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Obesity and Heart Failure: Understanding the Paradox

Joseph Odeyemi MD, MPH[1*]; Omotola Nofisat Akinade MD[2]; Anita Osabutey MD, MPH[1]; Efeturi Maxwell Okorigba MD[3]; Theodora Esomonye MD[4]; Aduwa Oboasekhi MD[5]; William Funsho Ogedengbe MD[6]

[1]University of North Texas Health Science Center, Texas, USA
[2]General Hospital, Ikorodu, Lagos State, Nigeria
[3]Badagry General Hospital, Lagos State, Nigeria
[4]Nissi Family Medicine, Austell, Georgia, USA
[5]Evercare Hospital, Lekki, Lagos State, Nigeria
[6]University of Lagos, Lagos State, Nigeria

E-mail: josephodeyemi@yahoo.com; omotolaakinade007@gmail.com; aosabutey92@gmail.com; efeokorigba@gmail.com; theodoraesomonye@gmail.com; aduwaoboasekhi@gmail.com; funshowilliam15@gmail.com

*Corresponding author details: Joseph Odeyemi MD, MPH; josephodeyemi@yahoo.com

ABSTRACT

Obesity is a long established risk factor for cardiovascular diseases including heart failure. However, recent evidence suggests that obese patients with heart failure report more favorable outcomes than heart failure patients with normal weights. This paper presents, reviews, and discusses some of the currently available evidence describing the association between obesity and heart failure, especially obesity as a risk factor for heart failure and the obesity-heart failure paradox. Pathophysiological evidence and data from longitudinal studies are considered.

Keywords: cardiovascular diseases; heart failure; obesity-heart failure paradox; pathophysiological evidence

INTRODUCTION

According to the World Health Organization (WHO), obesity is generally defined in terms of body mass index, with a value ≥ 30kg/m2 regarded as obesity [1]. Obesity is of growing concern due to its increasing prevalence globally; this rising prevalence has been linked to the transition of countries from under-developed to developing and developed and the associated increased consumption of high-calorie processed food [2]. Currently, over 30% of the world's adult population is reported to be obese [2]. Risk factors for obesity include individual factors like genetics, poor diet, sedentary lifestyle and socio-economic factors like residence in food deserts, low income, and low levels of education [2].

Heart failure is of major clinical and public health concern [3]. Over 60 million people worldwide have been diagnosed with heart failure, with a worldwide prevalence of about 9 cases/1000 people [3]. With the global increase in life expectancy, the prevalence of heart failure, which is more prevalent in the elderly, has also risen [4]. While there are various forms of heart failure and no universal definition, heart failure can be simply defined as a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling and/or ejection of blood or a failure of the heart to pump enough blood to meet the body's needs [4].

Obesity has been shown by several longitudinal studies to be a major risk factor for cardiovascular diseases including heart failure [5]. However, certain studies have observed that obese patients with heart failure tend to have better outcomes [6]. This has generated some controversy in the field of cardio-metabolic medicine with different proposed explanations for this observed paradox. Some commentators have proposed that confounding factors such as age and gender and other problems with the study designs may have been responsible for this observed paradox [7]. Others have postulated various physiological mechanisms that potentially explain this concept [8,9]. This paper reviews some of the currently available evidence describing the association between obesity and heart failure, especially obesity as a risk factor for heart failure and the obesity-heart failure paradox.

OBESITY AS A RISK FACTOR FOR HEART FAILURE

Obesity has been identified as an independent risk factor for the development of heart failure by numerous cohort studies [5]. The pathophysiological mechanisms linking obesity and heart failure are exceedingly complex. These processes include but are not limited to hemodynamic changes, alteration in cardiac structure, insulin resistance, diet, adipokines, cardiac lipotoxicity, and the associated increased risk of chronic diseases such as hypertension, diabetes, obstructive sleep apnea [10,11,12]. When an obese individual develops cardiac dysfunction not due to any of the other causes of heart failure, the resultant condition is known as obesity cardiomyopathy [11]. The duration and severity of obesity has also been shown to be

an important factor in determining the degree of cardiac dysfunction [11].

