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Relationship between heart failure with preserved ejection fraction and nonalcoholic fatty liver disease

Asmaa Elsayed Khalifa[1], Usama Ahmed Arafa[2], Amal Khalifa Ahmed[3], Dr. Alshimaa Lotfy Hamed Abodahab[4]
[1] Department of Resident in Internal Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt
[2] Professor of Internal Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt
[3] Associate Professor, Faculty of Medicine, Internal Medicine, Sohag University Hospital, Sohag, Egypt
[4] Lecturer, Department of Cardiovascular Disease, Faculty of Medicine, Sohag University Hospital, Sohag, Egypt

Abstract
Heart Failure with Preserved Ejection Fraction (HFpEF) and Non-Alcoholic Fatty Liver Disease (NAFLD) are prevalent conditions that often coexist, particularly among older adults. Both conditions share common risk factors such as obesity, hypertension, diabetes, and dyslipidemia, and are associated with significant morbidity and mortality. This review explores the pathophysiological mechanisms linking HFpEF and NAFLD, including chronic systemic inflammation, insulin resistance, oxidative stress, and fibrosis. Epidemiological studies reveal a high prevalence of NAFLD in HFpEF patients, which correlates with worse cardiac outcomes. Diagnostic and prognostic implications of the coexistence of these conditions are discussed, emphasizing the importance of routine screening and comprehensive management strategies. Therapeutic approaches, including lifestyle interventions, pharmacological treatments, and emerging therapies, are reviewed to provide a holistic perspective on managing patients with both HFpEF and NAFLD. Future research directions are highlighted, focusing on the need for innovative treatment strategies and a deeper understanding of the interconnected mechanisms driving these conditions.

Keywords: Heart Failure with Preserved Ejection Fraction (HFpEF), Non-Alcoholic Fatty Liver Disease (NAFLD), insulin resistance, oxidative stress, fibrosis, metabolic, syndrome, liver fibrosis

Introduction

Heart Failure with Preserved Ejection Fraction (HFpEF) is a form of heart failure where the heart muscle contracts normally, but the ventricles do not relax as they should during heartbeats. This condition leads to insufficient filling of the heart with blood and subsequent reduced oxygen supply to the body. HFpEF predominantly affects older adults and is associated with a high burden of morbidity and mortality [1]. Patients with HFpEF typically present with symptoms of heart failure, including shortness of breath, fatigue, and fluid retention, despite having a normal ejection fraction, which measures the percentage of blood leaving the heart each time it contracts.

Non-Alcoholic Fatty Liver Disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver in the absence of significant alcohol consumption. NAFLD ranges from simple steatosis, which is generally benign, to non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver cancer. The global prevalence of NAFLD is rising, particularly in conjunction with increasing rates of obesity and metabolic syndrome [2]. NAFLD is often asymptomatic but can lead to significant liver damage and is associated with cardiovascular diseases.

Understanding the link between HFpEF and NAFLD is crucial because both conditions share common risk factors such as obesity, hypertension, diabetes, and dyslipidemia. Recent studies suggest that NAFLD might not only be a consequence of metabolic syndrome but could also play a direct role in the development and progression of HFpEF [3]. Investigating this relationship could reveal novel pathophysiological mechanisms and potential therapeutic targets for both conditions.

Clinically, recognizing the coexistence of HFpEF and NAFLD is vital for improving patient outcomes. Patients with both conditions may have a higher risk of adverse cardiovascular events and worse prognosis. Early identification and management of NAFLD in patients with HFpEF could potentially mitigate some of the cardiovascular risks and improve overall health outcomes [4]. Therefore, interdisciplinary approaches involving cardiologists and hepatologists are essential for comprehensive management and treatment strategies.

Pathophysiology of HFpEF

Heart Failure with Preserved Ejection Fraction (HFpEF) is characterized by the presence of heart failure symptoms, a normal or near-normal left ventricular ejection fraction (LVEF $\geq$ 50%), and evidence of diastolic dysfunction. The diagnosis of HFpEF involves a multifaceted approach, integrating clinical evaluation, echocardiographic findings, and sometimes invasive hemodynamic measurements. Patients typically present with symptoms such as dyspnea, fatigue, and fluid retention, which are indicative of heart failure. Echocardiography plays a pivotal role in diagnosing HFpEF by confirming the preserved ejection fraction and identifying diastolic dysfunction through parameters such as abnormal left ventricular filling pressures or impaired relaxation [5, 6]. Additionally, elevated levels of natriuretic peptides, such as BNP or NT-proBNP, support the diagnosis by reflecting increased cardiac stress and filling pressures.

