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Review Article

Obesity across Heart Failure

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Abstract

Obesity is a global pandemic of the 21st century. Prevalence in Europe has nearly tripled since the 1980s. In 2019, 52.7 % of the adult EU's population was overweight and by 2025, 20% of the world population will be obese, with body mass index ≥ 30 kg/m2. Obesity is associated with an increased risk of developing heart failure (HF) as both direct and indirect effects of obesity contribute to development of HF. The risk of HF increased by 5% in men and 7% in women for every 1 kg/m2 increase in BMI and BMI higher than 30 kg/m2 doubled the incidence risk for development of heart failure. Ironically, despite proven increased health risks associated with obesity, many studies documented obesity paradox. Phenomenon, in which overweight and class I obese HF patients demonstrate a better prognosis compared with lean or underweight HF patients. This review provides present understanding of pathophysiological mechanisms contributing to the development of HF in obese people. Additionally, we discuss the existence of obesity survival paradox. Extant evidence supports this phenomenon and numerous reasons and mechanisms for its existence have been postulated. However, emerging evidence disprove existence of obesity paradox, mostly based upon BMI, and many believe that no such phenomenon as obesity-survival paradox even exists, if only better ways of measuring body fat were used in initial studies. Finally, despite the obesity paradox, we address potential role of intentional weight reduction in the prevention and treatment of HF.

ABBREVIATIONS

HF – heart failure, BMI – body mass index, HFpEF – heart failure with preserved ejection fraction, HFrEF, heart failure with reduced ejection fraction, CVD – cardiovascular disease, AH – arterial hypertension, CAD – coronary artery disease, LV-left ventricle, WtHr - waist-to-height ratio, LVEF – left ventricle ejection fraction, IRR - incidence rate ratio, WHO- World Health Organization, AT – adipose tissue, WAT - white adipose tissue, FM-fat mass, CO - cardiac output, NP- natriuretic peptides, TNF α - tumour necrosis factor alpha

INTRODUCTION

Obesity has truly reached epidemic proportions worldwide. This global epidemic can be attributed to urbanization, industrialization, advancing economies, commercial growth, the adoption of mechanized transport with a progressively more sedentary lifestyle and a nutritional transition to processed foods with high calorie diets and lack of physical exercise. Today, globally, overweight and obesity account for more deaths than malnutrition and underweight and presents a major challenge to chronic disease prevention and health across the planet [1].

Changes in body composition caused by obesity affect haemodynamics, alters heart structure and induce cardiac systolic and diastolic dysfunction [2]. Furthermore, obesity has been implicated as one of the major risk factors for arterial hypertension, type 2 diabetes, lipid disorders, coronary artery disease, atrial fibrillation – all conditions, that are strongly related to the development of heart failure (HF) [2,3]. Therefore, HF incidence and prevalence is markedly increased in obese patients [2].

Regardless of heightened risk of HF in obese patients, there is more than two decades confirmed evidence suggesting that HF patients with reduced ejection fraction (HFrEF) and with higher body mass index (BMI) have a survival advantage and better prognosis than their normal-to-low BMI counterparts, phenomenon known as 'obesity paradox'[4]. This also results in uncertainty regarding the management of obesity in HFrEF patients. On the other hand, in patients with heart failure with preserved ejection fraction (HFpEF), obesity is not just a comorbidity, but apparently plays one of the main pathogenetic roles in the development and progression of this disease.

In this review paper, we will discuss role of obesity in heart failure, review the evidence suggesting and contradicting the existence of an obesity paradox. We will discuss the potential mechanisms through which obesity may exert protective effects and analyse whether or not it is feasible for HF patients to lose weight.

Obesity and Heart Failure

Obesity - definition: Obesity is defined as excess fat mass in individuals that impairs health. World Health Organization (WHO) classifies obesity according to BMI, calculated as BMI = weight (kg) / height (m^2), in both sexes as seen in table [5]. Obesity is mostly defined as per established classification metrics relative to BMI, whereas adiposity refers to body fat [6].

BMI was originally developed by Adolphus Quetelet, a Belgian mathematician, statistician and astronomer in 1832 [7]. It is being used as body mass index from 1972, after Ancel Keys' article comparing different ratios of height and weight. BMI had the best correlation of weight to height and subcutaneous fat thickness [8] (Table 1).

