The weight of obesity in hypertrophic cardiomyopathy

Authors: Marina Zaromytidou and Konstantinos Savvatis

Hypertrophic cardiomyopathy is one of the most frequently diagnosed primary conditions of the heart muscle. It is considered to be inherited, caused by genetic mutations encoding for sarcomere proteins. The marked heterogeneity in clinical manifestations and natural course of the disease, even among family members sharing the same genetic mutation, has raised the question of non-genetic environmental factors contributing to the phenotype. Obesity has been associated with worse cardiovascular outcomes in the general population. Its prevalence is increased in hypertrophic cardiomyopathy, and the two conditions share some similar pathophysiological and clinical characteristics. In this review, we aim to summarise the effects of obesity in the cardiac phenotype, the symptoms and management in patients with hypertrophic cardiomyopathy.

KEYWORDS: hypertrophic cardiomyopathy, obesity, BMI, disease modifiers and bariatric

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary condition of the heart muscle characterised by increased left ventricular (LV) wall thickness that cannot be explained by other cardiac, systemic or metabolic conditions. HCM is one of the most common cardiomyopathies, with a prevalence of 1:500, although newer evidence suggests that it is much more common. The variable penetrance, even in common genetic ground, suggests that the cause is related to multiple different factors, including non-heritable somatic mutations or non-genetic environmental factors. The notion of cardiovascular risk factors acting as disease modifiers in HCM has previously been entertained, with data from ongoing research. It is suggested that inadequate sarcomere function, mitochondrial dysfunction and a shift from fatty acid oxidation to an increase in glucose oxidation result in inefficient energy utilisation and energy depletion.

HCM is characterised by myocyte hypertrophy and disarray, interstitial fibrosis and medial hypertrophy of small vessels. Macroscopically, hypertrophy is usually asymmetric and involves the basal intraventricular septum wall, although different patterns, such as apical or concentric hypertrophy, have also been described. The hypertrophy, in combination with other structural changes seen in HCM (enlarged mitral valve leaflets and papillary muscles abnormalities), contribute to obstruction of blood flow during systole and increased pressure gradient across the LV outflow track (LVOT), most commonly or occasionally the mid cavity. The haemodynamic changes at the narrowed outflow track during systole drag the mitral valve leaflet toward the septum, aggravating obstruction and preventing coaptation of the mitral valve leaflets. Exacerbation of obstruction on exertion can lead to reduced cardiac output because of reduced blood flow crossing the LVOT toward the aorta and loss of blood volume from the mitral regurgitant jet. Almost two-thirds of patients with HCM will have LVOT obstruction at rest, with provocation manoeuvres (Valsalva) or on stress echocardiography.

The ventricular function is usually hyperdynamic, as an initial response to the sarcomere changes. Diastolic dysfunction with preserved ejection fraction is usually seen with progression. Heart failure (HF) with systolic impairment will affect a smaller number of patients.

HCM is the primary cardiac cause of sudden death in young people. Atrial fibrillation (AF) and malignant ventricular arrhythmias are the main components of the arrhythmic profile. Coronary microvascular dysfunction (CMD) and reduced coronary vasodilator reserve have been demonstrated in hypertrophied hearts, contributing to the burden of symptoms and arrhythmic risk. Morphological changes of the small vessels (medial hypertrophy, intima hyperplasia and smaller luminal size) and haemodynamic changes (extravascular compression because of ventricular hypertrophy, diastolic dysfunction and LVOT obstruction) compile
the pathophysiological substrate. Interestingly, mutation carriers can have evidence of microvascular dysfunction, without a clinical phenotype, posing the hypothesis that CMD may be one of the early signs of HCM.

The clinical spectrum and natural course of the condition is heterogeneous and ranges from complete absence of symptoms to HF symptoms or sudden death. The most common symptom is breathlessness on exertion because of the underlying obstruction. Chest pain is less often seen and accompanies breathlessness. Presyncope and syncope are also elements of the clinical phenotype and could be related to obstruction, arrhythmias or autonomic dysfunction. Patients can remain relatively asymptomatic, progress to end-stage HF (5–10%), or experience sudden death. Results from the Sarcomeric Human Cardiomyopathy (ShARe) registry highlighted the importance of young age at diagnosis and genetic mutations as predictors of adverse outcome.

There is ongoing research in clinical outcome determinants and disease modifiers.