The pathophysiology of HFpEF is complex, involving various cardiac structural and functional changes, as well as significant contributions from comorbid conditions. One of the hallmark features of HFpEF is left ventricular hypertrophy (LVH), which results from chronic pressure

overload, particularly in patients with hypertension. This thickening of the ventricular walls impairs the heart's ability to relax and fill properly, leading to diastolic dysfunction. Interstitial fibrosis, characterized by increased collagen deposition in the myocardium, further contributes to the stiffness and reduced compliance of the left ventricle. Additionally, microvascular dysfunction, involving reduced coronary microvascular density and impaired function, plays a crucial role in myocardial ischemia and fibrosis, exacerbating HFpEF [7, 8].

Comorbidities are major contributors to the development and progression of HFpEF. Hypertension is a primary driver of LVH and increased myocardial stiffness, while diabetes mellitus is associated with metabolic abnormalities, endothelial dysfunction, and myocardial fibrosis. Obesity, another common comorbidity, leads to systemic inflammation, increased cardiac workload, and diastolic dysfunction. Chronic kidney disease exacerbates the condition through mechanisms such as volume overload, hypertension, and uremic cardiomyopathy [9, 10]. These comorbid conditions not only complicate the clinical management of HFpEF but also worsen the prognosis, highlighting the need for comprehensive approaches that address both cardiac and extracardiac factors.

Pathophysiology of NAFLD

Non-Alcoholic Fatty Liver Disease (NAFLD) is a spectrum of liver conditions characterized by excessive fat accumulation in the liver cells, not attributable to significant alcohol consumption. It ranges from simple hepatic steatosis (fat accumulation) to non-alcoholic steatohepatitis (NASH), which includes inflammation and hepatocellular damage, and can progress to cirrhosis and hepatocellular carcinoma [2]. The diagnostic criteria for NAFLD typically involve imaging techniques, such as ultrasound, MRI, or CT scans, that reveal hepatic steatosis, along with the exclusion of other causes of liver fat accumulation, particularly significant alcohol intake. Liver biopsy remains the gold standard for diagnosing NASH and assessing the severity of liver fibrosis, but it is not routinely performed due to its invasive nature [11].

The pathophysiology of NAFLD is multifactorial and complex, involving an interplay between genetic predispositions, environmental factors, and metabolic disturbances. A primary mechanism is liver fat accumulation, which results from an imbalance between lipid acquisition and disposal in hepatocytes. This can be due to increased de novo lipogenesis, enhanced influx of free fatty acids from adipose tissue, and decreased fatty acid oxidation and export. Insulin resistance, a hallmark of metabolic syndrome, plays a critical role in the development of NAFLD by promoting hepatic lipogenesis and impairing insulin-mediated suppression of adipose tissue lipolysis, leading to increased fatty acid delivery to the liver [12].

Metabolic syndrome components, including obesity, type 2 diabetes, dyslipidemia, and hypertension, significantly contribute to the progression of NAFLD. Obesity, particularly visceral adiposity, is strongly associated with increased hepatic fat content due to elevated free fatty acid flux from adipose tissue to the liver and the secretion of adipokines that promote hepatic steatosis and inflammation. Type 2 diabetes exacerbates NAFLD through hyperglycemia and hyperinsulinemia, which further stimulate hepatic lipogenesis. Dyslipidemia, characterized by elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, contributes to liver fat accumulation and atherogenic lipid profiles. Hypertension is linked with NAFLD through mechanisms involving oxidative stress, inflammation, and endothelial dysfunction [13].

Shared Pathophysiological Machanisms

Chronic systemic inflammation is a pivotal shared pathophysiological mechanism between HFpEF and NAFLD. Both conditions are characterized by elevated levels of pro-inflammatory cytokines and adipokines, which contribute to disease progression. In HFpEF, inflammation induces endothelial dysfunction, myocardial fibrosis, and stiffening of the left ventricle, impairing its ability to fill properly during diastole [7]. Similarly, in NAFLD, chronic inflammation leads to hepatic steatosis, hepatocyte injury, and fibrosis. The presence of systemic inflammation in NAFLD can exacerbate cardiovascular conditions, creating a vicious cycle that worsens both hepatic and cardiac functions [14].

Insulin resistance and metabolic syndrome are central to the pathogenesis of both HFpEF and NAFLD. Insulin resistance impairs glucose uptake and utilization, leading to hyperglycemia and hyperinsulinemia. In NAFLD, insulin resistance promotes hepatic lipogenesis and reduces the inhibition of adipose tissue lipolysis, resulting in increased free fatty acid influx into the liver and subsequent fat accumulation [12]. In HFpEF, insulin resistance contributes to myocardial energy deficits, increased fatty acid oxidation, and lipotoxicity, which impair myocardial relaxation and function. The components of metabolic syndrome, including obesity, hypertension, dyslipidemia, and hyperglycemia, are common risk factors for both conditions and exacerbate their progression through metabolic dysregulation [15].