Different types of adipose tissues, its function and distribution

Adipose tissue (AT) has three main functions - lipid storage, secretory function, and insulin sensitivity. Energy is stored in the form of fatty acids. AT secretes a variety of effectors, such as exosomes, lipids, miRNA, inflammatory cytokines and peptide hormones that act in both paracrine and endocrine signalling to impact local and systemic metabolic responses. In addition, adipocytes are highly sensitive to insulin and therefore are involved in the regulation of blood glucose levels. In short, adipose tissue maintains lipid and glucose homeostasis [1].

To date several types of adipose tissue have been identified, namely white, brown, beige. The cellular architecture, secretome and location of these adipose depots define their main function [1,9].

White adipose tissue (WAT) comprises the largest fat volume in humans and is composed of subcutaneous and visceral WAT. Large 'unilocular' lipid droplet occupies over 90% of the cell volume. Storing and releasing fatty acids that supply fuel to the organism during fasting periods or exercise is the main function. Other than that, metabolic functions include lipogenesis and lipolysis, fatty acid oxidation, and the endocrine functions include the production of adipokines [1,9].

In lean individuals, subcutaneous WAT depot represents circa 80% of all adipose tissue and depots primarily in the abdominal and gluteal-femoral regions. It prevents heat loss, work as a barrier against dermal infection and as a protective layer against physical external stress. During times of limited energy expenditure and/or excess energy intake, subcutaneous WAT acts as a metabolic physiological buffer for excess lipid storage. When the storage capacity is exceeded due to limited adipocyte hyperplasia or hypertrophy, fat begins to accumulate ectopically (i.e. liver, skeletal muscle, and pancreas).

Table 1: WHO classification according to BMI

BMI < 18,5 kg/m^2	Underweight
BMI 18,5 - 24,9 kg/m^2	Normal range
BMI 25 - 29,9 kg/m^2	Overweight
BMI 30 – 34,9 kg/m^2	Class I obesity
BMI 35 – 39,9 kg/m^2	Class II obesity
BMI > 40 kg/m^2	Class III obesity (morbid obesity)

Visceral WAT is localized within the visceral compartment - omental, mesenteric, and retroperitoneal. Lean people have little amounts of visceral fat that is highly metabolically active and is constantly releasing free fatty acids into the portal circulation. Therefore, contributes to various features of the metabolic syndrome (i.e. systemic inflammation hyperinsulinemia, dyslipidaemia, and atherosclerosis). Visceral adiposity has a strong relationship with epicardial fat mass [10]. Surprisingly, studies have demonstrated that the removal of small amounts of omental AT in obese people provided no metabolic health benefits. Likewise, liposuction (~10 kg) of subcutaneous AT in humans neither harmed nor improved the cardio-metabolic profile.

Epicardial WAT lies between the visceral pericardium and the myocardium and shares a blood supply with the coronary arteries. Epicardial WAT behaves similarly to brown AT and protects the coronary vessels and myocardium against hypothermia and provides fatty acids for energy used by the heart. Due to its proximity to the heart, it is roughly twice as metabolically active as other WAT depots. Obese humans possess an increased epicardial WAT depot, which is clinically related to the metabolic syndrome. It secretes adipokines, vasoactive substances, inflammatory cytokines and chemokines that impact the adjacent myocardium. As a result, lipid accumulation in atherosclerotic plaques is facilitated, Moreover, it can induce atrial fibrosis. In fact, diffusion of fatty acids and other bioactive hormones from epicardial WAT to myocytes and coronary vessels is easily facilitated, due to the complete lack of a fibrous fascial layer.

In obesity, adipose tissue becomes dysfunctional, promoting a pro-inflammatory, hyperlipidaemic and insulin resistant environment. We recognized "metabolically healthy obesity" (10-30% of individuals with obesity) and "metabolically unhealthy obesity". Currently, no consensus for parameters to classify these two groups exists. However, metabolically healthy obese individuals have enlarged subcutaneous WAT, without excessive accumulation of visceral and ectopic fat. Metabolically healthy obesity is characterized by reduced systemic inflammation, normal insulin sensitivity, normal fasting glucose levels, low incidence of hypertension, and blood lipid profiles in the healthy range. In contrast, metabolically unhealthy obese individuals, who have comparable BMI, have less favourable metabolic profiles. Metabolic health risk should not solely dependent on body weight [1,9].

Obesity – classification: WHO suggests the use of BMI for an initial nutritional status assessment, nonetheless, cautions against absolute reliance on BMI, as it may misclassify severity of fat mass (FM).

