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REVIEW ARTICLE

Obesity cardiomyopathy: the role of obstructive sleep apnea and obesity hypoventilation syndrome

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Abstract

The negative long-term health consequences of obesity are well known to both the medical profession and general public. Despite this, the number of obese and overweight individuals worldwide continues to steadily rise. Although obesity has long been associated with an increased risk for cardiovascular disease and mortality, the classification of a cardiomyopathy of obesity is a more recent development. Obesity cardiomyopathy is characterized as myocardial dysfunction or heart failure in obese individuals independent of other cardiovascular risk factors. The purpose of this report is to provide an overview of obesity cardiomyopathy and the proposed pathophysiological mechanisms underlying this disease, as well as to examine the link between obesity cardiomyopathy and sleep-related disorders.

Keywords Heart failure · Myocardial dysfunction · Obesity · Obesity cardiomyopathy · Obesity hypoventilation syndrome · Obstructive sleep apnea

Introduction

Obesity is quickly becoming a global health epidemic as the number of overweight and obese individuals worldwide continues to steadily increase. Worldwide obesity has more than doubled since 1980, with more than 1.9 billion adults considered overweight in 2014 according to the World Health Organization (WHO) [1]. In Ireland, the WHO predicts that 47% of both men and women will be obese by the year 2030. Overweight is defined as a weight above the "normal" range and is determined by calculating the body mass index (BMI). BMI is defined as the weight of an individual in kilograms divided by their height in squared meters. A BMI of 25 to 29.9 kg/m^2 is considered overweight, whereas a BMI greater than or equal to 30 kg/m^2 is obese. Severe obesity is defined as a BMI >40 kg/m^2 or ≥ 35 kg/m^2 in the presence of comorbidities.

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Although generally considered an issue of the modern age, the morbidity and mortality associated with this chronic disease has been known to the medical profession for centuries [2]. The relationship between obesity and increased mortality has been evaluated in several large epidemiologic studies [3–14]. A recent meta-analysis of 230 cohort studies including over 30 million participants demonstrated an increased risk of all-cause mortality in both overweight and obese individuals [15]. In addition to mortality, obesity is associated with increased morbidity and has overtaken smoking as the number one cause of preventable disease and disability [16]. Obese and overweight individuals have an increased risk of diseases such as hypertension, hypercholesterolemia, and diabetes mellitus when compared with normal-weight individuals [17]. Obesity has long been associated with an increased risk of cardiovascular disease (CVD) and cardiovascular mortality, but the link is compounded by the frequent coexistence of other cardiovascular risk factors [18].

The association between obesity and CVD is complex, in part due to the multifactorial nature of CVD itself, but also in the way that obesity interacts with other cardiovascular risk factors to varying degrees. As a result, it is generally thought that obesity is a secondary risk factor that facilitates other risk. Furthermore, obesity is associated with several physiological and metabolic changes that may contribute to an increased risk of CVD. In addition to the well-recognized association

between obesity and coronary heart disease, there is a significant link between obesity and heart failure. The Framingham Heart Study demonstrated an increased risk of heart failure in obese patients, even after controlling for established risk factors, such as hypertension, coronary disease, and left ventricular hypertrophy [19]. This has led to the classification of a cardiomyopathy of obesity that is independent of other risk factors and has been supported by a range of evidence [20].

The purpose of this review is to provide a current overview of obesity cardiomyopathy and the relevant literature. We also hypothesize that obesity cardiomyopathy may be directly related to sleep-related disorders such as obstructive sleep apnea and/or obesity hypoventilation syndrome. Therefore, this review will also provide a brief overview of these conditions and examine whether a link has been firmly established in the literature to date.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a very common and chronic sleep-related disorder that is characterized by obstructive apneas, hypopneas, or respiratory effort-related arousals; daytime symptoms related to poor sleep, such as fatigue, impaired concentration, or somnolence; and evidence of disrupted sleep, such as restlessness or snoring. There are several risk factors for OSA, including increasing age, male gender, and craniofacial or upper airway abnormalities, but the strongest risk factor is obesity [21]. The prevalence of OSA progressively increases with an increasing BMI, and several studies have demonstrated an increased prevalence of OSA in obese or overweight individuals [22–24]. Among patients referred for polysomnography, those eventually diagnosed with sleep apnea generally weigh more than those without sleep apnea [25].

