Obesity paradox in heart failure: a heavy matter

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Abstract

Obesity and heart failure are two of the leading causes of morbidity and mortality in the world. The relationship between obesity and cardiovascular diseases is complex and not fully understood. While the risk of developing heart failure has been shown to be higher in patients who are obese, there is a survival advantage for obese and overweight patients compared with normal weight or low weight patients. This phenomenon was first described by Horwich *et al.* and was subsequently confirmed in other large trials. The advantage exists irrespective of the type, aetiology, or stage of heart failure. Patients with morbid obesity (body mass index >40 kg/m^2), however, do not have the same survival advantage of their obese counterparts. There are several alternative indices of obesity available that may be more accurate than body mass index. The role of weight loss in patients with heart failure is unclear; thus, providing sound clinical advice to patients remains difficult. Future prospective trials designed to evaluate the link between obesity and heart failure will help us understand more fully this complex relationship.

Introduction

Obesity is one of the leading causes of morbidity and mortality in the world. Globally, the prevalence of overweight and obesity has risen at an alarming rate over the past two decades, with over two billion people now meeting the definition of these two categories.[1] From a public health standpoint, it is believed that the prevailing obesity trends in the USA may have the net effect of decreasing life expectancy trends.[2] Numerous studies have shown a clear relationship between obesity and risk of developing cardiovascular disease (CVD). A follow-up analysis from the Framingham study demonstrated high body mass index (BMI) as an independent risk factor for developing heart failure (HF), coronary artery disease (CAD), stroke, and overall CVD death.[3] The risk of developing HF in the obese population was twice as that seen in the normal BMI population.[4] Despite this increased risk of HF in the elevated BMI population, recent studies have demonstrated that there is, in fact, a survival advantage in overweight and obese HF patients in comparison with their normal-to-low BMI counterparts. This observation, known as the 'obesity paradox', was first described by Horwich *et al.*[5] in their seminal work evaluating the role of obesity in the prognosis of HF patients. These findings were supported by a large meta-analysis that showed HF patients who were overweight or obese had a significant reduction in all-cause and cardiovascular mortality.[6] The obesity paradox has been reported in other CVD conditions such as hypertension, CAD, and atrial fibrillation.[7,8] This paper reviews the effects that obesity has on cardiovascular function, including the risk of developing and prognosis of HF. It also reviews evidence of the obesity paradox in various stages and types of HF and explores alternative indices of obesity. Multiple studies have investigated the role of obesity paradox in heart failure patients and the notable studies are mentioned in *Table 1*. Finally, the benefits and risks of weight reduction in HF will be discussed.

Definitions and epidemiology

Definitions

Obesity is traditionally classified in terms of BMI. The World Health Organization classifies obesity into different categories based on BMI as described in *Table 2*.[9] Central adiposity indices are becoming more frequently employed, as BMI does not take into account adipose distribution and may misrepresent cardiovascular risk for certain populations.[10,11] A waist

Table 1 Notable studies investigating obesity paradox

Author	Study population	Patients	Year	NYHA class	Comments
Kenchaiah et al.[31]	CHARM	7599	2007	II–IV	Underweight or low BMI associated with increased mortality in symptomatic HF patients with reduced or preserved LVEF
Haass et al.[32]	I-PRESERVE	4109	2011	II–IV	U-shaped relationship demonstrated with highest rate of adverse outcomes in lowest and highest BMI categories
Cicoira et al.[37]	Valsartan HF trial	5010	2007	II–IV	Higher BMI associated with improved prognosis independent of other clinical variables
Davos et al.[38]	Single-centre study	589	2003	I–IV	Patients with cachexia have poorer prognosis
Lavie et al.[39]	Single-centre study	209	2003	I–III	Major clinical events increased by 13% for every 1% absolute reduction in body fat. BMI and total body fat also independently predicted event-free survival
Fonarow et al.[42]	Acute Decompensated Heart Failure National Registry	108,927	2007	I–IV	10% reduction in risk adjusted mortality with every five-unit increase in BMI
Nagarajan et al.[44]	Single centre study	501	2013	II–IV	Re-emphasized the presence of obesity paradox even in patients with very advanced heart failure
Kapoor Jr[45]	Single centre study	1236	2010	I–IV	BMI <20 kg/m^2 had the highest mortality followed by patients with BMI >45 kg/m^2
Khalid et al.[46]	ARIC study	1487	2014	I–IV	Overweight or obese patients based on pre-morbid weight have lower mortality after HF diagnosis compared with normal BMI patients
Oreopoulous et al.[6]	Meta-analysis of nine observational studies	28 209	2008	I–IV	Overweight and obese patients demonstrated a lower all-cause and CV mortality rate

