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New Insights into the "Obesity Paradox" and Cardiovascular Outcomes

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Introduction

Overweight and obesity are increasing in epidemic proportions both in the United States (US) and throughout the Western World [1]. A considerable burden from cardiovascular disease (CVD) in the US has been "heavily" impacted by the obesity epidemic, with the current estimation of obesity prevalence in US children and adolescents being just under 20%, with a prevalence >33% in adults 24-74 years of age [2]. Alarmingly, the proportion of patients with either severe or morbid obesity is increasing even more so than are overweight and obesity per se [1]. Almost all of the major CVD risk factors, including glucose abnormalities (impaired fasting glucose, metabolic syndrome, and type 2 diabetes mellitus), lipid disorders (especially elevated levels of triglycerides and low levels of high-density lipoprotein cholesterol), hypertension (HTN) and left ventricular hypertrophy, and physical inactivity ,as well as sleep apnea, are all adversely impacted by overweight and obesity [1,3-5]. In addition, overweight and obesity may be independent risk factors for coronary heart disease (CHD) and have adverse impacts on almost all CVD, including HTN, heart failure (HF), atrial fibrillation (AF), and sudden cardiac death [1,3-5].

Despite the powerful impact, however, that overweight and obesity have on CHD risk factors, CHD, and other CVD, numerous studies and meta-analyses have addressed the "obesity paradox," which indicates that once CVD becomes established, including CHD, HF, HTN, and AF, overweight and obese have a better prognosis than do their lean counterparts with the same CVD [1,3-7]. The obesity paradox has been discounted by some experts who have suggested that this may be due to such factors as sample size errors or by unmeasured confounding factors, as was also suggested in a recent major study of in-hospital mortality in acute myocardial infarction [3,8,9]. However, even very large meta-analyses have demonstrated this paradox in CHD and HF [6,7]. In fact, Romero-Corral and colleagues [6] 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 or "normal" BMI group had the highest all-cause mortality, whereas better survival was observed in higher BMI groups. The overweight had the lowest relative risk, whereas obesity and severe obesity have no increased mortality risk. Likewise, in HF, Oreopoulos and colleagues [7] reviewed 29,000 patients from 9 major HF studies and demonstrated reductions in CV and total mortality of 19% and 16%, respectively in the overweight and 40% and 33%, respectively in the obese compared with normal-weight patients with HF.

Many have blamed the obesity paradox on relatively poor accuracy of BMI to reflect true body fatness, and we agree that other measures of body composition [including waist circumference (WC), waist-to-hip ratio, and measures of visceral and peripheral adiposity] may all be superior to BMI in the assessment of body fatness [1,3-6,10-15]. We have demonstrated the obesity paradox, however, in both HF [14,16] and CHD [13,15,17-19] with both BMI and percent body fat (BF), demonstrating that BF was an independent predictor of better event-free survival. In CHD, we have demonstrated that low BF (≤ 25% in men and ≤ 35% in women) predicted a nearly three-fold increase in mortality compared with high BF [10,12,14]; also, we demonstrated that the combination of low BF and low BMI (< 25 kg/m^2) [13] and, particularly, low BF and low lean body mass [15] was associated with the worst survival in stable CHD. In HF, for every one percent increase in BF, there was a 13% increase in event-free survival [16].

Interestingly, the data regarding central obesity/WC and the obesity paradox has been mixed [19-25]. Several recent studies in CHD have indicated that central obesity was associated with mortality in patients with both "normal" BMIs as well as an overweight/obese BMIs [20,21], and this was also noted in end-stage renal disease [22]. However, another recent CHD paper from me and my colleagues in a very large cohort demonstrated that the obesity paradox was present even in those with central obesity (high WC), at least in those with low levels of cardiorespiratory fitness (CRF; discussed below) [19]. Another recent study in HF indicates that a high WC was an independent predictor of better event-free survival, with the best survival occurring in those with both a high WC and high BMI [23,24], and preliminary data from our Ochsner group suggest the same for CHD [25].

The reasons for the obesity paradox have been difficult to decipher. Certainly, none of the major studies or meta-analyses have been able to account for the possibility of non-purposeful weight loss prior to study entry, which clearly would be expected to be associated with poor survival [1,3-5,14,24]. Overweight and obesity have lower expression of brain natriuretic peptide, which may cause obese patients with HF to present earlier due to increased symptoms at an earlier stage of disease [26], but this mechanism would hardly explain the obesity paradox in stable patients with CHD or HTN or in those referred for exercise stress testing or echocardiographic assessment (even with normal left ventricular systolic function) [1,3-5,14,18,24,27-29]. Overweight and obese may also develop symptoms/signs, such as dyspnea and peripheral edema that mimic those of CVD but are instead due to deconditioning, restrictive lung disease, and venous insufficiency, but

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nevertheless lead to an earlier presentation with milder disease [30]. Additionally, overweight/obese may also have lower plasma renin activity and higher levels of arterial pressure, allowing these patients to tolerate more proven medications at higher doses than do leaner patients with CVD [1]. Confounding factors, such as less smoking and lower age, could partly impact the obesity paradox, but this paradox is still present when these factors are adequately accounted for in multivariate analyses [13,15,31-33]. Quite possibly, overweight and obese patients who develop CVD may have avoided CVD in the first place had significant weight gain during adulthood been prevented, whereas the lean patients who develop the same CVD do so for other reasons, such as genetic predisposition, which could be associated with a worse prognosis [3-5, 24].

So far, however, one confounding factor that has been consistent is the impact of CRF on the obesity paradox. In four separate studies of cohorts with CHD, overweight/obese with high CRF have a low mortality and there does not appear to be an obesity paradox, whereas the obesity paradox is present in those with low levels of CRF [18-20,34]. preliminary data from a large multicenter study in HF suggest the same [35]. Importantly, CRF appears to significantly impact the relationship between adiposity and subsequent CVD and mortality risk in both CHD and HF. Therefore, assessing adiposity without understanding CRF may be misleading, since CRF markedly influences the importance of body composition on CVD prognosis.

In conclusion, overweight and obesity worsen almost all of the CVD risk factors and are associated with a high prevalence of almost all major CVD, including CHD, HF, HTN and AF. Despite these factors, an obesity paradox exists, in that overweight/obese with established CVD have an overall favorable prognosis, even more so than do their lean counterparts with the same CVD. Nevertheless, the overall "weight" of evidence all supports purposeful weight reduction for overweight/obese, for both the primary and secondary prevention of CVD [1,3-5,24,36-38]. However, randomized controlled clinical trials of varying intensity of exercise training (to improve both CRF and muscular strength) [39] and weight reduction (including the newer weight loss medications) [1,3-5,24,36-38] are clearly needed to evaluate the impact of purposeful weight loss, especially in secondary prevention of CVD.

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