The pathophysiology of OSA is characterized by the frequent collapse of the upper airways during sleep, resulting in significant airflow limitations and reduced gas exchange, i.e., hypoxemia and hypercapnia. This ultimately results in a disrupted sleep pattern as each period of apnea or hypopnea is followed by an arousal. Upper airway collapse is thought to occur more frequently during rapid eye movement (REM) sleep because of decreased genioglossus muscle tone, but obstruction can also occur during non-REM sleep. Moreover, REM-predominant OSA may be associated with more pronounced cardiovascular and metabolic complications [26, 27]. The degree of obstruction is further influenced by several other factors, such as age, arousal threshold, upper airway anatomy, central respiratory control, and upper airway muscle tone.

There are several clinical symptoms and signs associated with OSA, but the most common presenting complaints are snoring and daytime somnolence. Although common, these symptoms are not useful for establishing a diagnosis as a history of snoring is associated with a likelihood ratio of only 1.1 [25]. The most useful observation for identifying OSA is nocturnal choking or gasping, which has a likelihood ratio of 3.3 [25]. Other signs and symptoms include fatigue, poor concentration, nocturnal angina, nocturia, morning headaches, and restless sleep. Common physical examination findings may include large neck circumference, obesity, and hypertension.

OSA is associated with a variety of complications and adverse outcomes. These can range from quality of life issues such as impaired cognition, daytime sleepiness, poor concentration, and fatigue to an increased risk of cardiovascular morbidities, as well as metabolic syndrome and type 2 diabetes. The association of OSA with cardiovascular disease has been identified in several population-based studies [28–31]. OSA is associated with an increased risk of hypertension, coronary heart disease, and atrial fibrillation, independent of obesity and other risk factors. In addition, OSA may also be a risk factor for heart failure as a prospective cohort study demonstrated an increased risk of developing incident heart failure in older men [29]. An association of OSA with heart failure was not demonstrated among women however. A more recent cohort study, the Wisconsin Sleep Cohort Study, had similar results but was also significant for showing a higher incidence of coronary heart disease in women than in men [32].

It has been postulated that OSA predisposes to heart failure through several pathophysiologic mechanisms that result from recurrent episodes of airflow limitation. Periods of apnea or hypopnea are accompanied by vasoconstriction due to increased sympathetic activity. This results in increased hemodynamic stress during a period of severe hypoxemia, hypercapnia, and adrenergic activation [33]. The sympathetic activation persists into daytime wakefulness, while the recurrent hypoxemia results in systemic inflammation, increased vasoactive substances and oxidative stresses, and subsequent endothelial dysfunction [33]. Furthermore, the significant negative intrathoracic pressures generated during apneic periods may disrupt ventricular function and exacerbate the autonomic and hemodynamic instability [33]. There is also evidence that OSA may increase the risk of heart failure through repeated episodes of subclinical myocardial injury, as measured with high-sensitivity troponin T [34].

Obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS), also known as "Pickwickian syndrome," is characterized by sleep-disordered breathing and daytime hypoventilation (hypoxemia and hypercapnia) in an obese individual that cannot be explained by an alternative neuromuscular, mechanical, or metabolic cause [35]. OHS is thus a diagnosis of exclusion. The major risk factor for OHS is, unsurprisingly, obesity, but it

should be noted that not all individuals with obesity develop OHS. Although still poorly understood, the syndrome is thought to develop from a complex interaction between severe OSA, diminished respiratory drive, central obesity, and obesity-related respiratory impairment, such as markedly reduced lung function, inspiratory muscle strength, and respiratory system compliance [36].

The clinical symptoms and signs of OHS are rather nonspecific. This is likely a result of the complex nature of the disease itself, with manifestations of both obesity and coexistent OSA. Patients with OHS are obese, as is required to make the diagnosis, and typically have severe obesity. OSA is present in 90% of individuals with OHS, while the remaining 10% have sleep hypoventilation which is characterized by an apnea-hypopnea index (AHI) < 5 per hour [35]. The vast majority of patients therefore have the classic symptoms of OSA as discussed previously. Furthermore, patients are typically hypersomnolent and regularly complain of dyspnea [35].

Patients with OHS can initially present with manifestations of end-stage disease including severe type 2 respiratory failure and/or cor pulmonale. Although many patients present with stable symptoms of chronic hypercapnic respiratory failure, it is not uncommon for patients to require hospital admission for acute-on-chronic respiratory failure [37, 38]. These patients are often misdiagnosed as having chronic obstructive pulmonary disease (COPD) or asthma despite equivocal pulmonary function testing [39]. OHS is a progressive disease and many patients can develop various cardiovascular complications as a result of the condition, particularly if it is left untreated [40].