ARIC, Atherosclerosis in Communities; BMI, body mass index; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association.

circumference of >102 cm in men and >88 cm in women, waist-to-hip ratio of >0.9 in men and >0.85 in women, and a waist-to-height ratio of ≥0.5 for men and women have been proposed as cut-offs for central adiposity.[12–14] A recent study of ~360 000 individuals in nine European countries demonstrated that both general and central adiposities were associated with increased risk of death and supported the use of central adiposity indices, in concert with BMI, as assessment tools.[15]

Epidemiology

The prevalence of HF is staggering, affecting an estimated 5.8 of 300 million Americans and 15 of 900 million Europeans.[16,17] The economic burden of HF on healthcare systems is tremendous. In the USA alone, an estimated HF annual cost increased from $24.3 bn in 2003 to $39.2 bn in 2010 with hospitalizations accounting for a majority of this cost and loss of productivity.[16] HF has a significant impact on both morbidity and mortality with an estimated 40% mortality at 5 years.[18] A clear relationship between HF hospitalization and mortality has been demonstrated: data from the Atherosclerosis in Communities study showed that 30-day, 1-year, and 5-year mortality rates following hospitalization for HF were 10.4%, 22%, and 42.3%, respectively.[19]

The duration of morbid obesity has been shown to be the strongest predictor of HF in a study by Alpert *et al.* showing an HF prevalence rate of 70% after 20 years and greater than 90% after 30 years of living with morbid obesity.[20] This correlation is alarming given the estimated 154.7 million American adults who are overweight or obese, with roughly one in every three US adults classified as obese.[21] This epidemic is not limited to the USA alone. The World Health Organization reported the prevalence of obesity has risen three-fold in the European region since the 1980s.[22]

Table 2 Definitions of obesity and cut-offs for central obesity

Definitions of obesity and cut-offs for central adiposity
BMI WHO classification
BMI <18.5 kg/m^2 ➔ Underweight
BMI 18.5–24.9 kg/m^2 ➔ Normal range
BMI 25.0–29.9 kg/m^2 ➔ Overweight
BMI 30.0–34.9 kg/m^2 ➔ Class I obesity
BMI 35.0–39.9 kg/m^2 ➔ Class II obesity
BMI ≥40.0 kg/m^2 ➔ Class III or morbid obesity
Waist circumference
>102 in men and >88 in women
Waist-to-hip ratio
>0.9 in men and >0.85 in women
Waist-to-height ratio
≥0.5 for men and women

BMI, body mass index; WHO, World Health Organization.

Obesity and the risk of developing heart failure

Obesity has been shown to be an independent risk factor for cardiovascular morbidity. Kenchaiah *et al.*, using the Framingham Heart Study cohort, showed a 5–7% increase in HF for every 1 kg/m^2 increase in BMI based on a 14-year follow-up.[4] This is due to both direct and indirect effects that obesity has on the cardiovascular structure. Obesity increases an individual's risk of developing multiple debilitating chronic

diseases including hypertension, CAD, diabetes mellitus, kidney disease, and obstructive sleep apnoea. These conditions have a synergistic effect in increasing the patient's risk of developing HF.[23]