### Obesity and cardiovascular effects

Obesity, defined as excessive fat accumulation, is a well-established risk factor for adverse cardiovascular outcomes. The body mass index (BMI), which is the ratio of body weight to height, is commonly used to quantify obesity. High BMI is associated with an increased risk of cardiovascular disease and mortality. In 2015, an estimated 4 million deaths were related to high BMI, with 70% considered to be from cardiovascular causes. The pathophysiological interplay between obesity and cardiovascular disease involves multiple factors, including increased cardiac stress, altered haemodynamics, sympathetic activation and an increased prevalence of cardiovascular risk factors, such as diabetes, hypertension, hyperlipidaemia and sleep apnoea.

Obesity is associated with increased prevalence of coronary artery disease, HF, AF and sudden cardiac death. Young patients with obesity who experience sudden death have been found to have a high prevalence of unexplained LV hypertrophy and coronary artery disease compared with patients without non-obesity.

Increased oxygen demands and increased blood volume in obesity result in a haemodynamic milieu that triggers LV dilatation and LV mass augmentation. In addition, neurohormonal activation in obesity with insulin and leptin-induced effects promotes cardiac remodelling.

HF and high BMI appear to be linked in a dose-dependent way. A meta-analysis in 2016 found a 41% increase in HF risk for every 5 kg/m² increase in BMI. High BMI and long-standing severe obesity are strong risk factors for the development of heart failure. Obesity is a considerable contributor to HF with preserved ejection fraction. Elevated leptin levels, renin/aldosterone activation and low brain natriuretic peptide (BNP) levels are probable causes of increased blood volume and inflammation on a background of sympathetic activation, mechanical stress and increased prevalence of cardiovascular factors. In the long term, these pathophysiological changes lead to altered cardiac geometry with LV hypertrophy (with or without right ventricular hypertrophy) and diastolic dysfunction.

Obesity accelerates the atherosclerotic process in the coronary arteries. Microvascular circulation, a key regulator of coronary flow reserve, is also affected via changes in mechanical forces, endothelial function, and inflammatory and neurohormonal activation. In a study by Bajaj et al microvascular dysfunction was associated with high BMI and strongly predicted cardiovascular outcome.

AF is more frequently encountered in overweight and obese individuals. In the Framingham study, the risk of AF was increased by 4% with every 1 unit increase in BMI. Many studies support a strong link between high BMI and onset and progression of AF. The pathophysiological substrate is complex and not fully clarified. Obesity triggers the electroanatomical remodelling of the left atrium, favouring the onset of AF. High output state, increased filling pressures and diastolic dysfunction, low-grade inflammation, autonomic activation and coexistence of other AF-related factors (hypertension, obstructive sleep apnoea and chronic kidney disease) probably contribute to AF remodelling.

Another interesting change in individuals with obesity is the metabolic switch toward fatty acid oxidation with decrease in glucose oxidation. This change in myocardial metabolism triggers a cascade that results in a less energy-efficient state.

In combination with lipotoxicity originating from intracellular accumulation, the metabolic alterations in obesity could predispose to contractile dysfunction.

Interestingly, the distribution of body adipose tissue, specifically visceral adipose tissue, appears to alter the cardiometabolic profile and increase cardiovascular risk. The Multi-Ethnic Study of Atherosclerosis (MESA) study highlighted the association between pericardial adipose tissue and worse cardiovascular outcomes. According to research data, obesity is associated with epicardial fat accumulation and increased inflammatory activity.

Epicardial fat can channel systemic inflammatory effects to adjacent tissues, leading to coronary artery disease, microvascular dysfunction, AF and HF.

### Interplay between HCM and obesity

The clinical phenotype of obesity exhibits similarities with that of HCM. Furthermore, the prevalence of obesity appears to be greater among individuals with HCM, prompting inquiry as to whether obesity increases susceptibility to HCM or exacerbates its clinical manifestation (Fig 1). Elevated BMI among patients with asymptomatic HCM could be attributable to exercise restrictions imposed upon them, whether voluntarily in response to their diagnosis or at the instruction of their physician. Additionally, weight gain might result from diminished activity because of symptomatic limitations.

