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Body Composition and Heart Failure Prevalence and Prognosis: Getting to the Fat of the Matter in the "Obesity Paradox"

Obesity has been increasing in epidemic proportions in both adults and children in the United States.[1,2] Overweightness and obesity are now critical problems, with the prevalence among adults increasing by nearly 50% during the past 2 decades[3]; currently nearly 70% of adults are classified as being either overweight or obese compared with fewer than 25% 40 years ago.[2,3] Moreover, the distribution of body mass index (BMI) in the United States has drastically shifted in a skewed fashion toward higher values, such that the proportion of the population meeting criteria for morbid obesity has increased more markedly than for overweight and mild levels of obesity.[1-4] If we fail to stop this ongoing obesity epidemic, we may soon witness an abrupt end to, or even worse a reversal of, the steady increase in life expectancy noted during the past century.[2,5]

The adverse effects of obesity on overall cardiovascular (CV) health (Table),[2] including heart failure (HF), are numerous. In a 14-year follow-up study of 5881 Framingham Heart Study participants, Kenchaiah et al[6] found a graded increase in the risk of HF as BMI increased, and for every 1 kg/m^2 increase in BMI, the risk of HF increased 5% in men and 7% in women. Clearly, obesity has profound effects on both systolic and diastolic left ventricular function; epidemiological data demonstrate a strong link between obesity, as determined by BMI, and hypertension and coronary heart disease (CHD), 2 powerful risk factors for HF. Despite this evidence, many studies have suggested that obese patients with HF have a better prognosis than leaner patients, which is termed the *obesity paradox*.[2,7] In a meta-analysis of 9 observational HF studies (n=28,209), Oreopoulos et al[8] demonstrated that, compared with individuals without elevated BMI, overweight and obese patients with HF had reductions in CV (–19% and –40%, respectively) and all-cause (–16% and –33%, respectively) mortality during a 2.7-year follow-up period. In an analysis of BMI and in-hospital mortality from 108,927 patients with decompensated HF, higher BMI was associated with lower mortality, with a 10% lower mortality (P<.001) for every 5-unit increase in BMI.[9]

Most studies reporting the obesity paradox have used BMI to classify obesity (eg, BMI [calculated as weight in kilograms divided by height in meters squared]: ≥25 is overweight and ≥30 is obese). Although BMI is the most common method to define overweightness and obesity in both epidemiological studies and major clinical trials, clearly this method does not necessarily reflect true body fatness, and BMI/body fatness may differ considerably among people of different age, race, and sex.[2,10-12] As we have discussed previously,[2,12] defining obesity by other methods, including waist circumference, waist-hip ratio, and percent body fat (BF), may be more accurate. In fact, researchers at Mayo Clinic have reported that BMI performed suboptimally in predicting obesity as defined by the National Institutes of Health criterion standards (BF >25% in men and >35% in women)[13] in cohorts with CHD and in the general population.[10,14] The accuracy of BMI in diagnosing obesity appears to be particularly limited in the intermediate BMI ranges, as well as in men and in the elderly. This is of great importance because it is precisely in the intermediate ranges of BMI in which the obesity paradox was first noted (better survival in overweight individuals). Also, historically men comprise the majority of the sample studied in most epidemiological CV studies. Finally, in the elderly in whom most of the outcomes (eg, deaths, myocardial infarction, stroke) occur, BMI has its poorest diagnostic accuracy, probably because the elderly have a relatively low amount of muscle mass. In

See also page 609

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TABLE. **Adverse Cardiovascular Effects of Obesity**

Increases in insulin resistance
Glucose intolerance
Metabolic syndrome
Type 2 diabetes mellitus
Hypertension
Dyslipidemia
Elevated total cholesterol
Elevated triglycerides
Elevated LDL cholesterol
Elevated non-HDL cholesterol
Elevated apolipoprotein-B
Elevated small, dense LDL particles
Decreased HDL cholesterol
Decreased apolipoprotein A1
Abnormal left ventricular geometry
Concentric remodeling
Left ventricular hypertrophy
Endothelial dysfunction
Increased systemic inflammation and prothrombotic state
Systolic and diastolic dysfunction
Heart failure
Coronary heart disease
Atrial fibrillation
Obstructive sleep apnea/sleep-disordered breathing

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Adapted from *J Am Coll Cardiol*,[2] with permission from Elsevier.

fact, a BMI cutoff of 30 or greater has good specificity but misses more than half of patients with excess BF.[12]

