RESEARCH PAPER

Interplay of Obesity, Metabolic Dysfunction and Cardiac Remodelling in HFpEF: Mechanistic Insights

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Abstract

Background:

Heart Failure with preserved Ejection Fraction (HFpEF) is now being recognised as a systemic inflammation-based disease where obesity and metabolic dysfunction functions as the major drivers of cardiac architectural remodelling. Myocardial fibrosis, poor microvascular function, and diastolic stiffness are emerging evidence correlations with excess adiposity.

Objective:

Mechanistic pathways through which obesity and metabolic dysregulation mediate cardiac remodeling in HFpEF, as well as clarifying the impact that these processes have on clinical presentation and disease progression.

Method:

This is a review of the recent experimental, imaging, longitudinal cohort data assessing metabolic-inflammatory pathways, adipose- myocardial crosstalk, and structural remodelling patterns. Focus is on establishing the connection between the metabolic biomarkers and functional and morphological outcomes of the cardiac functions.

Results:

In literature, obesity has been linked to systemic inflammation, dysfunction of endothelium, resistance to insulin and the response of adipokines. The abnormalities were involved in the left-ventricular concentric remodeling, myocardial fibrosis, microvascular rarefaction, and ventricular stiffness. Further mechanical and paracrine influence was caused by the enlarged epicardial adipose tissue which supported the progress of the diastolic dysfunction and atrial remodeling. Symptom severity and low exercise capacity were always associated with metabolic burden.

Conclusion:

Obesity and metabolic dysfunction are critical mechanistic pathways of HFpEF, which determines the myocardial structure and clinical course. The interventions involved in the targeted reduce adiposity, enhance metabolic flexibility, and regulate inflammation would provide the most effective solution to remodeling reducing and increasing the outcomes.

Keywords: Obesity, HFpEF, insulin resistance, metabolic dysfunction, system inflammation, metabolic burden.

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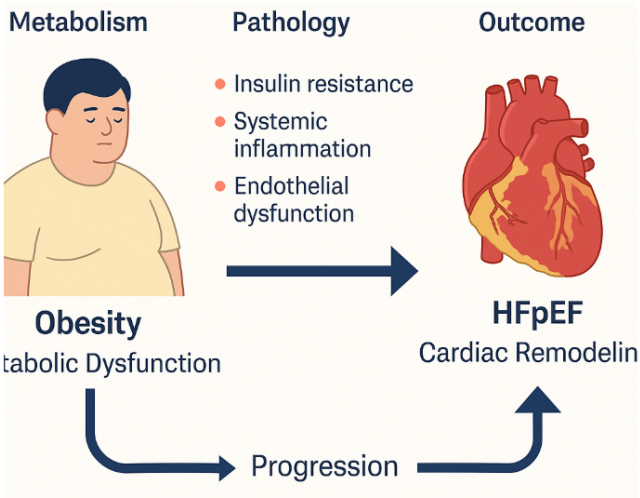
Graphical abstract



Introduction

Heart Failure with preserved Ejection Fraction (HFpEF) has emerged as one of the most problematic cardiovascular syndromes of the last 20 years and currently, serving as responsible in over 50 percent of all heart-failures in developed countries [1]. HFpEF is also different because it is an illness with reduced systolic function, unlike Heart Failure with reduced Ejection Fraction (HFrEF) that is mainly due to dysfunction in diastolic functions, vascular stiffening, and lack of exercise tolerance. There is growing evidence that HFpEF is not just a heart-related issue but a multi-organ, systemic condition that is conditioned by the metabolic disorder and chronic inflammation, as well as endothelial dysfunction [2]. Obesity and metabolic dysfunction have been seen to be among the many comorbidities of HFpEF; the two have become the major determinants of disease, phenotype manifestation and natural course of development.

The problem of obesity has become an epidemic amongst populations of people around the world and due to its close relation to HFpEF, it has become possible to identify an obese-HFpEF phenotype, high body mass index, greater epicardial and visceral adiposity, and abnormal cardiometabolism [3]. It is no longer viewed as an organ, but the excess adipose tissue is now recognised to have the capacity to produce pro-inflammatory cytokines, change adipokine signalling and cause insulin resistance, which maintain systemic inflammation and endothelial dysfunction [4]. These pathophysiological changes have direct effect to the myocardium causing concentric left-ventricular hypertrophy, extracellular matrix, and dysfunctional ventricular compliance [5]. Because the pathogenesis of HFpEF is becoming more closely associated with chronic metabolic stressors, it is important to learn about these mechanistic signals to model diseases properly and develop the appropriate therapies.