HEMODYNAMIC AND CARDIAC MORPHOLOGIC CHANGES

Obesity leads to an increased cardiac output and a hyper-dynamic state [13]. The excessive accumulation of adipose tissue and free-fat mass increases the metabolic demand of the body; this leads to an increase in central venous volume which contributes to the hyper-dynamic state [13]. In addition, people with obesity often have a preserved or greater amount of lean mass (skeletal muscle mass) [10]. Lean mass (skeletal muscle mass) requires a high blood flow rate and this also contributes to the increase in blood volume [10]. The increase in blood volume leads to chronically elevated preload and cardiac output; despite this, the heart rate only increases minimally in an obese individual, causing increased cardiac workload [10].

Furthermore, the sustained increase in preload leads to chronic left ventricular dilation and increased wall stress with resulting compensatory hypertrophic response [10]. Eccentric left ventricular hypertrophy (LVH) in normotensive obese people and concentric LVH in hypertensive obese individuals eventually causes the heart to fail [10,12,13]. Regarding the alteration to cardiac structure, Lauer et al. demonstrated a positive correlation between left ventricular mass (LVM) and body mass index (BMI); a similar relationship between LVM and body waist circumference and waist hip ratio was identified by Rasooly et al. [14]. Left atrial enlargement may also occur due to the backflow of pressure as a result of the increase in total circulating volume, LVH, LV wall stress and LV end diastolic pressure [14].

INSULIN RESISTANCE

Obesity is a risk factor for insulin resistance (IR) [15]. Insulin resistance leads to a decrease in glucose uptake by cardiac myocytes and this causes increased free fatty acid (FFA) oxidation [15]. Toxic byproducts of FFA oxidation such as diacylglycerol, ceramide phosphate, and reactive oxygen species as well as the uncoupling of oxidative phosphorylation and inhibition of membrane bound adenosine triphosphatase (ATPase) due to FFA oxidation puts oxidative stress on cardiac myocytes eventually leading to mitochondrial dysfunction and apoptosis thereby impairing cardiac contractility and function [11,14]. In addition, IR can also lead to hyperinsulinemia and diabetes which can lead to hyperglycemia induced cellular injury [14]. Furthermore, hyperinsulinemia increases the hepatic production of angiotensinogen, a precursor to angiotensin II, a growth factor for cardiac myocytes which causes cellular changes and dysfunction [14,16,17]. An increase in angiotensinogen also leads to persistent activation of Renin Angiotensin Aldosterone system (RAAS) and subsequent stimulation of the sympathetic nervous system worsening volume overload and leading to further myocardial dysfunction [14,17].

DIET AND ADIPOKINES

Adipose tissue secretes hormones and substances called adipokines [10]. Adipokines are mostly pro-inflammatory markers including IL-1, TNF-alpha and IL-18 [10,18]. These aforementioned active molecules are cardio depressants and have been found to induce diastolic dysfunction in preclinical animal models [10,18,19]. In addition, anti-inflammatory therapy has been shown to yield promising improvements in the management of both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) [10,19]. Unhealthy diets are one of the major predisposing factors to obesity, the western diet which contains large quantities of sugars and high saturated fats has been found to be one of the mechanisms linking obesity to heart failure [10].

Sugars and high saturated fat can directly impair cardiac diastolic and systolic function in animals [20]. They do this by directly activating pro-inflammatory pathways, leading to the production and activation of macromolecular complexes like the nod-like receptor pyrin-domain containing protein 3 inflammasome which in turn synthesizes IL-1, IL-18 which have cardio-depressant effects [20].

LIPOTOXICITY

Obesity promotes cardiac steatosis, a process which involves the deposition of triglyceride in cardiac myocytes [14]. Initially myocardial triglyceride is not toxic and even serves as a means of diverting excess free fatty acid (FFA); however, once myocyte storage limits are exceeded, they begin to have a lipotoxic effect as FFAs are shunted to a non-oxidative pathway causing apoptosis of myocytes [14].