The obesity paradox has been blamed in part on the limitations of the BMI assessment for defining overweightness/obesity.[2,12,15] In this issue of *Mayo Clinic Proceedings*, Oreopoulos et al[16] report a detailed body composition assessment in 140 patients with chronic HF, including assessment of BF, by dual energy X-ray absorptiometry (DEXA). Compared with DEXA, use of BMI misclassified BF status in 41% of their cohort. Increased BMI was significantly associated with lower *N*-terminal pro B-type brain natriuretic peptide and lower exercise capacity; higher BF was associated with lower exercise capacity and increased levels of C-reactive protein. Moreover, when BMI was divided into fat and lean mass components, a higher lean body mass and/or lower fat mass was independently associated with factors that appear to be advantageous in chronic HF. A limitation of the study is that the authors did not assess waist circumference, which is the major component of the metabolic syndrome and is a marker of insulin resistance and at-risk obesity.[2,12] Although DEXA is often considered the criterion standard for the assessment of BF, magnetic resonance imaging may better differentiate subcutaneous from visceral fat, which is more proinflammatory. Finally, the authors assessed surrogate markers of CV disease and lacked data for "hard" end points. This becomes important because evidence-based medicine has taught us that the presence of a surrogate marker of CV disease does not always translate into similar data regarding survival.

In fact, we have previously shown in a study of 209 patients with advanced chronic systolic HF that both BMI and percent BF (assessed by the sum of the skinfold method as opposed to the more precise DEXA scanning method) are independent predictors of better event-free survival (Figure 1).[17] For every 1% increase in BF, clinical events were independently reduced by 13%. Our preliminary data in 875 patients with advanced HF also demonstrate the paradoxical independent prognostic impact of BF by the sum of the skinfold method on all-cause mortality.[18]

Similar to HF, this obesity paradox has been demonstrated in cohorts with hypertension, peripheral arterial disease, atrial fibrillation, chronic kidney disease, and, especially, CHD.[2,19] In a recent systematic review of 40 cohort studies involving more than 250,000 patients followed up for 3.8 years, Romero-Corral et al[15] reported that overweight and obese patients with CHD have a lower risk of total and CV mortality compared with underweight and normal-weight patients with CHD. However, of importance is the fact that

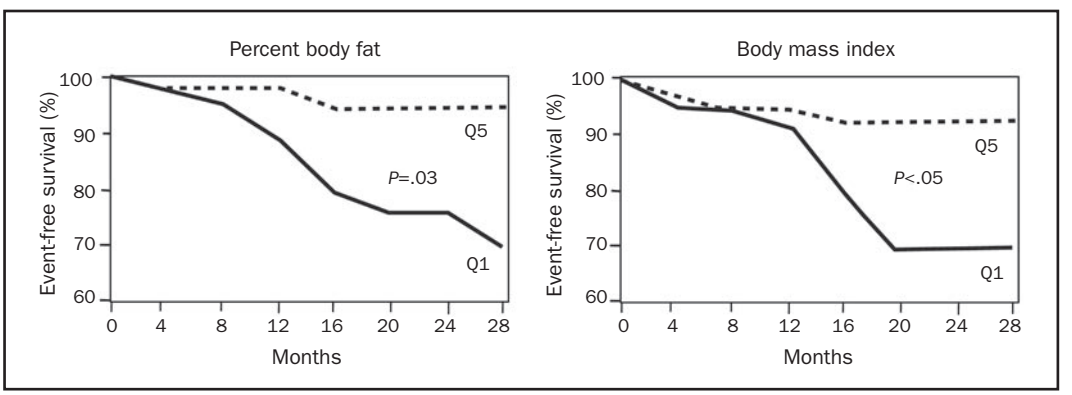

FIGURE 1. Freedom from cardiovascular death or urgent transplant in patients in quintiles (Q) 1 and 5 for percent body fat (left) and body mass index (right).
From *Am J Cardiol* 2003,[17] with permission from Elsevier.