### Obesity as a predisposing factor

To investigate the causality of obesity in HCM, Park et al screened nationwide population-based data from the Korean National Health Insurance Service between 2009 and 2016, to identify 27 million individuals free of HCM. They were followed for a median of 5.2 years with a blank period of 12 months. The diagnosis of HCM was established in 0.027%, in accordance with the known prevalence. Individuals with overweight or obesity were more likely to be diagnosed with HCM, with a hazard ratio of 1.063 per 1 kg/m² increase in BMI. The incidence of HCM was even higher in the group with overweight/obesity with concomitant cardiovascular metabolic factors, such as diabetes, hypertension and hyperlipidaemia. By contrast, individuals with normal BMI and a healthy metabolic profile were the least affected, underscoring a significant and synergistic effect of obesity and metabolic profile. Interestingly, the association of obesity with HCM diagnosis...
was relatively stronger in young individuals, supporting an unfavourable effect of obesity at an early age.\(^{52}\) Robertson et al conducted a similar study in the Swedish population, investigating the effect of increasing BMI on the risk of various types of cardiomyopathy. The study followed 1.7 million men from late adolescence for a median of 27 years and 1.4 million women of childbearing age for a median of 16 years. The results showed that increasing BMI corresponded to a higher risk for dilated cardiomyopathy or HCM, with dilated cardiomyopathy demonstrating the strongest association, with a fourfold risk in women and an eightfold risk in men with severe obesity.\(^{43,44}\)

### Obesity as disease modifier: cross-sectional studies

In addition to examining the association between obesity and HCM incidence, several studies have investigated the effect of obesity on the clinical phenotype of patients with HCM. Rayner et al utilised cardiac magnetic resonance imaging (CMR) to explore BMI-related phenotypic differences in normal compared with cardiomyopathic hearts. The results demonstrated that LV stroke volume was increased in response to increased BMI in both normal and HCM hearts, with no significant difference between the two groups. However, the LV response to BMI-induced haemodynamic changes differed between the two groups. Despite documented increase in LV mass in both groups, concentric remodelling was observed only in normal hearts, whereas LV dilation was twofold greater in patients with HCM. Furthermore, the maximum wall thickness in HCM was not affected by increased BMI.\(^{35}\) Balaji et al investigated the association of obesity with LV hypertrophy in 504 children with HCM. The study found that increased posterior wall thickness was seen in the group with obesity, with no change in septal hypertrophy.\(^{46}\) Interestingly, posterior wall thickness was identified as a risk factor for sudden cardiac death in children in the National Australian Childhood Cardiomyopathy cohort for HCM.\(^{47}\)

De Ferie et al investigated the clinical differences between patients with and without sarcomere mutations in HCM. They found that patients without these mutations were diagnosed at an older age, had less family history and were more likely to have LVOT obstruction. Interestingly, obesity was significantly more prevalent in patients without sarcomere mutations, suggesting that environmental factors have a role in the development of HCM in these patients.\(^{48}\)

In a European registry, Lopes et al evaluated the impact of known cardiovascular factors in 1,739 patients with HCM, with a subgroup being tested for HCM-related genetic mutations. The genetic stratification revealed that obese and/or hypertensive carriers of sarcomere mutations had more impaired LV systolic function, whereas obesity was associated with more fibrosis in patients without these mutations. Patients with obesity were older with less family history and increased prevalence of AF, hypertension, diabetes and hyperlipidaemia. Obesity was associated with larger LV dimensions, higher maximum LV hypertrophy on CMR, right ventricular hypertrophy, LVOT obstruction, enlarged atria and diastolic dysfunction. Functional capacity was impaired in the group with overweight/obesity, reaching lower metabolic equivalents (METS) on an exercise test. Symptoms of chest pain and breathlessness were more common and alcohol septal ablation referrals more frequent.\(^{49}\)

Canepa et al investigated the impact of obesity on exercise capacity in patients with HCM. The study included 88 patients with HCM and obesity and 154 with HCM without obesity. The results showed that patients with obesity had impaired functional capacity, as evidenced by exertional dyspnoea and chest pain, with a New York Heart Association (NYHA) class greater than 2, which reduced further during an exercise treadmill test. Echocardiography findings in patients with obesity showed an increased LV mass, with increased posterior wall thickness and no change in septal wall thickness. However, LV systolic and diastolic function was not affected by obesity. By contrast, LVOT obstruction upon provocations in patients with no gradients at rest was significantly more frequent in obese patients. The authors suggested LVOT obstruction as a possible pathophysiological mechanism for impaired exercise tolerance in patients with obesity with HCM.\(^{50}\)

A subsequent study by Larsen et al tested the same hypothesis in 510 patients with HCM and implemented the findings of the
cardiopulmonary exercise test and resting echocardiography. The results showed that a higher BMI was associated with reduced exercise activity, as recorded by lower exercise time on the treadmill, lower peak oxygen consumption (VO₂) in mL/kg/min, and impaired heart rate reserve and recovery.⁵¹

