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Obesity and the Obesity Paradox in Heart Failure

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ABSTRACT

Obesity is a growing public health problem in the general population, and significantly increases the risk for the development of new-onset heart failure (HF). However, in the setting of chronic HF, overweight and mild to moderate obesity is associated with substantially improved survival compared to normal-weight patients. Evidence exists for an "obesity paradox" in HF, with the majority of data measuring obesity by body mass index, but also across various less-frequently used measures of body fat (BF) and body composition including waist circumference, waist–hip ratio, skinfold estimates of percent BF, and bioelectrical impedance analysis of body composition. Other emerging areas of investigation such as the relationship of the obesity paradox to cardiorespiratory fitness are also discussed. Finally, this review explores various explanations for the obesity paradox, and summarizes the current evidence for intentional weight loss treatments for HF in context.

Prevalence of obesity in general and HF populations

Obesity is a growing public health problem in the United States and worldwide. Between 1960–1962 and 2009–2010 the percentage of obese patients as identified by body mass index (BMI) in the U.S. National Health and Nutrition Examination Survey nearly tripled, from 13.4% of patients with BMI ≥30 kg/m^2 and 0.9% with BMI ≥40 kg/m^2 initially, to 36.1% with BMI ≥30 kg/m^2 and 6.6% with BMI ≥40 kg/m^2 in the most recent study period.[1] During this time, the percentage of overweight (BMI 25.0–29.9 kg/m^2) remained stable at approximately one-third of the population, meaning that the distribution of BMI in the U.S. has now drastically shifted toward higher values. Overweight and obesity, as defined by BMI, are highly prevalent in heart failure (HF) populations as well. While prevalence varies by population studied, 32%–49% of HF patients are obese (BMI ≥30 kg/m^2) and 31%–40% are overweight (BMI 25.0–29.9 kg/m^2).[2,3] Of note, obesity is significantly more prevalent in HF patients with preserved ejection fraction as compared to those with reduced ejection fraction.[4]

Obesity as a risk factor for HF

Obesity as measured by elevated BMI is a major risk factor for the development of HF. Among 5,81 patients in the Framingham Heart Study, BMI was found to correlate with HF risk in a dose-dependent fashion: HF risk increased by 5% for men and 7% for women for each single-unit increase in BMI, even after adjustment for demographics and other known risk factors such as diabetes, hypertension, and cholesterol.[5] This positive correlation between BMI and HF risk for both overweight and obese was confirmed in the larger Physicians' Health Study of 21,094 men without known coronary artery disease, where overweight participants had a 49% increase in HF risk compared with lean participants and obese participants had a 180% increase (95% CI, 124–250).[6]

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Abbreviations and Acronyms

BIA = bioelectrical impedance analysis

BF = body fat

BMI = body mass index

CRF = cardiorespiratory fitness

DEXA = dual-energy x-ray absorptiometry

EATE = picardial adipose tissue

HF = heart failure

WC = waist circumference

These same trends have been demonstrated in non-U.S. populations. A study of 59,178 participants demonstrated the graded link between BMI and HF risk, with multivariable-adjusted hazard ratios of HF for normal, overweight, and obese BMI of 1.00, 1.25, and 1.99 for men and 1.00, 1.33, and 2.06 for women, respectively.[7] Levitan and colleagues[8] analyzed two population-based prospective cohorts of 80,630 Swedish men and women; not only higher BMI but higher waist circumference (WC), waist–hip ratio, and waist to height ratio were associated with higher risk of HF hospitalization and mortality.

