major coronary heart disease (CHD) risk factors, including lipid disorders (especially elevated triglycerides and low levels of high-density lipoprotein cholesterol), glucose abnormalities, the metabolic syndrome, and diabetes mellitus, hypertension or left ventricular hypertrophy, and physical inactivity, are all adversely affected by overweight and obesity. Additionally, overweight and obesity may be independent risk factors for CHD and have adverse impacts on other cardiovascular (CV) disorders that may accompany CHD, including heart failure (HF), atrial fibrillation, and risk for sudden cardiac death (1).

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The Obesity Paradox

Despite these adverse effects that overweight and obesity have on CHD risk factors and CHD, numerous studies have addressed the “obesity paradox,” which suggests that once CV diseases are established, including CHD, the overweight and obese seem to have a better prognosis than do their leaner counterparts. Although some experts have discounted the obesity paradox as being partly explained by sample size errors or by unmeasured confounding factors, even large meta-analyses of CHD (2) and HF (3) have

demonstrated better event-free survival in patients with overweight and obesity compared with “normal”-weight patients.

Romero-Corral et al. (2) evaluated 40 studies of more than 250,000 patients with CHD and demonstrated that in patients grouped according to body mass index (BMI), those in the lowest BMI group had the highest all-cause mortality, whereas better survival was observed in higher BMI groups. The overweight patients (BMI 25 to 29.9 kg/m²) had the lowest relative risk, whereas obese and severely obese patients had no increased risk. In HF, Oreopoulos et al. (3) reviewed 9 major studies of nearly 29,000 patients with HF and demonstrated that overweight and obese patients had reductions in CV mortality of 19% and 40%, respectively, and reductions in total mortality of 16% and 33%, respectively, compared with normal-weight or ideal-weight patients with HF. In an analysis of more than 100,000 patients admitted to the hospital with decompensated HF, overweight and obese patients had better survival, and higher BMI was an independent predictor of lower mortality. In fact, for every 1 kg/m² increase in BMI, in-hospital mortality was reduced by 10% (4).

Mechanisms

The reasons for the obesity paradox have been difficult to decipher. Clearly, none of the major studies or meta-analyses have been able to account for nonpurposeful weight loss before study entry, which would be expected to be associated with poor survival (5). Overweight and obese patients may have lower expression of circulating atrial natriuretic peptides, which may cause patients with HF to present earlier because they are more symptomatic at an earlier stage of disease (6), but this mechanism would hardly explain the obesity paradox in patients with CHD or hypertension or in those referred for exercise stress testing or echocardiography (1,7,8–11). Overweight and obese patients may also have lower plasma renin activity and higher levels of blood pressure, allowing these patients to tolerate more proven medications at higher doses than leaner patients.

Many have blamed the obesity paradox on poor accuracy of BMI to reflect true body fatness (1,12,13). Although we agree that other measures of overweight and obesity, including waist circumference, waist-to-hip ratio, and measures of visceral and peripheral adiposity, may all be better measures of true body fatness than BMI (1,5,12,13), we have demonstrated the obesity paradox with percent body fat in both HF (14) and CHD (12,13), in which high body fat was found to be an independent predictor of better event-free survival. In recent studies in patients with CHD, central obesity was associated with mortality in patients with both “normal” BMIs as well as BMIs ≥ 30 kg/m² (15,16), and this was also noted in patients with end-stage renal disease (17). However, a recent study in patients with HF indicated that a high waist circumference was an independent predic-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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tor of better event-free survival (18,19), and our recent data suggest the same for CHD (20).

Quite possibly, overweight and obese patients who develop CV diseases may have avoided these diseases in the first place had significant weight gain been prevented, whereas the lean patients who develop CV diseases do so for other reasons, such as genetic predisposition, which could be associated with a worse prognosis.

Confounding Factors

Certainly, experts have suggested that confounding factors may partly explain the obesity paradox (21). However, prior studies have not found that even smoking or chronic obstructive pulmonary disease could completely explain this paradox (13,22,23). In contrast, 2 recent studies have suggested that obese patients with low fitness seem to have higher mortality (9,16). In our studies, in which peak oxygen consumption was clearly a significant independent predictor of better event-free survival in both HF (14) and CHD (13), we nevertheless determined that low BMI and low body fat remain independent predictors of higher mortality. However, in our patients with CHD, the obesity paradox appears to be mostly present in the unfit patients.

In the report by Das et al. (24) in this issue of the *Journal*, the investigators report the impact of extreme obesity on in-hospital outcomes in patients with ST-segment elevation myocardial infarction (STEMI). An equally important finding is their explanation of the obesity paradox, for which they describe a U-shaped mortality curve, with the highest mortality in the "normal"-BMI group, followed by patients with Class III obesity (BMI >40 kg/m²). After adjusting for potential confounding factors, only the Class III obese patients appeared to have significantly higher in-hospital mortality (but not major bleeding complications). The investigators indicate that the higher mortality in the "normal"-weight patients that disappears after adjustment is due to confounders in these patients. Although many prior studies have disputed this finding, in this very large cohort of patients with STEMI, it appears that confounding factors partly explain the obesity paradox, at least regarding in-hospital mortality. Although Das et al. (24) also propose that the "normal"-weight patients are actually "abnormal" considering today's obese society, and that the mildly obese should now be the true reference group (at least in this STEMI population), we believe that the markedly increased rate of CV diseases associated with overweight or obesity does not support classifying mild obesity as the "new normal."

Class III Obesity

The major emphasis in the present report by Das et al. (24) is in those patients with Class III obesity. Although this group represented only 5.1% of the STEMI population, as mentioned earlier, this group is "ever growing" in size and represents more than 2,500 patients in the present study.

Although the normal-BMI group had the highest unadjusted in-hospital mortality (hazard ratio: 1.84; 95% confidence interval: 1.63 to 2.08), patients with Class III obesity had increased mortality in both the unadjusted (hazard ratio: 1.43; 95% confidence interval: 1.20 to 1.71) and adjusted models (hazard ratio: 1.64; 95% confidence interval: 1.32 to 2.03) compared with the Class I obese (BMI 30 to 34.9 kg/m²) "reference group." Clearly, Class III or "morbid" obesity is not benign and is associated with extremely high prevalence of CHD, HF, atrial fibrillation, and most CV diseases, as well as with a poor prognosis, including high in-hospital mortality, in patients with STEMI.

Conclusions

Overweight and obesity are associated with high prevalence of almost all major CV diseases, including HF, atrial fibrillation, hypertension, and CHD. Although confounding factors may partly account for the obesity paradox (at least in the in-hospital mortality for STEMI), the "weight" of evidence still supports an obesity paradox in most CV disorders. Studies of purposeful weight loss using major CV end points are needed in the prevention and treatment of various CV disorders, especially CHD and HF (25,26).

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Key Words: extreme obesity ■ obesity ■ outcomes ■ quality of care ■ STEMI.