Obese individuals have a higher risk of developing myocardial dysfunction independent of the aforementioned causes.[24] The haemodynamic and structural changes imposed on the heart as a result of obesity can range from a hyperdynamic state to overt systolic dysfunction. In addition, excessive adipose accumulation and fat-free mass result in increased left ventricular (LV) stroke volume that can be attributed to increase in blood volume and hyperdynamic circulation.[25] The subsequent increase in cardiac output causes LV enlargement and increased wall stress. LV hypertrophy (LVH) develops in these patients, with eccentric LVH predominating in individuals with normal blood pressures and concentric LVH predominating in those with long-standing hypertension.[25] Changes in LV filling pattern occur because of increased LV mass and poor compliance that result in LV diastolic dysfunction leading to the manifestation of HF symptoms.[26] Metabolic abnormalities including activation of the renin–angiotensin–aldosterone system, sympathetic nervous system, insulin resistance, inflammatory markers, lipotoxicity, and adipokines in the obese are also believed to contribute to LVH and LV dysfunction.[25,27] A study by Wannamethee and colleagues found that in patients with no prior history of coronary artery disease, increased risk of HF in obese patients was associated with increased leptin levels in plasma, which is secreted by adipocytes.[28]

Does aetiology or ejection fraction matter in 'obesity paradox'?

There have been numerous ways of defining HF, but there are two most important classifications that have received the most attention: one classification uses the presence or absence of systolic or diastolic dysfunction while the other classification uses an aetiology-based approach (ischaemic vs. non-ischaemic). HF with reduced ejection fraction (EF), also known as HFrEF, has predominant systolic HF, while HF with preserved EF (HFpEF) has predominant diastolic dysfunction.[29] Ischaemic and non-ischaemic cardiomyopathy definitions are based on the presence or absence of coronary ischaemia as the primary aetiology of HF. Approximately half the number of patients with HF have preserved EF, with the incidence of HFpEF on the rise similar to the obesity trends. Importantly, patients with HFpEF have similar long-term prognosis to systolic HF.[30] The 'obesity paradox' has been reported in patients with HFrEF and HFpEF. In a post-hoc analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study, 7599 patients with different ranges of EF were analysed.

Mean EF was 39%, and they performed an excellent multivariate analysis separately in patients with EF less than and greater than 40% (3023 patients). In this analysis, the survival advantage was highest in patients with BMI between 30 and 34.9 and the association between BMI and mortality did not change based on LV EF.[31] One of the larger studies that specifically studied HFpEF patients, the Irbesartan in Heart Failure with Preserved Systolic Function trial, evaluated outcomes on 4109 patients.[32] In this study, overweight patients with BMI of 26.5 and 30.9 kg/m^2 had the lowest all-cause mortality and rates of hospitalization for HF exacerbation. This difference existed even after correcting for multiple variables. These two studies are good examples of the existence of the obesity paradox in patients with HFpEF. Many of the following studies specifically analysed patients with HFrEF. Other studies that have evaluated the obesity paradox based on the aetiology of HF have shown that obese patients have improved survival compared with patients with normal BMI in both ischaemic and non-ischaemic cardiomyopathies.[33]

Although obesity paradox was found to be present in multiple studies, there were some studies that yielded negative results as well. Pozzo et al. investigated 222 patients with non-ischaemic cardiomyopathy and found the obesity paradox disappeared after correcting for VO2 max (peak oxygen uptake).[34] Similarly, Adamopoulos et al. performed propensity-matched analysis of 7788 chronic HF patients separately as two groups—with and without diabetes mellitus. Interestingly, they found the obesity paradox only in the non-diabetic population, but it was absent in HF patients with diabetes.[35] One of the other notable articles on this topic was published recently from Cleveland Clinic querying the role of gender on patients with HF. Authors performed an extensive statistical analysis on 3811 patients with HF and found that overweight women had a significant survival advantage, but their male counterparts had higher adjusted mortality in the obese/overweight group.[36]