Evidence for an obesity paradox in HF

Although elevated BMI is well established as a risk factor for HF, a surprising relationship between BMI and outcomes in those with established HF has been observed. Obesity as measured by BMI and various other indices has been linked to improved HF survival in observational studies. This counter-intuitive epidemiologic association between survival outcomes and traditional risk factors, reverse epidemiology or "obesity paradox," has now been well documented in numerous studies in the HF medical literature. It was first described by Horwich et al.[9] in 2001 in a cohort of 1203 advanced systolic HF patients followed at a single university transplant center, where patients with higher BMI (>27.8 kg/m^2) were found to have significantly improved risk-adjusted, transplant-free survival (Fig 1). The worst outcomes were seen in the underweight group, followed closely by normal-weight HF patients. A subsequent analysis of 7767 stable outpatients with chronic HF enrolled in the Digitalis Intervention Group also revealed lower risk-adjusted mortality rates in the overweight and obese compared to normal-weight patients, with hazard ratios of 0.88 (0.80–0.96) and 0.81 (0.72–0.92), respectively.[10] Another large, randomized controlled trial of 7599 patients with symptomatic HF with either reduced or preserved systolic function showed that patients in lower BMI categories (underweight and normal weight) had a graded increase in the risk of death; the group with the highest BMI (>35 kg/m^2) had similar risk to those with a BMI of 30.0–34.9 kg/m^2).[2] Larger investigations such as a meta-analysis of nine observational HF studies (n = 28,209) by Oreopoulos et al.[11] also found that overweight and obese individuals respectively had reduced cardiovascular (−19% and −40%, respectively) and all-cause (−16% and −33%) mortality during 2.7 years of follow-up as compared with those without elevated BMI. Another analysis of BMI and its relationship to in-hospital mortality for 108,927 patients with decompensated HF identified a 10% reduction in mortality for every 5-unit increase in BMI ($P < 0.001$).[12]

Most studies of the obesity paradox have used BMI to estimate body composition and identify overweight and obese patients, for reasons of widespread acceptance and ease of use. However, the reliability of BMI as a measure of adiposity has been questioned. Numerous alternate techniques may be more accurate to define obesity, including the currently clinically used waist circumference (WC), waist–hip ratio, skinfold estimates of percent body fat (BF), and bioelectrical impedance analysis (BIA) of body composition. Dual-energy x-ray absorptiometry (DEXA) is useful for assessment of BF and body compartments, but has limited application due to expense and required technical expertise.[13,14] The current gold standards for assessing body composition are computed tomography (CT) and magnetic resonance imaging (MRI), which are thought to provide the most reliable information on internal adipose tissue depots and lean mass, but application of these methods are also limited by expense.[15]

WC is a simple and inexpensive way to assess for abdominal obesity, and an established predictor of cardiovascular risk in the general population.[16,17] Not only higher BMI but also higher WC has been shown to be associated with improved outcomes in both men and women with advanced HF. In fact, patients with both overweight or obese BMI and high WC (defined as ≥88 cm in women and ≥102 cm in men) had the best survival in a cohort of advanced systolic HF patients at a university transplant referral center.[18,19]

A study of 209 HF patients used the average of three skinfolds to measure BF (thigh, chest, and abdomen skin folds in men; thigh, triceps, and suprailiac in women).[20] Increased percent body fat independently predicted better event-free survival in a linear fashion: every 1% absolute increase in

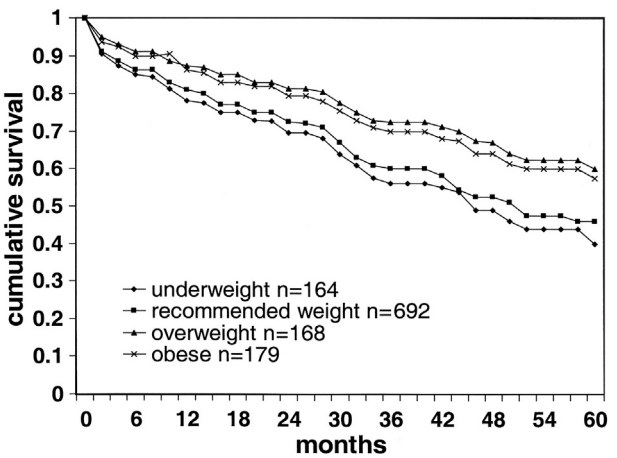

Fig 1 – Risk-adjusted survival curves for the four body mass index (BMI) categories at 5 years. The variables entered into the equation were age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak VO_2), mitral regurgitation, tricuspid regurgitation, medications and serum sodium, creatinine and lipid levels. Survival was significantly better for the overweight and obese BMI categories. (Adapted from Horwich et al.,[9] with permission from Elsevier.)