Increased BMI is highly correlated with a rise in FM, paralleled by a rise in fat-free mass. Fat-free mass accounts for most of the total body mass, as it consists of lean mass, skeletal muscle mass, bones and it includes total body water (intra- and extra-cellular water). Yet, BMI does not take into consideration different body

composition compartments and distribution. This limitation is extremely relevant as body weight changes may reflect changes in different compartments.[10] In short, the assessment of obesity with BMI has two major drawbacks; it does not take into consideration the body composition (fat, muscle, bones, other body compartments) and similarly, it is not able to take into account adipose tissue distribution.

Visceral fat mass accumulation, also known as central obesity, is recognized as a major cardiometabolic risk, so it is crucial to differentiate individuals with similar/same BMI and different cardiovascular risk profile [11]. Indirectly, we measure central adiposity as waist circumference with cut-off limits of>88 cm in women and >102 cm in men, waist-to-height ratio of ≥0.5 for women and men or waist-to-hip ratio of >0.85 in women and >0.9 in men [12]. In recent update of the National Institute for Health and Care Excellence in the UK (NICE) guidelines is waist-to-height ratio determined as a strong predictor for cardiovascular disease (CVD) development. Waist-to-height ratio is more accurate to estimate central adiposity than BMI without the need to consider all ethnic and sex differences [13].

Classical obese phenotype is linked to aligned increase in fat, lean and skeletal muscle mass. In obese people with very limited physical activity, obesity may also be accompanied with reduction of the amount and/or functionality of lean mass, creating sarcopenic obesity. Sarcopenic obesity, defined as excess of fat mass and reduction of amount and/or functionality of lean mass, is associated with worse functional capacity and prognosis in several chronic diseases including heart failure [10].

The gold standard for assessing body composition is CT and MRI scanning. It provides the most accurate qualitative and quantitative information on adiposity and lean mass; however, its use is limited by expense, availability and radiation [14]. Other possibilities to measure adiposity include anthropometry and dual-energy X-ray absorptiometry (DEXA) [1].

Heart failure – definition: In accordance with universal definition of HF, it is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. HF is classified according to ejection fraction as heart failure with reduced ejection fraction (HFrEF) - LVEF ≤40%, heart failure with mildly reduced ejection fraction (HFmrEF) – LVEF 41–49% and heart failure with preserved ejection fraction (HFpEF) – LVEF ≥50% [15,16].

Classification based on LV-ejection fraction suggests that HFrEF and HFpEF are similar entities. Nevertheless, both HF subtypes are caused by profoundly different pathophysiological processes.

HFrEF is characterized by substantial cardiomyocyte loss, resulting in the development of systolic dysfunction. Remodelling leads to an imbalance in the heart wall structure, causing eccentric remodelling, often with LV dilation, but a normal wall thickness. Acute or chronic loss of cardiomyocytes is often due to ischemia, a genetic mutation, valvular disease, arrythmia, or myocarditis. Systemic and cardiac inflammation present in HFrEF is secondary to the causes of cardiomyocyte loss [15,17].

On the contrary, HFpEF is a complex cardiovascular syndrome originating from high prevalence of concomitant comorbidities. It is defined by structural and cellular alterations, including cardiomyocyte fibrosis, hypertrophy and inflammation, all leading to an inability of the LV to relax properly. Comorbidities (chronic obstructive pulmonary disease, metabolic syndrome, anaemia, chronic kidney disease, etc.) and particularly obesity induce a systemic proinflammatory state. A systemic proinflammatory state leads to coronary microvascular endothelial inflammation. Endothelial inflammation results in decreased production and release of nitric oxide, cyclic guanosine monophosphate content and protein kinase G activity. In adjacent cardiomyocytes, low protein kinase G activity leads to hypophosphorylation of titin that increases resting tension and favours concentric hypertrophy development. Increased stiffness and interstitial fibrosis contribute to elevation of filling pressures and diastolic and heart failure development [17,18]. In an Italian study, AH and obesity were more prevalent in HFpEF than HFrEF patients [19]. Statistically, more than 80% of patients with HFpEF are overweight or obese [20].

