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The metabolic basis for the obesity paradox in heart failure

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Abstract

A higher body mass index (BMI) carries a survival benefit in patients with heart failure. Data from more than 28 000 patients with heart failure support the view that the optimal BMI ranges between 30 and 35 kg/m^2 as opposed to the common belief that weight loss and being slim is generally good. In chronic diseases such as heart failure, chronic kidney disease, or chronic obstructive pulmonary disease, this assumption no longer holds true, a phenomenon called the "obesity paradox", and weight loss is no longer advisable. The origin of this clinical observation is not entirely clear, but some factors may have an influence: obese patients with heart failure are on average younger, have better nutritional status and appetite, present at an earlier stage of the disease, are less catabolic, have lower levels of natriuretic peptides and have higher muscle mass. An optimal BMI has not been defined, and it is not clear if fat mass is as beneficial as muscle mass when looking at absolute BMI values. ■ Heart Metab; 2013;61:4–7

Keywords: Heart failure; muscle; obesity; obesity paradox.

Introduction

The first description of the obesity paradox dates back to 1999. However, many physicians have still never heard of the obesity paradox at present. The reason may be that the time frame is simply not long enough to allow for paradigm shifts, and it seems that nothing less is necessary with regard to our perception of obesity in patients who are chronically ill. Therefore, it is not surprising that current guidelines for heart failure issued by the large European and American societies do not mention the existence of an obesity paradox [1, 2]. Clinicians involved in the everyday care of patients may thus not be aware that the advice to lose weight commonly advocated for overweight or obese individuals with cardiovascular disease may not make sense for all of them.

We should, however, approach the obesity paradox in an orderly manner. The term describes a common phenomenon seen in many chronic illnesses, including coronary artery disease, arterial hypertension, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and several others. Among patients with these illnesses, overweight and mild obesity are counterintuitively but commonly associated with better survival than underweight or what is usually called normal weight, ie, a body mass index (BMI) up to 25 kg/m^2. In terms of survival, heart failure patients seem to fare best with a BMI between 30 and 35 kg/m^2.

Survival benefit with higher BMI

The first description of the phenomenon stems from data of more than 1300 patients with chronic kidney

Abbreviations

BMI: body mass index; **CI:** confidence interval; **RR:** relative risk

disease undergoing hemodialysis [3]. The authors' conclusion was that "nutrition aimed to achieve the high end of normal body mass index may help to reduce the high mortality and morbidity in hemodialysis patients". This notion is of particular interest, because the authors of that study did not even analyze nutritional intake and thus extrapolated far beyond their data using proxies such as serum albumin or prealbumin. However, the study paved the way for an avalanche of publications dealing with the subject. Indeed, only one year later, Davos et al [4] described the existence of an obesity paradox in an abstract at the annual meeting of the American Heart Association, only to be published in 2003 as a full report. In the meantime, other groups had taken up the issue, leading to a larger publication using data from 1203 patients with advanced heart failure to show that cardiopulmonary exercise testing, pulmonary capillary wedge pressure and serum sodium were strong predictors of survival in this group of patients. Importantly, the authors concluded "higher body mass index was not a risk factor for increased mortality, but was associated with a trend toward improved survival" [5]. Several independent groups have confirmed these results using large databases mainly from prospective trials now involving more than 28 000 patients. A meta-analysis of those patients [6] with a mean follow-up of 2.7 years has shown that individuals with a BMI between 25.0 and 29.9 kg/m^2 (relative risk [RR] 0.84, 95% confidence interval [CI] 0.79–0.90) and those with a BMI of 30 kg/m^2 or greater (RR 0.67, 95% CI 0.62–0.73) had lower all-cause mortality than individuals with a normal BMI. This finding could be confirmed for cardiovascular mortality, and it remained true after adjusting for several risk factors. However, it has to be taken into account that the available data do not permit an upper threshold to be given for the beneficial effects of obesity, simply because the number of individuals with a BMI greater than 40 kg/m^2 remains small, both in real life and in clinical studies.