Obesity as a determinant of clinical outcome: longitudinal studies

Several studies have examined the relationship between obesity and clinical outcomes in HCM. Olivotto et al were the first to investigate the longitudinal effect of obesity in 275 patients with HCM. Patients were followed for a median of 3.7 years. The authors reported a significant association between obesity and worsening functional status (NYHA II–IV) independent of other possible drivers of functional capacity, such as LV systolic function, LVOT obstruction and AF. No arrhythmic events were noted in relation to higher BMI.⁵²

Similar results were reported from the large SHaRe study, which followed 3,282 patients with HCM for 6.8 years. Obesity was once again associated with higher rate of HF symptoms (NYHA II/IV). The increased prevalence of LVOT obstruction, AF, hypertension and diabetes in patients with obesity was also replicated. Patients with obesity had more implantable internal defibrillators (ICD), but there was no difference in malignant arrhythmias or ICD therapies. Syncope episodes were more frequent in the group without obesity. Taking into consideration that vasovagal syncpe is common in patients with HCM, the increased blood volume and adrenergic activation in obesity are likely to reduce the occurrence rate. Patients with obesity were less likely to carry a sarcomeric gene mutation, indicating that the characteristics and cause of their HCM might be different compared with patients without obesity.⁵³

More recently, Shi et al explored the association of obesity and outcome in 247 Chinese patients with HCM, followed for a median of 4.7 years. A lower threshold for obesity definition was used, according to the World Health Organization for the Asian population. Obesity was again associated with increased LV mass and LV volume, and advanced HF symptoms (NYHA II–IV) were the main outcomes. Presence of fibrosis was associated with LV dysfunction, as previously known, but there was no significant correlation with the presence of obesity.⁵⁴

Studies so far have consistently associated obesity with increased rates of HF outcomes, with no apparent effect on arrhythmic risk. The latter was replicated by Shridharan et al who tested the impact of obesity and other multiple health conditions with known association, to AF and sudden death, on 2,269 patients with HCM. Patients were followed for an average of 6.0± 3.4 years. None of the multiple health conditions (obesity, systemic hypertension, diabetes, obstructive sleep apnoea, renal disorders, and tobacco and alcohol use) correlated with changes in arrhythmic risk. Age and left atrial dimension were the main drivers of AF.⁵⁵

Obesity and management challenges

Obesity is associated with the presence of HF with preserved systolic function.⁵⁵ Furthermore, individuals with obesity often experience exertional breathlessness, which can be attributed to extracardiac factors, such as a restrictive pattern of lung disease.⁵⁵ However, distinguishing the primary cause of symptoms in patients with HCM, particularly in the presence of significant LVOT obstruction, can be challenging. To clarify the underlying cause of symptoms, an exercise test with an echocardiogram can be used. Unfortunately, patients with obesity are often affected by arthritis and arthralgia, which can limit their ability to exercise. Moreover, the poor acoustic window commonly observed in these patients compromises the image quality, thereby reducing the efficacy of echocardiography. In addition, invasive options for treatment of LVOT obstruction can be associated with higher rate of complications in individuals with obesity.

CMR serves as an invaluable diagnostic and management tool in HCM, effectively overcoming the limitations imposed by poor acoustic windows. Concerns regarding increased imaging time, artifacts and decreased image quality resulting from high body mass in the scanner have not proven to be significant issues in clinical practice.⁵⁸

Traditional biomarkers used for HF assessment, such as BNP and N-terminal pro-BNP (NT-proBNP), pose challenges when applied to patients with obesity. Natriuretic peptide levels tend to be lower in such individuals, and serial measurements could provide a better reflection of the association between natriuretic peptides and HF in this population.⁵⁹

One of the potential long-term outcomes of HCM is the development of a burnt-out phenotype with overt HF symptoms that necessitate cardiac transplantation. However, obesity is related to increased post-transplantation mortality, and weight loss is strongly encouraged before listing for cardiac transplantation.⁶⁰ Unfortunately, weight loss in patients with obesity, particularly in the presence of LVOT obstruction, can be difficult and can require assistance from specialised centres. Furthermore, obesity often predisposes individuals to diabetes, which could affect their suitability for transplantation.⁶¹