Both HFrEF and HFpEF leads to reduced cardiac output, or normal cardiac output which can only be achieved at the cost of increased LV filling pressures [21]. While presence of signs and/or symptoms of HF and a reduced ejection fraction LVEF ≤40% are diagnostic for HFrEF [16], diagnosing HFpEF is more challenging, particularly in obese individuals. Obesity itself (even in the absence of HF) is regularly associated with exercise intolerance, shortness of breath and ventricular enlargement [22]. Physical signs of congestion are often masked in obese people (i.e. jugular distention due to increased neck girth). Echocardiographic examination of obese individuals is limited by particularly poor acoustic windows. Also, recent data have revealed that even echo-Doppler indicators such as the E/e′ ratio underestimate circulatory congestion in obese individuals [23]. Furthermore, level of natriuretic peptides (NP) is consistently lower, owing to inverse linear relation between BMI and circulatory NP concentration. Possible causes of low NP levels are existing clearance receptors for NP expressed in adipocytes, overexpressed neprilysin in obese patients, increased excretion of NP due to renal hyperfiltration, due to lipolytic effects of NP, patients deficient of NP are prone to obesity [24]. Confirmatory cardiopulmonary exercise testing, exercise stress testing and/or invasive haemodynamic testing is often needed [16].

As stated, HFrEF and HFpEF have contrasting proposed pathophysiological mechanisms of development. Moreover, distinct underlying aetiologies, diverse clinical spectrums, different epidemiology, prognosis and response to treatment is recognized [15].

Epidemiology of obesity and HF: Obesity is worldwide

one of the dominating causes of mortality and morbidity and its incidence is expeditiously expanding [25]. Data from the World Health Organisation (WHO) reporting that the prevalence of obesity in Europe has nearly tripled since the 1980s [26]. Moreover, in 2019, 39% of European adults (aged 18 years and over) were overweight and 13 % were obese [27]. Recent US statistics shows that 75% of the US population is either overweight or obese and 42% of US adults (aged 21 and over) have BMI ≥30 kg/m^2. 9% of adult Americans are morbidly obese, with BMI ≥40 kg/m^2 [3]. It is predicted that 20% of the world population will be obese by 2025 (BMI ≥ 30 kg/m^2) [27].

Worldwide, estimated HF prevalence is 1-2% of the population [28] counting to 64.3 million people [29]. Only in Europe, more than 15 million people are affected [30]. As studies usually include only recognized/diagnosed HF, the true prevalence is likely to be higher. Currently, the incidence of HF in Europe is 5/1000 person-years in adults[105]. It is expected that one in five people will be diagnosed with heart failure at some point in their life[7]. Prevalence is increasing with age, from 1% for individuals aged <55 years to >10% in those aged 70 years or over. Based on studies in hospitalized patients, about 50% of HF patients have HFrEF and 50% have HFpEF/HFmrEF [16].

In developed countries, the age-adjusted incidence of HF may be falling, presumably reflecting better management of CV diseases, however because of ageing, the overall HF incidence is increasing [16].

Nonetheless, it is very problematic to asses correctly prevalence and incidence of HFpEF. Firstly, it is challenging to correctly assess HFpEF diagnosis; some patients with invasively proved increased filling pressures have this abnormality only during exercise. Furthermore, some patients with proved HFpEF have normal natriuretic peptide levels. Also, diagnostic criteria for HFpEF multiple times changed through the past years [31].

Obesity – risk factor for HF development: Obesity is considered a known risk factor for the development of a heart failure [32], even in the absence of diabetes mellitus [33]. Approximately 50% of patients with HF are overweight or obese [49]. Various studies demonstrated clear relationship between obesity and onset of a heart failure, e.g., Framingham Heart Study illustrated high body mass index (BMI) as an independent risk factor for HF development [34]. The risk of HF increased by 5% in men and 7% in women for every 1 kg/m^2 increase in BMI [35] and BMI higher than 30 kg/m^2 doubled the incidence risk for development of heart failure [33]. National Health and Nutrition Examination Survey showed that obese patients are 30% more likely to develop heart failure compared with nonobese patients [36]. Besides, obesity is also responsible for the development of other CVD like stroke, metabolic syndrome, atrial fibrillation, coronary artery disease and eventually for overall CVD death [34].

Years lived with obesity have cumulative effect on HF development [37,38]. Duration of morbid obesity (BMI over 40 kg/m^2) is one of a predictors of heart failure development. In morbid obese individuals, after 20 years, the prevalence rate of HF was 70% and in 30 years, the prevalence rate of HF reached more than 90% [39].

Obesity - contribution to HF : Obesity participates directly and indirectly in development of HF.