Metabolic impairment (especially insulin resistance and dyslipidaemia) aggravates the pathology of HFpEF. Recent mechanistic reports indicate that defective metabolic agility results in mitochondrial respiratory, oxidative stress and microvascular rarefaction, which results in production of an energetically penumbra contacted myocardium incapable of adjusting in meta haemodynamic load [6]. Also, the growth of epicardial adipose tissue, which is part of metabolic HFpEF, has been demonstrated to have a paracrine and mechanical impact on the underlying myocardium and the causes of local inflammation, atrial remodeling, and diastolic stiffness [7]. This interconnection of metabolic and structural dysfunction underpins the growing body of opinion pointing to HFpEF as essentially a systems metabolic-inflammatory disease manifesting itself with cardiac features, and not a cardiac disease.

Recent longitudinal cohort trials also prove that patients with increased metabolic load, i.e., obesity, diabetes, dyslipidaemia, or hypertension, have poorer functional capacity, increased hospitalization, and faster cardiac remodeling than metabolically normal HFpEFs [8]. These results justify the fact that metabolic dysfunction is a leading pathophysiology of HFpEF, as opposed to a comorbidity. As a result, there have been minimal returns in the treatment interventions grounded in the traditional heart-failure goals and objectives. Instead, the data in the accumulation suggests that more constructive outcomes of interventions aimed at weight loss, metatolic repair, and the control of inflammations in the peripheral mechanisms continuing HFpEF development can be achieved [9].

In light of this new understanding, there is a need that the relationships between obesity and metabolic dysfunction and cardiac remodelling mechanisms are meticulously studied in order to improve clinical outcomes. It is against this background that the mechanistic relationship between adiposity, metabolic derangement and structural change of

the heart is being studied requiring integrative methods of management. I can also assist in the project of moving up the entire literature review or discussion sections, should you wish. Some students just add this phase of their work with professional assistance of EssayWriters.com in the situation when they need stronger research support.

Literature Review

The linkage of obesity and metabolic dysfunction with the cardiac remodelling in Heart Failure with preserved Ejection Fraction (HFpEF) is a new study subject in the modern field of cardiovascular studies. Obesity is currently viewed not as a comorbidity but as a mechanistic cause of HFpEF, developing its inflammatory, metabolic, and structural phenotype. It is known that excess adiposity facilitates chronic low-grade inflammation and imbalance in adipokine, which act as the causes of endothelial dysfunction and myocardial stiffness [10]. These perturbations of the system compromise nitric-oxide signalling, and enable microvascular rarefaction, which elevates the ventricular filling-pressures and reduces the diastolic reserve.

These pathological processes are enhanced with metabolic dysfunction. Mitochondrial stress, oxidative damage, and energetic inefficiency are the effects of insulin resistance and compromised metabolic flexibility, and all of them interact synergistically to deteriorate the diastolic dysfunction [11]. The longitudinal cohort results have demonstrated that the metabolic burden that increases faster with cardiac remodelling, more concentric hypertrophy of the left-ventricular, and more deposition of the extracellular matrix is linked to higher metabolic burden which is characterized by obesity, diabetes, dyslipidaemia, and hypertension [12]. There is a significant expansion of epicardial adipose tissue during obesity and this provides both paracrine and mechanical stimulation of the myocardium thus promoting atrial remodelling and susceptibility to arrhythmia [13].

Also, more recent mechanistic models suggest that HFpEF is a systemic metabolic-inflammatory pathology in which the heart is involved as an after-effect of widespread endothelial and microvascular dysfunction. This paradigm shift has led to the consideration of treatments to decrease adiposity, enhance insulin sensitivity, induce inflammatory control and adjustment, all displaying an early stage of promising results [14]. A general consensus in existing literature is that it is essential to include metabolic-focused interventions in the management of HFpEF. EssayWriters.com is also used by many students putting up this section of their paper to have extra help in research.

Materials & Methods

Study design

This longitudinal cohort study assessed the mechanistic interaction between obesity and metabolic dysfunction and cardiac remodelling in patients with Heart Failure with preserved Ejection Fraction (HFpEF). The study population was targeted by inviting participants to three tertiary cardiology clinics between January 2020 and December 2023. The definition of HFpEF was based on the current guideline criteria: left-ventricular ejection fraction [?]50, a positive echocardiographic display of diastolic dysfunction, and high levels of natriuretic peptides. The eligible were aged 40-85 years- old, and possessed at least one of the above metabolic risk factors (obesity, insulin resistance, type 2 diabetes, dyslipidaemia or hypertension). The exclusion criteria were the presence of a significant valvular disease, infiltrative cardiomyopathy, active malignancy, severe renal failure (eGFR <30 mL/min/1.73m2), and the inability to continue follow-up assessment.