Obesity paradox in chronic stable and acute decompensated heart failure

In earlier studies, the obesity paradox was demonstrated mainly in chronic stable HF. A post-hoc analysis performed on 5010 chronic stable HF patients from the Valsartan Heart Failure trial showed mortality rates to decline with increasing BMI: mortality rate was 27.2%, 21.7%, 17.9%, and 16.5% in patients with underweight (defined as BMI <22 kg/m^2), normal weight, overweight, and obesity, respectively.[37] This effect was shown to be independent of many important clinical variables including symptoms, EF and natriuretic peptide levels. One earlier study that focused on patients with chronic HF without cachexia[38] divided 589 patients into

five groups based on increasing BMI. Patients in the fourth group with median BMI ~29 kg/m² had the lowest 1-year and 3-year survival compared with groups with lower BMIs and also in the fifth group with the highest BMI. This demonstrated the 'U'-shaped curve associated with obesity paradox. Lavie *et al.* studied 209 ambulatory patients with chronic systolic HF and assessed different body composition parameters including BMI, body surface area, total body fat, percentage body fat, and lean body weight. In this study, clinical events increased by 13% for every 1% absolute reduction in body fat. BMI and total body fat were also independently predictive of event-free survival.[39] The existence of obesity paradox in chronic stable HF has been described extensively in the literature.[5,38,40,41]

Fonarow *et al.* analysed 108 927 patients admitted with acute decompensated HF enrolled in a national registry, assessing the presence of obesity paradox.[42] This registry included hospitalizations from 263 hospitals in the USA. When patients were divided into quartiles based on BMI, in-hospital mortality rates decreased with increasing BMI quartiles even after adjusting for multiple clinical laboratory risk factors. In this study, there was 10% reduction in risk-adjusted mortality with every five-unit increase in BMI. However, a smaller study involving 433 acute HF patients from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial did not show the obesity paradox.[43] Nonetheless, a large meta-analysis including nine studies and 28 209 patients provided confirmation that the 'obesity paradox' in HF does exist.[6] The nine studies included evaluated patients with the New York Heart Association class I–IV symptoms. Overall, patients with obesity (adjusted hazard ratio 0.88, 95% confidence interval 9.83–0.93) and overweight (adjusted hazard ratio 0.93, 95% confidence interval 0.89–0.97) had lower adjusted mortality compared with those with normal BMI, further supporting the protective benefit of obesity in patients with HF.

Obesity paradox in different stages of heart failure

The obesity paradox has also been reported across the spectrum of HF stages. We have demonstrated the presence of a 'U'-shaped relationship between BMI and mortality in 501 patients with Stage D end-stage HF referred to Cleveland Clinic for heart transplantation.[44] We divided patients into three groups—non-obese (≤30 kg/m²), obese (30.1–40 kg/m²), and morbidly obese (≥40 kg/m²). Obese patients had significantly better survival compared with non-obese and morbidly obese patients, and this relationship did not change when adjusted for multiple variables. A similar 'U'-shaped relationship was described by Kapoor *et al.* in 1236 consecutive patients presenting with HF with preserved EF.[45] Patients

with a BMI between 36 and 40 kg/m² had the lowest 1-year mortality in this study. Patients with BMI <20 kg/m² had the highest mortality, followed by patients with BMI >45 kg/m². Patients with 'normal' BMI also had higher mortality compared with obese patients.

Given that most of the studies that demonstrate the obesity paradox are based on the weight after development of HF, some experts argue that the patients with normal weight and HF may be in a more pronounced catabolic state or an advanced stage of HF compared with patients with obesity. This question was addressed by investigating 1487 patients enrolled in the Atherosclerosis in Communities study.[46] Investigators used pre-morbid BMI measured at least 6 months before the incident HF. Patients were followed for 10 years, and those with obesity and who were overweight had better survival compared with patients with normal BMI. Severe HF causing cachexia thus cannot be the sole reason for the phenomenon of the obesity paradox. There are many conflicting hypotheses in the literature to explain the reason for the obesity paradox.

Controversies around obesity paradox

Some counter arguments have been advanced against the phenomenon of the obesity paradox.[45,47] These arguments can be best summarized as follows:

(1) Most studies on the obesity paradox have been retrospective in nature.
(2) Obese patients with HF may present to clinicians early, leading to lag-time bias.
(3) There have been conflicting results with the use of alternative fat assessment tools such as dual-energy X-ray absorptiometry.[48]
(4) Obese patients may be able to tolerate guideline-directed medical therapy better owing to higher levels of arterial blood pressure.[42]
(5) Obese patients could have an attenuated renin–angiotensin–aldosterone system, which could favour a better prognosis.[49]