Haemodynamic studies demonstrated a positive correlation between the amount overweight and both total blood volume and cardiac output (CO) [40]. This leads to obesity-related hyperdynamic circulation [41]. These changes are due to expanded metabolic demands as a consequence of excessive adipose tissue and fat-free mass [42]. Heart rate does not differ significantly from that predicted for ideal body weight. However, stroke volume expands according to excess body weight. It leads to increased cardiac work [40,42]. Increased blood volume furthermore enlarges venous return to the both ventricles, which increases wall tension and subsequently dilatation of the chambers occurs [43]. Increased LV pressure and volume increases consumption of oxygen, so the arteriovenous oxygen difference is widened [44,45] and there is a leftward shift in the Frank-Starling curve [43]. In obese patients, frequently, increased baseline LV end-diastolic pressure (LVEDP) is found [40]. Right ventricular afterload can also be increased because of LV changes or obstructive sleep apnoea and/or obesity hypoventilation syndrome, which leads to hypoxia-induced vasoconstriction and pulmonary hypertension [42]. In most studies comparing lean and obese individuals, no significant differences in LV ejection phase indexes were found. And if so, the differences were small. Even in class III obesity, severe LV systolic dysfunction was uncommon in the absence of coexistent CV disease [2].

Obesity is linked to atrial and ventricular remodelling, known precursors of atrial and ventricular systolic and/or diastolic dysfunction, respectively [46]. The amount of cardiac remodelling is related to severity and duration of obesity [47]. Both eccentric and concentric LV hypertrophy have been identified in obesity. Concentric hypertrophy is more common, notably due to concomitant AH. Heart weight and body weight exhibit a linear relationship. Also, LV mass has strong positive correlation to BMI and both waist circumference and waist to hip ratio [48]. Concentric LV hypertrophy involves alterations in myocardial tissue architecture consisting of peri-vacuolar and myocardial fibrosis, myocyte hypertrophy and medial thickening of intramyocardial coronary arteries [48,49]. Disturbances of myocardial blood flow predispose to the development of an arrhythmogenic myocardial substrate and diastolic dysfunction. Also, expanded intravascular volume, LV stiffness, LVEDP, altered LV filling properties further contribute to diastolic dysfunction and larger left atrial size in obese individuals[58]. Furthermore, obesity is accompanied by an expansion of epicardial and visceral adipose tissue. Visceral FM can induce the synthesis of certain adipokines and pro-inflammatory cytokines, responsible for the characteristic low-grade systemic inflammation. Many products of the secretome of adipose tissue, namely interleukin (IL)-1β and IL-18, have cardio-depressant effects [50]. Metabolic disorders cause proliferation and dysfunction of adipocytes

in the epicardium and the secretion of adipocytokines leads to inflammation and fibrosis of the underlying myocardial tissues. In proximity to the LV, the result is an impairment of LV distensibility. However, in proximity to the left atrium, electroanatomical fragmentation and structural remodelling lead to an atrial myopathy. As a result, atrial fibrillation is often first sign of HFpEF, particularly in obese or diabetic patients [51]. Activation of the renin–angiotensin–aldosterone system, sympathetic nervous system, insulin resistance, inflammatory markers, lipotoxicity, and adipokines (i.e. hyperleptinaemia) are also believed to contribute to LV hypertrophy and diastolic dysfunction [41]. Altogether, present changes results in LV diastolic dysfunction and manifestation of HF symptoms [2,40,41].

Indirect effects of obesity are a result of increased predisposition to the other HF risk factors. Metabolic syndrome, coronary artery disease, obstructive sleep apnoea, chronic kidney disease- all have synergic effect in increasing individual patient's risk for developing HF [41].

Obesity paradox

Although obesity is clearly associated with increased risk of HF development and HF-related risk factors [10], in patients with established HF, BMI in the mildly obese range (BMI 25-30 kg/m2) is associated with better prognosis than those with a normal body weight [52]. Observation known as the obesity paradox.

Obesity paradox was initially observed in patients with advanced HF, where coexistence of overweight or class I obesity was linked to improved prognosis compared to normal weight or underweight counterparts. Multiple subsequent studies further supported existence of the obesity paradox in both HFrEF and HFpEF and also in acutely decompensated HF [45,53]. The relationship between BMI and survival outcome of HF patients is likely not linear, but shows rather "U-shape" relationship. HF patients with BMI <20 kg/m^2 had the highest mortality, followed by morbid obese patients with BMI >45 kg/m^2. Individuals with HF and normal range BMI had higher mortality compared with obese and overweight patients [54,55], lowest mortality was observed at a BMI between 22.5–25 kg/m^2 [56]. This is potentially a dangerous message to promulgate from retrospective data in today's environment saturated with an obesity epidemic and obesity-related conditions (such as coronary artery disease, diabetes mellitus…)

Evidence supporting existence of obesity paradox

The obesity paradox was observed for the first time in patients on maintenance haemodialysis [57]. Since then (year 1999), many authors [2,14,57-60] and large studies demonstrated significant reduction of all-cause and cardiovascular mortality in mildly obese HF patients, namely Framingham Heart Study [61], CHARM study [62], I-PRESERVE trial [63], recent post-hoc analysis of PARADIGM-HF trial [64].