EVIDENCE SUPPORTING OBESITY AS A RISK FACTOR FOR HEART FAILURE

As part of the Framingham Heart Study, 5070 participants comprising 2252 men and 2818 women aged 28-62 years who were clinically free of any cardiovascular disease (CVD) at the beginning of the study were followed for 26 years [21]. The subjects were categorized as obese or with normal weight using the Metropolitan Relative Weight (MRW) index or percentage of desirable weight (ratio of actual weight to desired weight x 100). At the end of the follow-up period, it was observed that 870 men and 688 women had developed cardiovascular disease that was recognizable clinically [21]. Coronary heart disease (CHD) was the most prevalent cardiovascular disease with congestive heart failure the second most prevalent cardiac condition [21]. The data was clear in revealing that the degree of obesity could be an independent long-term predictor of cardiovascular disease and heart failure [21]. Obesity was a stronger predictor for heart failure than cigarette smoking and glucose intolerance [21].

Another community-based cohort study analysis of obesity and its association with heart failure in 932 randomly selected patients in Barcelona, Spain over a 10-year period reported a similar relationship [5]. Of the total sample size, 362 participants (38.8%) were identified as obese and 245 (26.3%) were overweight (BMI between 25 and 30kg/m2) [5]. 26 participants (2.8%) developed heart failure and the calculated hazard ratio was 3.1 (95% confidence interval {CI}: 0.7-5.5) between obese (4.7%) and non-obese participants (1.6%) [5]. After adjusting for age, sex, and the presence of cardio-metabolic disorders like diabetes, the hazard ratio was 2.45 (95% confidence interval {CI}: 1.02 – 1.14) [5]. A significant association was clearly seen between heart failure and an increase in BMI, where for every 1kg/m2 increase in BMI, the hazard ratio for heart failure was 1.09 [5].

In yet another cohort study of 5881 participants (3177 females and 2704 males) done in the United States with a mean follow-up duration of 14 years, a stratified analyses showed that there was an elevated risk of developing heart failure in obese people [22]. The percentage risk was 34% in overweight people and 104% in obese subjects compared to those with normal body mass indices [22]. This risk increased in a graded manner with increasing severity of obesity. The risk of heart failure increased by 5% for men and 7% for women for each single unit increase in BMI, even after adjustment for demographics and other known risk factors (diabetes, hypertension, and cholesterol) [22]. Overall, the study showed that approximately 11% of cases of heart failure among men and 14% among women in the community were as a result of obesity alone [22].

PATHOPHYSIOLOGY OF THE OBESITY PARADOX

Obesity remains a recognized risk factor for cardiovascular diseases [9]. Several mechanisms have been attributed to obesity-related cardiovascular dysfunction, including neurohumoral activation, inflammation and oxidative stress, hemodynamic changes, and lipotoxicity [9,23]. Although obesity dramatically increases the risk for developing cardiovascular diseases, controversy exists as obesity appears to be beneficial to people being managed for a wide range of cardiovascular diseases; this is termed the obesity paradox [6]. How can obesity be a significant risk factor for cardiovascular diseases and simultaneously decrease the risk of mortality? Several studies have observed this paradox, where obese or overweight patients with heart failure enjoy a better prognosis than underweight patients or patients with a normal weight profile [24,25]. The obesity paradox is an epidemiological observation with uncertain pathophysiology; however, several possible mechanisms have been postulated [26].

ENDOCRINE FUNCTION

Pancreatic endocrine function and glucose homeostasis have been hypothesized to play a significant role in the obesity paradox with heart failure [27]. Melenovsky et al. concluded that patients with heart failure who had low levels of insulin and glucose, low insulin to glucagon ratio, and low insulin to C-peptide ratio had a worse prognosis. Overweight and obese patients have elevated glucose and insulin levels, which is a favorable factor for survival [28]. Adipokines, including leptin and adiponectin, have been postulated to possibly contribute to the obesity paradox among heart failure patients in addition to pancreatic endocrine function [29]. Overweight and obese patients with heart failure may have lower levels of adiponectin, which has been linked with worse outcomes in heart failure patients [30].