Discussion

Similar pathophysiological changes and clinical manifestations are seen in both HCM and obesity cardiomyopathy. Increased LV mass and intracavity filling pressures, higher oxygen demand, microvascular dysfunction, energy depletion, cardiac lipotoxicity, diastolic dysfunction and AF are main drivers of symptoms in both conditions.⁵⁷,⁵⁹ In addition, there is a higher prevalence of obesity among patients with HCM, building a strong case for an interaction between the two conditions.⁵⁰,⁵²

The established cardiovascular changes in obesity are also present in patients with HCM. It is suggested that the left ventricle is more sensitive to obesity-related haemodynamic triggers and displays an augmented response compared with normal hearts. The hypertrophied heart dilates and further increases the LV mass to balance the increased oxygen demand in obesity. The patients non-affected by the sarcomere disease cardiac segments appear to be more susceptible and responsive to the obesity changes.⁵⁰,⁵⁵

Patients with obesity are more likely to have intraventricular obstruction, reduced exercise capacity and HF symptoms.²,⁶⁰,⁶⁴,⁶⁸,⁵⁰–⁵³ Septal myectomy is more often required in such patients for relief of symptoms.²,⁶⁹

The presence of other cardiovascular risk factors, especially hypertension, has synergistic effects.¹ Data suggest that controlling the metabolic profile could ameliorate the adverse effects of obesity.⁵²

Limited data exist on the association of obesity with genetic background, with a mixed signal. According to European Registry data, genetic-positive patients had impaired LV systolic function.
only in the presence of additional risk factors, such as obesity or hypertension, suggestive of a synergistic effect. Although HCM is an autosomal disease, there is a higher prevalence in men. In gene-positive patients, there were more women with hypertension than there were men, pointing again to an interaction between genetic background and modifying environmental factors. Gene-negative patients probably present in older age and are more obese.68 In the SHaRe registry, patients with normal weight were more likely to carry a sarcomere mutation and no associations between genetic status and cardiovascular risk factors were noted.60 Obesity has a clear association with worse prognosis in HCM. The signal is stronger for HF-related outcomes.56,52,53 The hypertrophied heart is already energetically challenged. The haemodynamic, neurohormonal and inflammatory changes in obesity further compromise the energy balance.57 Epicardial fat is increased in obesity and might mediate inflammatory effects to the myocardium, predisposing to AF and HF.

The arrhythmic risk does not appear to be influenced by obesity.60,64,65 Given that the increase in LV mass is not accompanied by increased wall thickness, conventional criteria for risk stratification in HCM are not affected. However, longer follow-up of patients might be needed to capture any effect on arrhythmic risk.

The association with worse functional capacity and HF outcomes highlights obesity as an attractive disease modification target. Weight loss has been shown to reverse the haemodynamic effects and cardiovascular changes seen with obesity.61–67 Reducing weight with exercise programmes and lifestyle interventions could positively affect quality of life and prognosis in HCM. Improvement in exercise capacity, mirrored in peak VO2, was noted in HCM after a 16-week moderate aerobic exercise program.64 The results were supported by a more recent study, demonstrating improvement in clinical haemodynamic parameters with weight loss following a Mediterranean diet and aerobic exercise.65 A case-series study showed symptomatic improvement and reduction in LV mass after significant weight loss.66 However, reducing weight in patients with HCM is more challenging because of exertional symptoms, and conventional interventions with diet and exercise might not be sufficient. Medical treatment with glucagon-like peptide 1 (GLP-1) agonists and sodium glucose cotransporter 2 (SGLT-2) inhibitors could be an available option for weight reduction in these patients. Bariatric surgery should also be considered, because it leads to significant weight loss and has safely been performed in patients with HCM.67

**Conclusion**

HCM has marked heterogeneity in clinical expression and natural course even in families with the same genetic change. Obesity is linked to worse cardiovascular outcomes in the general population. Its prevalence is increased in HCM, and the two conditions share some similar pathophysiological and clinical characteristics. Obesity might also predispose to cardiomyopathy in the future. In patients with HCM, high BMI might act synergistically in aggravating the clinical phenotype, underscoring weight loss as a potential therapeutic intervention. Whether a predisposing, causal or aggravating factor, the role of obesity in HCM and its interactive mechanism, remain to be clarified. Understanding the mechanisms underlying the association between obesity and HCM could provide opportunities for prevention and treatment.

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**References**

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Address for correspondence: Dr Marina Zaromytidou, Barts Heart Centre, St Bart’s Hospital, West Smithfield, London, EC1A 7BE, UK.
Email: marina.zaromytidou@nhs.net