Mechanism of obesity paradox

Several explanations are proposed for obesity paradox phenomenon.

Increased body weight may hinder the metabolic consequences of HF and of its treatment by providing adequate muscle and adipose reserves. Also, obese individuals are prone to AH, so have better tolerability of cardioprotective medication (B-blockers, Ca-blockers, ACEi, ARNI, MRA, diuretics...) and have higher volume of distribution [65,66].

Advanced HF is a catabolic state, often associated with a state of cachexia, frailty and sarcopenia [65,3] obese patients with HF may have more metabolic reserve[50].

The healthy heart does not express tumour necrosis factor alpha (TNF-α), while the failing heart produces enormous quantities of TNF-α. Obese subjects with HF exhibit lower concentrations of TNF-α. Subcutaneous adipose tissue produces soluble TNF-α receptors I and II, production is correlated with BMI and percent body fat. It is assumed that these receptors bind TNF-α and neutralize its adverse effects on the myocardium. Furthermore, several adipokines (e.g., adiponectin, apelin, omentin, and others) produced by adipose tissue have shown to be cardioprotective and to exert a variety of favourable effects on cardiovascular function [66-68].

Additionally, obese individuals with HF may have an attenuated response of the renin-angiotensin-aldosterone system, which may also lead to a better prognosis [2].

Increase in ghrelin production/sensitivity has been showed to be a compensatory mechanism to hinder the evolution of HF. It increases LV function by improving cardiac contractility and exercise capacity and reduces muscle wasting in patients with chronic HF. Furthermore, ghrelin affects appetite, so can be responsible for a parallel rise in food intake and subsequently weight gain.

Prothrombotic factors (e.g., thromboxane B2) are negatively correlated with BMI and leptin. Their production is influenced by endothelial function and is paradoxically better in obese than in non-obese individuals [69].

High circulating lipoprotein levels in obese subjects can bind and detoxify/neutralise lipopolysaccharides that play a role in stimulating the release of inflammatory cytokines. Hence, it has antiinflammatory effects [66].

Evidence contradicting existence of obesity paradox

Marked heterogeneity and limitations were found across analyses studying obesity paradox. This cast doubt whether this phenomenon actually exists.

All studies favouring existence of obesity paradox were observational, they did not prove causality and are prone to confounding. We also need to acknowledge biases like reverse

causation, attrition bias, lead-time bias, selection bias of healthy obese subjects or resilient survivors, length of follow-up, study population, differences in treatments/management strategies, degree of control for confounding factors [41,70] Also, analyses were retrospective; therefore, each study has been limited by an inability to adjust for all confounding variables (i.e. stage and grade of the disease, smoking habits, etc.). None of the studies accounted for non-purposeful weight loss before study entry, and certainly such patients would be expected to have a poor prognosis [2]. Furthermore, none of the databases used were specifically designed to study the obesity paradox as a primary goal. Thus, authors are limited to analysing only the available data and covariates [61].

The use of BMI as obesity marker is limiting in defining nutritional status [71,72]. It fails to determine adiposity distribution and body composition, the degree of metabolic disturbances and is omitting presence of sarcopenic obesity [73] and undernutrition in overweight individuals [74]. BMI together with mortality tend to be altered by cardiorespiratory fitness status [75]. In the elderly in whom most of the poor outcomes (eg, deaths, myocardial infarction, stroke) occur, BMI had the poorest diagnostic accuracy. Probably because the elderly people have consistently lower amount of lean mass. In fact, a BMI cut-off of 30 kg/m^2 or higher has good specificity, but misses more than half of patients with excess body fat [50].

It is believed, that cardiorespiratory fitness level modifies survival obesity paradox. In patients with CAD, in whom an obesity paradox was also demonstrated, normal weight but high aerobic fitness capacity showed favourable prognosis. Study demonstrated, that obesity paradox was present only among HF patients with low cardiorespiratory fitness. These findings indicate, that favourable cardiorespiratory fitness level might eliminate the impact of the obesity paradox in HF [2].