Metabolic differences in obesity

A matter of ongoing debate is whether the obesity paradox really does exist and if it does, what is the metabolic basis for its existence? Indeed, a number of factors need to be considered when looking at the data. On average, obese patients with heart failure are younger, have better nutritional status and appetite, present at an earlier stage of the disease, are less catabolic, have lower levels of natriuretic peptides, have higher muscle mass and potentially higher left ventricular ejection fraction (*Figure 1*) [7, 8]. Our group has recently shown that patients with heart failure and appendicular skeletal muscle mass 2 SD below the mean of a healthy young population are significantly older and have significantly less body weight than patients with normal skeletal muscle mass [9]. Indeed, obesity leads to unavoidable exercise simply by carrying one's own weight, and such exercise – as recommended by the guidelines – may help to maintain skeletal muscle [8]. Obesity may thus primarily be a marker of a different status [8]. On the other hand, the guidelines state that the presence of obesity is a risk factor for the development of heart failure, because obesity is in many cases associated with the clustering of cardiovascular risk factors, ie, the metabolic syndrome, and because obesity leads to an increase in circulating blood volume and consequently to higher cardiac output, cardiac work and systemic blood pressure [1]. Other changes in obese individuals include an enhanced turnover of free fatty acids, increased sympathetic tone, the activation of inflammatory mediators, and a hypercoagulable state [10]. In addition, obesity itself may be involved in the chief complaint of heart failure patients, shortness of breath, thus creating an overlap of symptoms derived from the obese status and from the failing heart.

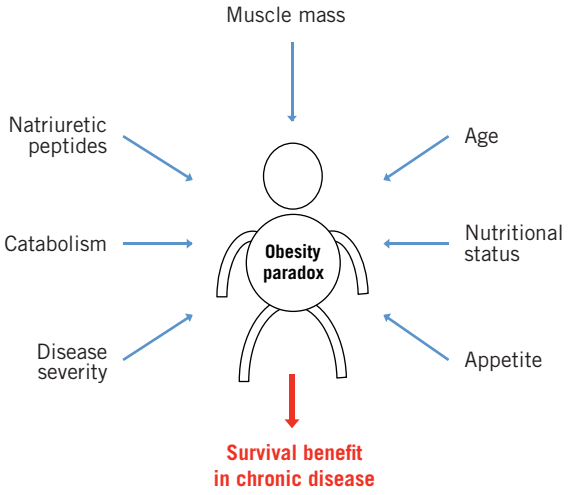

Fig. 1 *Factors influencing survival benefits in obese patients with heart failure.*

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Body composition issues in heart failure

Taking these data together it seems that both is true – obesity is a risk factor for developing heart failure, but obesity also carries a survival benefit when heart failure has become manifest. A low BMI or the development of cachexia are certainly detrimental in patients with heart failure [6, 10, 11]; mild or even moderate obesity, on the other hand, may well be acceptable. There is no need to ask heart failure patients to gain weight, but there is good reason to make them stop losing it. Having said this, the discussion needs to be extended to matters of body composition, as it is not clear if there is such a thing as an optimal body composition [12], ie, content of lean mass versus fat mass, in patients with heart failure. The BMI, originally described by Adolphe Quetelet in 1832 (Quetelet index) and renamed "body mass index" in 1972, was originally used as an estimation tool of body fat content [13]. Critics of the BMI have argued that it fails to distinguish between fat mass and lean mass, and that for that reason muscular people are frequently misclassified as overweight or obese. Factors such as the course of body composition changes over the lifespan need to be considered. Indeed, after the age of 30 years, lean mass decreases at the expense of increases in fat mass [14]. Despite the loss in muscle mass, this usually leads to a net increase in body weight. Some 5 or 10 years before death, BMI usually starts to decline as a consequence of inactivity, anorexia and poor nutritional intake [7]. The term "sarcopenia" describes loss of muscle mass and strength with advancing age. On average, 5–13% of elderly people between 60 and 70 years are affected by sarcopenia, and the numbers rise to 11–50% for those aged 80 years and above [15, 16]. It was therefore surprising to see that the criterion of sarcopenia or muscle wasting, ie, muscle mass 2 SD below the mean of a healthy young cohort, was present in almost 20% of stable heart failure outpatients with a mean age of 67 years [9]. The mean BMI of patients affected by muscle wasting was significantly lower than that of those not presenting with muscle wasting. It is clear now that a higher BMI is beneficial in heart failure, but it is tempting to speculate that higher muscle mass is even better than fat mass, even though fat mass as an energy depot may also help in decreasing mortality rates.

Conclusions

We are only starting to understand the obesity paradox in heart failure as many questions still remain unanswered. However, the obesity paradox is there – as the data are more than convincing – and it is there to stay. The optimal BMI in heart failure seems to be somewhere between 30 and 35 kg/m^2 and certainly not in the region commonly considered as normal BMI. It cannot be stressed too often that patients with chronic disease and healthy individuals are different. The influence of age, nutritional status, appetite, disease severity, catabolic status and muscle mass all need to be considered as they all contribute to the obesity paradox. In particular, muscle mass and strength require more research, as we do not yet know whether only a higher BMI is beneficial or whether higher muscle mass is also required. An upper threshold for the BMI needs to be defined. In the meantime, clinicians' advice to their patients should be to stop losing weight once heart failure is present. ■

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