Alternative indices of obesity

Although the BMI is the most well-known index of obesity, there are other methods for quantifying obesity. The BMI was originally developed by Adolphus Quetelet. Quetelet was a Belgian mathematician, astronomer, and statistician who developed the index in 1832 after conducting cross-sectional studies of human growth.[50] The Quetelet index became the BMI in 1972 after Ancel Keys' article comparing different ratios of height and weight. BMI was found to have

the best correlation of weight to height and subcutaneous fat thickness.[51] There are several limitations to the BMI that have prompted researchers to search for alternative indices of classifying obesity. The most important limitation of BMI is that it ignores the scaling law, which states that mass increases to the third power of linear dimensions. For instance, if two individuals have the same body composition, the taller individual will have a higher BMI.[52] Applying different indices of obesity to the Physicians' Health Study and Women's Health Study has shown that a higher weight-to-height ratio had the strongest association with CVD. The association was stronger than BMI, waist-to-hip ratio and waist circumference.[53] Similar results were found in a study of German patients.[54] A meta-analysis of studies that evaluated different measures of obesity as predictors of cardiovascular events also found that waist-to-height ratio was the best predictor of cardiovascular events.[55] So while BMI might be the most commonly used index of obesity, it is not the best index to predict future cardiovascular events.

Natriuretic peptides in obesity

The natriuretic peptides are a group of peptides that are secreted by cardiomyocytes in response to myocardial stretching. Brain natriuretic peptide (BNP) is released by the ventricle and atrial natriuretic peptide by the atria. These peptides lower systemic vascular resistance and induce natriuresis. BNP is released with an inactive N-terminal fragment (NT-proBNP). Immunoassays are available for both molecules and are used clinically to aid diagnosis of HF in patients with shortness of breath. NT-proBNP has been shown to be both sensitive and specific for HF.[56] A comparison of natriuretic peptide levels with BMI was performed using a cohort of 3389 patients without HF from the Framingham population. It was found that obese individuals had lower mean BNP and atrial natriuretic peptide levels compared with overweight and lean individuals.[57] BNP levels have also been shown to be suppressed in obese patients that have HF, independent of symptom class.[58] A British trial randomized 52 obese patients without HF to an intensive diet and exercise programme or diet counselling. After 52 weeks, BMI had decreased by 20% and BNP levels had nearly doubled.[59] The exact mechanism for this is unclear, but recent studies suggest decreased production is the cause.[60] Despite lower levels of natriuretic peptides in the obese patient, circulating levels can still be used for prognosis.[61]

Adiponectin may play a role in the obesity paradox. Adiponectin is an adipocytokine that has an inverse relationship to BMI in healthy individuals, and low adiponectin is usually associated with higher cardiovascular events and mortality. Kistorp *et al*. investigated the relationship of adiponectin with BMI and mortality in 195 chronic HF patients. Although adiponectin and NT-proBNP had an inverse relationship with BMI in this study, patients with lower adiponectin levels paradoxically had a better prognosis.[62] This was thought to be secondary to cardiac wasting in advanced HF.

Weight loss in heart failure

Cachexia is a serious sequela of chronic HF and is associated with a poor prognosis. It has been suggested that weight loss of 6% defines the presence of cachexia.[62] Clearly, cachexia should be avoided, but the role of purposeful weight loss is not clear. Major cardiovascular societies recommend weight loss strategies for those with a BMI greater than 40.[26] The benefits of weight loss on the heart are well known. They include reductions in cardiac work, LV mass, LV thickness, and diastolic dimensions.[63] Obese patients with LV systolic dysfunction have improvement in LV systolic function after substantial weight loss. While weight loss improves haemodynamics, it is unclear if weight loss improves mortality in patients with underlying HF. To date, there are no large trials assessing the impact of intentional weight loss on mortality in the HF population.

Conclusions

There are many published studies now confirming the existence of the obesity paradox phenomenon. Currently, the aetiology remains unclear. In addition, there is insufficient evidence to clearly recommend weight loss in obese patients with HF. Large prospective trials are needed to clarify the issue of weight loss for obese HF patients.

Conflicts of interest

None declared.

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