Post-hoc analysis of PARADIGM-HF trial further supported, that HFrEF patients with a BMI of 25 kg/m^2 or more had better survival outcome. Also, that greater adiposity was linked to a higher risk of HF hospitalization in both BMI and WtHr. being more evident in WtHr. However, the survival obesity paradox was far less evident in relation to WtHr, and it disappeared after adjustment for prognostic variables. After adjustment, both BMI and WtHr demonstrated that more body fat was associated with a greater risk of death or hospitalisation for HF; this was more evident for WtHr. Authors suggest it is because waist circumference and height used in WtHr reflect body fat distribution (particularly central adiposity) more precisely. In WtHr, weight differences are not influenced by ethnic, sex, frailty, oedema and skeletal weight changes, as are when using BMI [76].

Weight loss and pharmacological interventions in HF patients

Role of intentional weight loss in overweight/mildly obese HF patients is unclear. Currently, there is no specific recommendation for obesity management in ESC, AHA/ACC/HFSA guidelines (except recommended BMI >35 kg/m^2 before performing heart transplantation [16]). Most cardiovascular societies recommend weight loss in patients with a BMI > 40 kg/m^2 [2].

HFSA published a consensus statement regarding nutrition, obesity and cachexia in patients with HF. It states, that at least 5–10% weight loss is recommended for HF patients with BMI ≥ 35 kg/m^2. The statement was based on small randomized controlled trials, in which the positive effects of weight loss on atrial fibrillation, insulin resistance, LV hypertrophy and reduced incidence of HF was observed [14].

Weight loss reduces cardiac work, LV mass, LV thickness, diastolic dimensions [77], circulating blood volume, LV stroke volume, cardiac output [2] and with improved haemodynamic changes obese patients may have improvement in LV systolic function, if impaired before. Also, in obese HF patients with AH, weight loss is often accompanied by reduction of mean arterial pressure [2].

Extant evidence shows that weight loss in obese patients without HF reduces the risk of developing HF. For instance, Swedish Obese Subjects (SOS) cohort study recruited people without HF and with obesity (BMI in men ≥34 kg/m2 and in women ≥38 kg/m2) for weight loss surgery matching them with controls (little or no weight loss). From baseline, in the surgically treated group (baseline mean BMI 42.4 kg/m^2) there was BMI drop by 25% after 1 year, 18% at 6 years and 16% after 20 years with almost unchanged BMI in the control group (group difference of –8.3 kg/m^2). After 20 years, 35% lessened risk of developing HF in surgical weight loss group was recorded in comparison with controls [78,79].

Post-hoc analysis of SOLVD trial showed, that any unintentional weight loss in chronic HF patients is related to impaired survival and suggest that significant weight loss of >6% should be defined as cachexia, however no specific comment on obese HF patients was proclaimed [80].

In the post-hoc analysis of the CHARM study, change in weight was analysed. Over the period of 6 months, weight change and its affiliation with subsequent mortality over a median of almost 33 months follow-up was studied. In broad spectrum of HF patients, there is a strong steady rapport between weight loss and increased mortality from all causes. In patients experiencing 5-7% weight loss, there was 50% increase in mortality hazard and in over 7% weight loss, mortality hazard reached 62%. Furthermore, there was monotonic increase in mortality hazard with increasing weight loss observed, compared to patients, who had <1% weight change. Interestingly, both weight loss and baseline leanness were concurrently linked with an increase in mortality. There was observed over 150% increase in mortality in patients, who were both lean (mean baseline and 6-month BMI < 22.5 kg/m2) and lost over 5% of baseline weight in 6 months, compared with heavier counterparts, who did not significantly change weight. Authors did not provide clear evidence proving that weight gain is related to an increase in mortality risk. Moreover, showed and inverse relationship between mean BMI

over 6 months with mortality rate in leaner individuals, from BMI 27.5 kg/m^2 downwards. Obese patients with BMI over 30 kg/m^2 had similar mortality risk than individuals with BMI 25-27.5 kg/m^2 [81].

In another study, in obese HF patients with BMI ≥30 kg/m^2 and ≥5% unintentional weight loss (over a 1-year follow-up period) worse prognosis was observed than in nonobese patients. More specifically, in these obese HF patients 138% increase in risk of death was identified, in comparison with HF patients with BMI <30 kg/m^2 (83% increase). This confounding result may be as a result of loss of metabolic reserves in individuals with obesity that furthermore may trigger unfavourable clinical outcomes, as authors suggest [82].