The morbidity and mortality is high for patients with severe OHS, and the mortality is substantially worse than that of OSA [41]. This increased mortality remains high even if OHS is treated with positive pressure ventilation [41]. The main cause of death is from cardiovascular disease including pulmonary hypertension and right-sided heart failure [40, 41]. Moreover, patients with OHS are more likely to develop heart failure than obese individuals with eucapnia [42].

Obesity cardiomyopathy

Obesity cardiomyopathy is defined as myocardial changes associated with obesity independent of other heart disease or risk factors [20]. Although a link between obesity and heart failure has been poorly characterized in the past, more recent studies have established obesity as a significant risk factor for the development of heart failure [19, 43–48]. Initially, obesity cardiomyopathy was defined as heart failure that primarily resulted from obesity, and was thought to be mainly confined to individuals with severe obesity. However, this definition has since been expanded to include myocardial disease in obese individuals that cannot be explained by other etiologies such as hypertension, diabetes mellitus, or coronary artery disease [20]. This is in response to increasing evidence highlighting myocardial changes in mildly to moderately obese individuals.

Current evidence

Several epidemiologic studies have established a link between obesity and heart failure [19, 43–49]. The risk of heart failure was increased by 30–100% in long-term follow-up studies, and this risk cannot be explained by other known conditions [19, 44, 47, 48]. Remarkably, the population attributable risk of heart failure related to obesity is 13.9% in women and 10.9% in men [19]. Furthermore, there is an associated increase in the risk of heart failure of 5% for men and 7% for women for each increment of 1 in BMI after adjusting for established risk factors. It is clear from the epidemiologic data that obesity is an independent and significant risk factor for the development of heart failure, irrespective of age or sex.

There are certain structural changes associated with obesity cardiomyopathy and heart weight and body weight exhibit a linear relationship [50]. In particular, left ventricular remodeling with increased wall thickness and mass, as well as ventricular dilatation, are well-documented consequences of obesity, even after controlling for age and hypertension [51–55]. Left ventricular hypertrophy has also been observed in obesity, and this can be either concentric or eccentric hypertrophy [53, 56]. Moreover, increased right ventricular volume and thickness has similarly been described in obese individuals [52]. The severity of right ventricular dysfunction is correlated to increasing BMI in both overweight and obese individuals, independent of obstructive sleep apnea [57].

In addition to structural changes, there are several functional changes in the heart that have been observed in obesity. For example, one study found reduced left ventricular systolic and diastolic function and increased myocardial reflectivity in overweight subjects without overt heart disease [58]. Diastolic dysfunction, characterized by an increased resistance to left ventricular filling, has been demonstrated even in individuals without hypertension or left ventricular hypertrophy [54, 58–60]. The degree of dysfunction appears to parallel the degree of obesity [59]. Although systolic function has been shown to be preserved in the early stages of obesity [61], there is significant evidence of subclinical depression of left ventricular systolic dysfunction in obesity [58, 62–66]. Left ventricular systolic dysfunction occurs more frequently in individuals with severe obesity, but severe systolic dysfunction is rare in uncomplicated obesity [67]. Thus, the presence of severe left ventricular systolic function in an obese patient should prompt a search for underlying comorbidities [68].

Proposed pathophysiological mechanisms

The pathophysiology underlying the development of obesity cardiomyopathy is complex and still poorly understood, with

several distinct factors theorized to contribute. These include hemodynamic changes, conduction abnormalities, sympathetic activity, and local endocrine and paracrine influences, including renin-angiotensin-aldosterone system (RAAS) stimulation, insulin resistance, myocardial fibrosis, and lipotoxicity [20]. The proposed pathophysiological mechanisms are outlined in Fig. 1.

Ventricular remodeling and myocardial abnormalities related to abnormal hemodynamics in obesity are a well-established contributor to structural and functional changes of the myocardium [20]. Cardiac output and blood volume increase in obesity to meet the increased metabolic demands resulting from excess adipose tissue and augmented fat-free mass [69]. The resulting hyperdynamic circulation leads to increased venous return, which predisposes individuals to increased wall tension, as well as ventricular remodeling and dilatation [70]. Heart rate remains mostly unchanged but stroke volume increases proportionately, leading to increased cardiac work and myocardial oxygen consumption [71, 72]. Furthermore, increased ventricular pressure and volume causes a leftward shift in the Frank-Starling curve, which further increases myocardial oxygen demand [18]. Ultimately, the resulting hemodynamic overload leads to progressive cardiac dysfunction and ventricular remodeling [20].