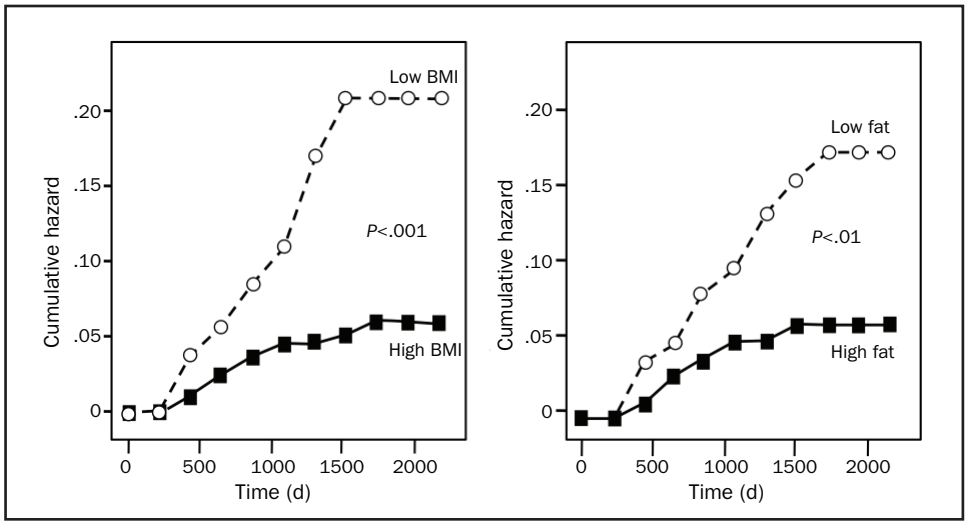

FIGURE 2. Actuarial cumulative hazard plot for survival time in 529 patients with coronary heart disease based on baseline body mass index (BMI) status (high, BMI ≥25 kg/m^2, vs low, BMI <25 kg/m^2) (left) and baseline percent body fat (high fat >25% in men and >35% in women vs low fat) (right). From *Am J Med,*[20] with permission from Elsevier.

those with morbid obesity had the highest risk of CV mortality. Like our results in HF, we also have demonstrated the obesity paradox with BMI and BF in patients with CHD (Figure 2).[20]

The reasons for the obesity paradox in CV diseases, especially HF, remain unclear.[2,7] Because advanced HF is a catabolic state, obese patients with HF may have more metabolic reserve.[21-23] Cytokines and neuroendocrine profiles of obese patients with HF may be protective, and adipose tissue produces stable tumor necrosis factor α receptors that could be protective.[8] Additionally, overweight and obese patients with HF have lower levels of brain natriuretic peptide.[21] High circulating lipoprotein levels in obese patients may bind and detoxify lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines, all of which may serve to protect the obese patient with HF.[21,24] In a study of a large non-HF cohort recently published by McAuley et al[25] in *Mayo Clinic Proceedings*, the obesity paradox was noted only in overweight and obese patients with a high level of cardiorespiratory fitness, suggesting that the obesity paradox may be modified by physical wellness or other unmeasured confounding factors that link the presence of chronic disease to outcomes.[26] Additionally, the obesity paradox in overweight/obese patients with higher levels of fitness may be due to these patients having a higher amount of lean muscle mass and not necessarily due to having more fat mass.[11] Finally, as we have suggested previously,[2,20,27] overweight and obese patients with CV diseases, including HF, might not have developed these diseases if weight gain had been prevented. In contrast, leaner patients who develop these same CV diseases and HF may have a different pathophysiologic etiology, including genetic predisposition, that leads to resistance to medical interventions. Although most studies that support the obesity paradox have corrected for baseline conditions, such as tobacco use and chronic obstructive pulmonary disease, these studies generally did not account for nonpurposeful weight loss before study entry, which may represent undiagnosed severe underlying diseases.[2,28]

Why higher BF by the sum of the skinfold method is protective and high BF by DEXA is associated with better HF prognostic markers is puzzling. Clearly, DEXA scanning is more accurate than the simple, inexpensive sum of the skinfold method.[20] Furthermore, other inexpensive and easier methods to measure BF, such as bioimpedance, may have a huge selection bias for the study between BF and HF with CV mortality, because bioimpedance is not recommended for patients with implantable pacemakers and defibrillators, which are commonly used in HF (especially in the sickest patients). Despite its limitations in very obese and elderly people, higher BF by the sum of the skinfold method has been shown to be protective in both HF and CHD.[17,20] Such data are not yet available for BF assessed by DEXA. However, preliminary data from 2004 from 3 European HF centers demonstrated that higher BF determined by DEXA was associated with lower mortality in patients with advanced HF; to our knowledge, these data have not yet been published in the peer-reviewed literature.[29]

We applaud Oreopoulos et al[16] for their excellent study. Certainly, precise determinations of body composition may

explain details of this puzzling obesity paradox in HF and other CV diseases. Currently, obesity clearly seems to be a predictor for the development of HF and most CV diseases. However, in cohorts with established CV diseases, including advanced HF, higher levels of BMI and BF currently appear to be protective.[2,7-9,17]

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