In a small study, morbidly obese HFrEF patients (mean BMI 46.2 kg/m^2) underwent bariatric surgery. There was observed significant weight loss (mean 26 kg), significant improvement of LV EF and significant reduction (0.5) of New York Heart Association (NYHA) classification. Authors demonstrated, that bariatric surgery is safe in severe HF, morbidly obese patient, however, mortality was not analysed [83]

In LIVE study, HFrEF patients were enrolled and effects of liraglutide on LV EF were investigated. Authors noted that from baseline to week 24 there was not significantly different change in LV EF, global longitudinal strain, s'max, LV end-systolic volume, or LV end-diastolic volume between treatment groups. Liraglutide treatment was associated with a weight loss of 2.2 ± 3.1 kg, whereas there was no change in the placebo group (0.0 ± 3.0 kg). Mean baseline BMI was 28.0 kg/m^2 (±3.8) in treatment group and 29.8 kg/m^2 (± 4.6) in placebo group- vast majority of patients were overweight. Treatment with liraglutide was associated with an increase in heart rate and more serious cardiac adverse events. The significant effect on heart rate, despite concomitant treatment with maximum tolerable beta-blocker dose, may be mediated through direct stimulation of GLP-1 receptors in the sinoatrial node. This raises safety concern with respect to the use of liraglutide in HFrEF patients [84]. Nonetheless, authors did not investigate mortality rate.

In the FIGHT study authors investigated, whether therapy with a GLP-1 agonist following hospitalization for acute heart failure improves clinical stability in advanced HFrEF patients. Compared with placebo, liraglutide had no significant effect in the number of deaths and rehospitalizations HF between groups. Median baseline BMI in Liraglutide group was 31 kg/m^2, in placebo group 33 kg/m^2. Liraglutide treatment was associated with greater weight loss at 30 days (intergroup difference, −1.7 kg) and 90 days (intergroup difference, −1.9 kg, with no statistically significant difference at 180 days (intergroup difference, −1.8 kg). Authors are concern whether enhancing endogenous insulin secretion in HFrEF patients is advantageous as it mitigates insulin resistance [85]. Moreover, authors of post-hoc analysis are concerned that in HFrEF patients, liraglutide might increase the risk of cardiovascular adverse effects. Possibly, adverse effects are driven by excess risk of arrhythmias and worsening HF events [86].

Planned body weight reduction over 6-month period using nutritional dietary changes and physical activity program was studied in obese/overweight individuals with chronic HF. Patients who lost at least 3kg (circa 3.2% body weight change) presented an improvement in both NYHA functional class and in LV EF, nonetheless, authors did not evaluate mortality [87].

Improvement in the 6-minute walking test and NYHA functional class in obese (BMI >30 kg/m^2) HF patients with EF LV ≤40% after significant weight loss (≥5%) in 12 weeks was noticed. Weight loss was achieved via an orlistat-assisted diet. Again, authors did not evaluate mortality [88].

On the other hand, authors analysed changes in weight in patients with acutely decompensated HF admitted to hospital during 1-year follow-up in the RICA registry. Circa one fifth (20.8% of all enrolled patients) of the patients lost ≥5% of baseline weight and authors did not observe changes in mortality or rehospitalization rate in comparison with HF patients with stable weight [89].

Currently is on-going the STEP-HFpEF study. Adults with HFpEF and a BMI ≥30 kg/m^2 were enrolled, baseline characteristics are median BMI of 37 kg/m^2, median EF LV 57%, frequent comorbidities, elevated NP and nearly half were women. Study will investigate whether semaglutide improves symptoms, physical limitations, and exercise function in addition to weight loss. Unfortunately, clinical events such as heart failure hospitalizations, urgent visits or mortality rate will not be primarily evaluated [90].

CONCLUSION

Obesity in HF patients is very complex issue as it may be a trigger and surely is strong risk factor for new onset of HF and simultaneously may have protecting effect regarding mortality in already diagnosed HF. We still have many gaps in proper understanding on how obesity contribute to developing HF. More importantly, we still lack relevant evidence on how to manage weight in obese HF individuals, as significant ≥5% weight loss might not be beneficial. Using BMI to identify and classify obesity is controversial, as it does not take into account adiposity distribution and omit sarcopenic obesity, believed to have worse prognosis. Clearly, long-term randomized trials investigating in particular weight loss interventions in overweight/obese HF patients are needed to clear up uncertainty regarding management of obesity in HF.

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