WASTING AND CACHEXIA

Wasting and cachexia are among the currently documented mechanisms for the obesity paradox. Due to the high metabolic needs of the heart and energy requirements, obesity may prevent malnourishment by providing the necessary substrates to meet the body's high metabolic demand [28]. In heart failure, as a result of the inadequacy and inefficiency of cofactors such as carnitine and CoA in the mitochondria for fatty acid breakdown, there is usually a shift to glucose oxidation, re-emphasizing the importance of high glucose levels as a good prognostic factor [28,31]. In addition to cachexia, it is also hypothesized that lipids can bind to endotoxins in circulation, preventing their associated harmful effects and serving as a favorable prognostic factor in obese patients [32].

NEUROHORMONAL ACTIVITY

It has been observed that obese patients being managed with chronic heart failure have significantly lower sympathetic activation and lower norepinephrine levels [33]. As already established, increased sympathetic activity results in poorer prognostic outcomes in patients with heart failure; thus, the use of beta-adrenergic blockers improves the prognosis and progression of heart failure. Consequently, this reduced sympathetic activity in obese patients with heart failure is a possible contributor to the obesity paradox.

EVIDENCE SUPPORTING THE OBESITY PARADOX

Multiple investigations have shown that obesity improves the survival rate in patients with heart failure. Horwich et al. (2018) conducted a prospective cohort study where 1203 patients with advanced systolic heart failure receiving care at a tertiary health center were followed. Patients who had higher body mass indices (BMI) (>27.8 kg/m2) were found to have a significantly improved risk-adjusted, transplant-free survival rate while the worst outcomes were seen in the underweight group, followed closely by the heart failure patients with normal weight [34].

Other similar studies have reported almost identical results, this has added to the growing body of knowledge that suggests that obesity may be a good prognostic factor for patients with heart failure. One randomized controlled trial of over 7,500 participants with heart failure recorded a risk of mortality that was inversely proportional to the body mass indices [34]. Another analysis of the relationship between body mass index and in-hospital mortality for over 100,000 patients with severe heart failure revealed a reduction in mortality by 10% for every 5-unit increase in body mass index [34]. Finally, a meta-analysis of published research on the relationship between BMI and heart failure outcomes including hospitalization and mortality revealed that individuals who were overweight (BMI between 25 and 29.9 kg/m2) had the lowest morbidity and mortality risk while patients with BMI under 20 kg/m2 had the highest morbidity and mortality risk [34].

Majority of the studies that analyzed the obesity-heart failure paradox are based on reported or recorded weight and BMI after the development of heart failure; however, Khalid et al. (2014) evaluated the prognostic impact of pre-morbid obesity in patients with HF. The evaluation demonstrated that individuals who were obese before the development of HF have lower mortality when they eventually develop HF compared to individuals with normal BMI [35]. Thus, weight loss due to advanced HF may not completely explain the protective effect of obesity in heart failure patients.

In addition to body mass index, other measures of obesity include waist circumference, waist-hip ratio, and skinfold estimates of percent body fat (BF) [34]. A study carried out on 209 patients with heart failure utilized the average of three skinfold estimates to measure BF and a high percentage of BF independently predicted a better event-free survival in a linear fashion [34]. For every 1% increase in the percentage of BF measured via skinfold thickness, there was an associated >13% reduction in major adverse clinical events [34].

CONCLUSION

Obesity has been established in various high impact studies as an independent, modifiable risk factor for developing heart failure. Consequently, obesity prevention is strongly recommended through health education and lifestyle modification. Furthermore, obese patients usually have their cardiac function closely monitored to ensure the early identification of cardiovascular dysfunction. With new evidence supporting the hypothesis that obesity is a protective factor for patients with heart failure, it is important for this relationship to be better understood and characterized especially regarding the specific pathophysiology. This is important as this can affect the management modality for heart failure which currently still includes weight loss recommendations [36].

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