

Editorial

The Obesity Paradox: Time for a New Look at an Old Paradigm

La paradoja de la obesidad: es hora de adoptar una perspectiva nueva sobre un paradigma antiguo

Preethi Srikanthan^{a,*} and Tamara B. Horwich^b

^aDivision of Endocrinology, Department of Medicine, UCLA Health System, Los Angeles, CA, United States

^bDivision of Cardiology, Department of Medicine, UCLA Health System, Los Angeles, CA, United States

Article history:

Available online 10 March 2012

Since the first description of the relationship between increased body mass index (BMI) and heart failure (HF) in 2001,¹ BMI has been used in numerous studies as a definition of obesity and has emerged with a reputation of being a good prognosticator of outcomes in patients with HF. Approximately two-thirds of HF patients are overweight or obese (BMI \geq 25 kg/m²). In that first study, of 1203 patients with severe HF, Horwich et al. reported that overweight and obese (BMI $>$ 27.8 kg/m²) HF patients had reduced risk-adjusted hazard ratio for mortality at 5 years. Curtis et al., in 7767 individuals with stable HF, noted that individuals with BMI $<$ 18.5 kg/m² had the worst survival, while those with BMI $>$ 30 kg/m² had the best survival.² Gustafsson et al., in 4700 patients with both systolic and diastolic HF, noted that increasing BMI across the 4 study groups (underweight, BMI $<$ 18.5 kg/m²; normal weight, BMI 18.5 to 24.9 kg/m²; overweight, BMI 25 to 29.9 kg/m²; and obese, BMI $>$ 30 kg/m²) was associated with increased chance of survival.³ A meta-analysis of 9 observational studies including over 28 000 HF subjects demonstrated overweight BMI (25–29.9 kg/m²) and obese BMI (\geq 30 kg/m²) to be associated with 16% and 12% decreased risk (risk-adjusted) for mortality, respectively, compared to normal BMI (20–24.9 kg/m²).⁴ Conversely, in a study of 1929 HF patients enrolled in a clinical trial, Anker et al. defined cachexia as individuals having more than 6% loss of total body weight from baseline, and by this definition found cachexia to be the strongest independent risk factor for mortality.⁵

By evaluating mortality in individuals with HF and a diagnosis of either obesity or malnutrition in the largest clinical study of its kind in Spain, Zapatero et al. assessed the mortality impact for individuals presumably at either extreme of body mass; however, they did not use BMI or weight as a part of this definition.⁶ Using the coding system established by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), 5th edition, Zapatero et al. were able to confirm the higher mortality associated with those defined as being malnourished, while a diagnosis of obesity reduces mortality and risk of hospital readmission.⁶ Such a move away from use of BMI is novel and

echoes recent concerns that BMI, as a surrogate marker of general adiposity, may have lead to incorrect assumptions about the relationship between obesity and HF outcomes.⁷ In fact, in patients with coronary artery disease BMI cannot discriminate between fat and lean mass.⁸ The actual association between fat mass and HF survival will need to be assessed by more accurately determining lean body mass and fat mass components in HF patients. While use of the ICD-9-CM by Zapatero et al. does avoid categorization by BMI, there is no description in the paper about the actual method used to reach the diagnosis of obesity or malnutrition, and its consistency across the patient cohort. Even so, the study by Zapatero et al. is timely, as it leads one to contemplate the clinical characteristics and body composition that define individuals with either obesity or malnutrition.

While it would appear to be intuitive that an increase in BMI, as a surrogate for generalized obesity, predicts all-cause mortality in the general United States population,⁹ this association wanes in those aged over 65 years¹⁰ presumably due to concurrent changes in lean body mass which make relative abdominal adiposity measures (such as waist hip ratio) more sensitive indicators of mortality risk.¹¹ Similarly, the positive association of increased BMI and risk of mortality in patients with HF—the well recognized “obesity paradox”—is at first glance counter-intuitive.^{1,12,13} It is possible that this paradox is the result of a similar disparity between mortality associations with adiposity vs muscle mass, accounting for the increased mortality observed with very low BMI (and in the setting of such cardiac cachexia, low muscle mass) and lower mortality in the higher BMI range (30–35 kg/m²) compared to “ideal” BMI values (as the former state is also likely to indicate an individual who is less catabolic, and hence has higher muscle mass).⁷ Yet, a study of waist circumference in HF patients also found higher waist circumference to be an independent predictor of improved survival.¹⁴

With regards to obese individuals, as noted in the study by Zapatero et al.,⁶ individuals in the higher BMI range (30–35 kg/m²) are younger and, as they have to carry their own weight and perform more antigravity work, they maintain some skeletal muscle mass. Indeed it has been noted that assessment of lean body mass vs fat mass may be more informative in understanding mortality risk,⁷ and while studies assessing body composition and survival in HF patients are needed, in chronic renal failure patients in hemodialysis (who also exhibit the “obesity paradox”) a survival benefit has been noted in those individuals with greater muscle

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DOI: [10.1016/j.rec.2011.09.014](https://doi.org/10.1016/j.rec.2011.09.014), Rev Esp Cardiol. 2012;65:421–6.

* Corresponding author: David Geffen School of Medicine at UCLA, Box 951679, A2-237 CHS, Los Angeles, CA 90095-1679, United States.

E-mail address: psrikanthan@mednet.ucla.edu (P. Srikanthan).

mass.¹⁵ A category of individuals with obesity and low muscle mass have been described as the sarcopenic obese; this condition has metabolic consequences including insulin resistance and dysglycemia, which add both the inflammatory burden of adiposity and associated adipokines.¹⁶ In individuals with low BMI and so-called cardiac cachexia, tumor necrosis factor alpha and interleukin-6 are implicated in causation of anorexia and muscle wasting.¹⁷ Further, as it has been noted that lower levels of muscle mass are associated with increased insulin resistance and dysglycemia in healthy individuals,¹⁸ the fall in insulin-like growth factor-1 levels and increased insulin resistance in HF patients results in decreased suppression of the ubiquitin-proteasome pathway, which has been identified as the pathway for accelerated proteolysis in many catabolic states.¹⁹

Hence the study by Zapatero et al.⁶ is a useful addition to the literature in this area, as it encourages us to look beyond BMI as a yardstick to define HF patient groups with differing mortality outcomes. However, better characterization of body composition, particularly in individuals at either extreme of weight status, is an important step towards understanding the best way to manage individuals at either extreme. Looking beyond anthropometrics and using research tools such as dual-energy X-ray absorptiometry, bioelectrical impedance, or near-infrared spectroscopy as well as further study of cytokines and adipokines may be useful in future investigations to better understand alterations in body composition in HF patients and thus strategically develop therapeutic interventions for this highly morbid condition.

CONFLICTS OF INTEREST

None declared.

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