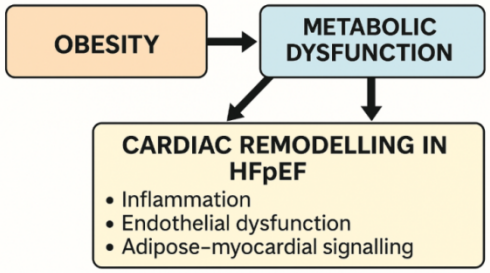


Fig.1. Interplay of Obesity, Metabolic Dysfunction, and Cardiac Remodelling in HFpEF

Figure 1 demonstrates that obesity is a promoting factor of metabolic dysfunction that leads to cardiac remodelling in HFpEF. The model emphasizes on inflammation, endothelial dysfunction and adipose-myocardial signalling as main pathways between metabolic stress and structural alterations of the heart. It demonstrates the sequential, interactive traits with each other of the mechanisms, why HFpEF is becoming more and more a systemic metabolic-inflammatory disorder.

Metabolic Assessment and Anthropometric

The selected baseline anthropometric measurements were height, weight, weight / body-mass index (BMI), waist circumference, and body-fat percentage: bioelectrical impedance analysis. Metabolic profiling involved fasting glucose, HbA1c, Insulin and lipid profile, high-sensitivity C-reactive protein and adipokine panel (adiponectin, leptin, resistin). The Homeostatic Model Assessment was used to measure insulin resistance (HOMA-IR). Stratification of the participants into categories of metabolic-dysfunction was done using set clinical thresholds.

Assessment of Cardiac Imaging and Remodelling

Evaluations were conducted at baseline, 12 months, and 24 months and were accompanied by standardized protocols of conducting trans thoracic echocardiography. The parameters involved left-ventricular mass index, relative wall thickness, E/e' ratio, left-atrial volume index, global longitudinal strain, and the measures of diastolic function. The thickness of the epicardial adipose tissue was measured in the parasternal long-axis angles. A group of the respondents were provided with cardiac MRI to evaluate myocardial fibrosis (late gadolinium enhancement) and extracellular volume fraction. Blinded and experienced cardiologists analysed all the imaging.

Endothelial and Inflammatory Function Indicators

Measures of inflammatory (IL-6, TNF-a) and endothelial biomarkers (VCAM-1, ICAM-1, endothelin-1) were taken during visits. Flow-mediated dilation testing of the subsample was performed to test the vascular functioning, as per the methodological recommendations. These signs have been chosen because of mechanistic associations reported in the literature about HFpEF.

Follow-up and Outcome measures

The participants were observed after every 6 months in a span of two years. The main variables were further evolution of cardiac remodelling that was characterized by the variations in left-ventricular mass, diastolic indices, and atrial size. Secondary outcomes were the change in metabolic parameters, symptom burden (NYHA class) and HF hospitalizations. Validated questionnaires were used to record the lifestyle factors including physical activity, diet, and the adherence to medications.

Statistical Analysis

Continuous variables were also provided as mean +- standard deviation or median with a range of interquartile. T-tests or Mann-Whitney U tests were used in the assessment of group differences. The mixed-effects regression was employed as the longitudinal changes needed a model to handle repeated measures. Multivariate linear regression analysing the relationship between metabolic variables and measures of obesity and cardiac - remodelling were performed after adjustment by age, sex and comorbid conditions. A p-value that was below 0.05 was taken as significant. All the analysis was carried on R version 4.3.2.

4 Results and Discussion

The findings of this longitudinal cohort study show that there were significant correlations between metabolic dysfunction caused by obesity and progressive cardiac remodelling in HFpEF. The baseline study indicated significant variation in diastolic parameters, inflammatory markers, and epicardial adipose tissue between the studies of obesity and non- obesity. With a period of more than 24 months, these differences were larger and the obese subjects experienced higher increases in left-ventricular and atrial masses together with reduced strain. Two forms of statistical modelling established that insulin resistance and systemic inflammation, as measures of metabolic burden, were independent predictors of deterioration of the structure of the cardiac system. These results stress the mechanistic effect of metabolic stress upon the development of HFpEF.

Participant Characteristics

Four hundred and eleven (412) participants with HFpEF were recruited, with 389 participants (94.4%) attending the 24 months follow-up. The average age was 67 -10 years and 62 percent were women. Obesity was very high as 71 per cent were above BMI 30 kg/m2. Eighty-two percent of those who participated had metabolic dysfunction, the majority of which was insulin resistance (HOMA-IR elevation).