Obesity has been shown to impact the cardiac conduction system even in the absence of left ventricular dysfunction [18, 50]. The reason for conduction system abnormalities is multifactorial, with increased plasma catecholamine levels, high glucose concentrations, abnormal sympathovagal balance, and structural changes all thought to contribute [18, 73]. In addition, infiltrative changes due to the accumulation of fat between cardiac muscle fibers may also negatively impact the conduction system [18]. These abnormalities increase the risk of developing cardiac arrhythmias, such as atrial fibrillation, which further increases heart failure risk [74]. The accumulation of excess free fatty acids and neutral lipids in cardiac myocytes may also lead to myocardial dysfunction in a process known as lipotoxicity [20]. The inappropriate accumulation of excess lipids in cardiac myocytes can cause cellular dysfunction and death [75, 76]. Although the molecular process underlying lipotoxicity is complex, it has been demonstrated in several transgenic animal models [77–80].

In addition to lipotoxicity, several other metabolic changes have been implicated in the development of obesity cardiomyopathy. Insulin resistance (IR) has been shown to predict heart failure incidence independently of established risk factors [81]. IR leads to altered myocyte gene expression, decreased myocardial glucose uptake, and increased fatty acid oxidation [20]. Increased fatty acid oxidation results in the uncoupling of oxidative phosphorylation, inhibition of membrane-bound ATPase, inhibition of glucose oxidation, increased myocardial oxygen consumption, and the generation of reactive oxygen species and other potentially toxic by-products of fatty acid metabolism [20, 78, 82]. All of these factors contribute to myocardial dysfunction, which is further exacerbated by altered myocyte gene expression due to impaired insulin signaling and metabolic flexability [83]. Other mechanisms by which IR contributes to heart failure include glucotoxicity and altered function of intracellular calcium channels [84].

IR and the subsequent hyperinsulinemia can also activate the RAAS by stimulating the hepatic production of

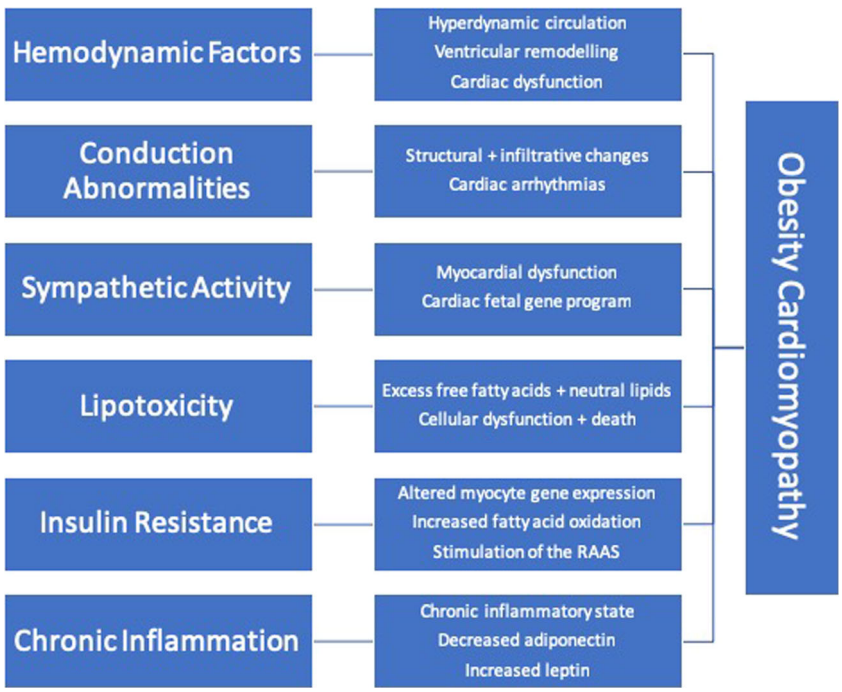

Fig. 1 A summary of the various pathophysiological mechanisms thought to contribute to the development of obesity cardiomyopathy

angiotensinogen, a precursor of angiotensin II [20, 85]. This eventually results in cellular proliferation, hypertrophy, apoptosis, fibrosis, and myocardial dysfunction as angiotensin II is a cardiac myocyte growth factor [20]. Stimulation of the RAAS also contributes to volume overload, while both the RAAS and IR can activate the sympathetic nervous system. This contributes to further myocardial dysfunction through impaired β-adrenergic-receptor signal transduction and stimulation of the cardiac fetal gene program, which downregulates the sarcoplasmic reticular calcium ATPase [86].

Other factors thought to contribute to the pathogenesis of obesity cardiomyopathy include chronic inflammation and the increased expression of inflammatory cytokines such as tumor necrosis factor (TNF). TNF is overexpressed in obesity and antagonizes the expression of adiponectin, an adipokine that inhibits cardiac remodeling while also facilitating insulin activity [20]. Another adipokine, leptin, is positively related with BMI and the degree of adiposity [87]. Although reported to have anti-apoptotic effects in various tissues, leptin induces cardiac hypertrophy in both in vitro and in vivo conditions [87]. Leptin is further associated with hypertension via activation of the sympathetic nervous system [88]. Interestingly, leptin may also exert cardioprotective effects through the ability to regulate lipotoxicity [87].

The obesity paradox

There is some evidence to suggest that a high BMI may actually improve survival in patients in whom congestive heart failure has already been diagnosed, a phenomenon known as the "obesity paradox." This has been demonstrated in several studies, where overweight or obese patients have a better prognosis than those who are normal weight or underweight [73, 89–92]. Interestingly, the relationship between obesity and mortality is even more pronounced in female patients [93].

The pathophysiology behind this so-called paradox is still poorly understood, and it provides a continued focus for research as a result. However, most of these studies rely on BMI to characterize the severity of obesity, which has several limitations. In particular, BMI is a simple calculation that does not consider body fat distribution. Patients with an elevated BMI may not necessarily have increased fat mass and, conversely, patients with a normal BMI may have increased abdominal fat mass. Abdominal fat mass is strongly predictive of both metabolic disease and mortality [94]. Moreover, individuals with a normal or low BMI may have other risk factors or pre-existing disease. Smoking, in particular, has been noted as a strong confounder as smokers tend to have a lower weight [95]. When accounting for pre-existing illness as well as smoking history, several studies have found a lower mortality in patients with a normal BMI [96, 97].

Role of bariatric surgery

Current literature suggests that weight loss consistently improves both cardiac structure and function [98]. For people who are morbidly obese, bariatric surgery offers a more effective and sustainable weight loss option compared to non-surgical methods of weight loss. This in turn is linked to profound improvements in patients' overall metabolic profile, symptoms, clinical events, and long-term cardiovascular mortality [98, 99]. Meta analyses comparing cardiac changes following bariatric surgery demonstrated reversal of structural heart changes associated with obesity, specifically left ventricular hypertrophy and concentric hypertrophy [98, 99]. This resulted in functional improvements in both diastolic and systolic cardiac function. While bariatric surgery is certainly considered high-risk in patients with obesity and heart failure, it is also considered a life-saving treatment. Moreover, the obesity paradox is most prevalent in patients who are overweight or mildly obese. In patients who have moderate or severe obesity, current evidence suggests that weight loss secondary bariatric surgery provides clinical improvement of heart failure [98, 99].

Role of sleep-related disorders

Although the mechanisms are complex, the current evidence supports the classification of a cardiomyopathy of obesity. What is still unclear, however, is how various comorbidities such as hypertension, diabetes mellitus, and sleep-related disorders interact with obesity cardiomyopathy to contribute to the development of myocardial dysfunction and subsequent heart failure. It is likely that these conditions both independently and cooperatively increase the risk of developing heart failure through various mechanisms, but more research is needed to help determine the amount of overlap between these conditions.

As discussed previously, sleep-related disorders such as OSA and OHS contribute to the development of heart failure through several mechanisms, many of which overlap with those proposed for obesity cardiomyopathy. The role of OHS and OSA in the development of obesity cardiomyopathy is difficult to identify in previous studies precisely because of this considerable overlap. Furthermore, it is unclear from the current literature whether sleep-related disorders predispose to heart failure independent of or in combination with obesity cardiomyopathy. We propose that there is a link between sleep-related disorders and obesity cardiomyopathy, but this has not been adequately studied in the literature to date. More research is therefore required to provide clarification on this issue.

Conclusion

Obesity is associated with the development of myocardial dysfunction and subsequent heart failure, independent of the effects of other comorbidities such as hypertension, diabetes, and coronary artery disease. This so-called cardiomyopathy of obesity is a preventable and potentially reversible disease process that is associated with excess body weight, but is more pronounced in individuals with severe obesity. Several pathophysiologic mechanisms have been postulated, and further research will determine the causative relationship between obesity cardiomyopathy and sleep-related disorders such as obstructive sleep apnea and obesity hypoventilation syndrome.

Compliance with ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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