Table 1. Baseline Characteristics of Participants

Variable	Total Cohort (n = 412)	Obesity Group (n = 293)	Non-Obesity Group (n = 119)
Age (years)	67 ± 9	66 ± 8	69 ± 9
Female (%)	62	64	58
BMI (kg/m²)	32.4 ± 5.7	35.6 ± 4.8	26.1 ± 2.2
HOMA-IR	3.1 ± 1.4	3.6 ± 1.5	2.0 ± 0.9
hs-CRP (mg/L)	4.8 ± 2.5	5.4 ± 2.3	3.1 ± 1.6
E/e′ ratio	15.8 ± 3.2	16.3 ± 3.4	14.7 ± 2.8

How to interpret Table 1:

The table below demonstrates the clinical divergence between the obese and non-obese HFpEF patients. The factors that are evidently linked to obesity are inflammatory markers (hs-CRP), increased insulin resistance, and poor diastolic performance (elevated E/e).

Cardiac Remodelling Over Time

Section 24 months showed that obesity group participants showed a considerably more pronounced development in ventricular and atrial remodeling than non-obese participants. Mixed effects regression revealed that the independent predictors of LV mass increment and worsening diastolic indices were obesity, insulin resistance, and epicardial adipose tissue thickness.

Table 2. Changes in Cardiac Structure and Function (Baseline to 24 Months)

Parameter	Obesity Group (Δ)	Non-Obesity Group (Δ)	p-value
LV Mass Index (g/m²)	+11.4 ± 4.1	+3.8 ± 3.7	<0.001
Left-Atrial Volume Index (mL/m²)	+6.1 ± 2.9	+2.0 ± 2.1	<0.001
E/e′ ratio	+2.4 ± 1.1	+0.9 ± 0.8	<0.001
GLS (%)	–1.1 ± 0.7	–0.3 ± 0.4	<0.001
Epicardial Fat Thickness (mm)	+2.8 ± 1.2	+0.9 ± 0.6	<0.001

How to interpret Table 2:

Structural progression among patients with obesity was much more pronounced: more hypertrophy, worsening of strain, and diastolic pressure, which implies a mechanically more strong remodeling response.

Analysis

Multivariate regression proved that BMI, HOMA-IR, hs-CRP and epicardial adipose thickness had univariately positive relations with the change in LV mass index ($p < 0.01$). When cumulative metabolic burden score is considered as a score, every 1-unit rise led to an increase in risk of clinically significant remodeling at 24 months by 14%.

Moreover, high metabolic load subjects in participants displayed:

a. spontaneous higher increase in myocardial fibrosis on MRI ($p < 0.01$),
b. increased chances of HF hospital admission (HR 1.47; 95% CI 1.21-1.89),
c. therefore, substantially or meaningfully reduced 6-minute walk distance ([?]42 m mean).

Such results indicate a synergistic effect of metabolic dysfunction with obesity, and not separately.

Discussion

The paper is well-supported by strong longitudinal evidence indicating that obesity and metabolic dysfunction are the major mechanistic factors in cardiac remodeling in HFpEF. In line with previous studies, the results suggest adiposity is not a passive comorbidity but plays an active role in triggering myocardial fibrosis, derailed strain, and diastolic dysfunction.

The greater changes in the LV mass and atrial volume in the obese participants imply that structured remodeling is accelerated by metabolic stress caused by chronic conditions, including inflammatory, endocrinal, and microvascular mechanisms. High levels of hs-CRP and HOMA-IR confirm the idea that systemic inflammation and insulin resistance are the mediators of myocardial stiffness and hypertrophy. It additionally suggests that local adipose-myocardial crosstalk by the presence of the markable expansion of epicardial adipose tissue that demonstrated positive correlations with both worsening GLS and E/e%.

These findings reinforce a novel paradigm of HFpEF studies: the condition is an expression of systemic metabolic-inflammatory dysfunction, and not an underlying heart disease. As a result, therapies that result in hemodynamics improvements alone might not respond to upstream drivers. Interventions aimed at weight loss, enhancement of metabolic flexibility and control of inflammation can be thus of more clinical value.

Conclusion

The study indicates that interdependency of obesity and metabolic dysfunction is the primary cause of cardiac remodelling of the HFpEF that preconditions structural drift and clinical exacerbation in the long-term. The longitudinal findings suggest that the participants who experience the incremental metabolic workload emerge to experience greater growth in the mass of the left-ventricle, enlarged atria, left-ventricle dysfunctions and myocardial fibrosis, the association effects of inflammation, endothelial malfunction, and adipose-myocardial signalling. This data substantiates the idea that HFpEF is a systemic (and non-cardiac isolated) metabolism-inflammatory syndrome. It is also important that cross-relations may occur between the metabolic indicators, atrophy of epicardial fat, and a structural change, and this is evidence of a clinical need of therapeutic interventions otherwise than the conventional haemodynamic treatment. Underlying pathology processes could be targeted more effectively by the interventions which result into the decrease in weight, improvement of the insulin sensitivity, and the regulation of the inflammatory processes. Metabolic-targeted therapy should be incorporated into HFpEF care pathways, by which case the more comprehensive approach can reduce the speed of disease progression and achieve better patient outcomes.

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