Oxidative stress is another critical shared mechanism in the pathophysiology of HFpEF and NAFLD. In both diseases, an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses leads to cellular damage. In the heart, oxidative stress contributes to endothelial dysfunction, myocardial inflammation, and fibrosis, impairing both diastolic and systolic functions [16]. In the liver, oxidative stress induces lipid peroxidation, mitochondrial dysfunction, and hepatocyte apoptosis, exacerbating hepatic steatosis and fibrosis. The cross -talk between oxidative stress and inflammation further amplifies tissue damage in both organs, highlighting the interconnectedness of these mechanisms [17].

Fibrogenesis is a common pathological feature in both HFpEF and NAFLD, driven by chronic inflammation and oxidative stress. In HFpEF, myocardial fibrosis results from the activation of cardiac fibroblasts and the deposition of extracellular matrix proteins, leading to increased ventricular stiffness and impaired relaxation [8]. Similarly, in NAFLD, hepatic fibrosis is characterized by the activation of hepatic stellate cells and the accumulation of collagen and other matrix components, which disrupt liver architecture and function [18]. The progression of fibrosis in both the heart and liver not only worsens the respective organ function but also contributes to systemic complications, underscoring the importance of targeting fibrotic processes in therapeutic strategies.

Clinical Ecidence linking HFpEF and NAFLD

Epidemiological studies have shown a significant prevalence of NAFLD among patients with HFpEF. For instance, recent research indicates that up to 70% of patients with HFpEF also have NAFLD, highlighting a substantial overlap between these two conditions [19]. This high prevalence underscores the need to consider NAFLD as a common comorbidity in patients diagnosed with HFpEF. Correlation studies further support this relationship, demonstrating that the presence of NAFLD is independently associated with worse cardiac outcomes in HFpEF patients. These studies suggest that NAFLD may contribute to the pathogenesis and progression of HFpEF through shared mechanisms such as inflammation, metabolic dysregulation, and fibrosis [20].

Clinical trials and observational studies have provided important insights into the outcomes of patients with both HFpEF and NAFLD. Evidence from these studies indicates that patients with concurrent HFpEF and NAFLD have poorer clinical outcomes compared to those with HFpEF alone. For example, a study found that HFpEF patients with NAFLD had higher rates of hospitalization for heart failure and cardiovascular mortality [21]. Observational cohort studies also show that the severity of NAFLD correlates with worse outcomes in HFpEF, suggesting that the degree of liver involvement may exacerbate cardiac dysfunction [22]. These findings emphasize the importance of monitoring and managing NAFLD in patients with HFpEF to improve clinical outcomes.

Meta-analyses and systematic reviews have synthesized data from multiple studies to provide a comprehensive understanding of the link between HFpEF and NAFLD. A systematic review summarized findings from various studies and concluded that NAFLD significantly increases the risk of incident heart failure, particularly HFpEF. This review highlighted that NAFLD isassociated with a 1.5 to 2-fold increased risk of developing HFpEF [23]. Another meta-analysis found consistent evidence that NAFLD is linked to adverse cardiac outcomes, including higher rates of heart failure hospitalizations and cardiovascular mortality [4]. These comprehensive reviews underscore the critical need for integrated clinical approaches to address both liver and heart conditions in affected patients.

Diagnostic and Prognostic implication

Screening for NAFLD in patients with Heart Failure with HFpEF and vice versa is essential for comprehensive patient care. Given the high prevalence of NAFLD in HFpEF patients, routine screening using non-invasive methods such as liver ultrasound or transient elastography can be highly beneficial [19]. These tools help detect hepatic steatosis and assess liver stiffness, which is indicative of fibrosis. In patients diagnosed with NAFLD, it is prudent to evaluate cardiac function, particularly in those with metabolic syndrome or obesity, as these are common risk factors for HFpEF. Echocardiography remains the cornerstone for diagnosing HFpEF, assessing left ventricular function, and identifying diastolic dysfunction [24].

The coexistence of NAFLD and HFpEF significantly impacts prognosis, making risk stratification crucial for these patients. Studies have shown that patients with both NAFLD and HFpEF have a higher risk of adverse cardiovascular events, including increased hospitalizations for heart failure and higher mortality rates [21]. The severity of liver disease correlates with worse cardiac outcomes, emphasizing the importance of monitoring liver health in HFpEF patients. Risk stratification tools that incorporate liver function tests and cardiac biomarkers can help identify high-risk patients and guide therapeutic interventions. For instance, elevated liver enzymes in HFpEF patients could signal advanced NAFLD, necessitating more aggressive management strategies to mitigate cardiovascular risk [4].

Therapeutic Strategies

Lifestyle interventions, including diet and exercise modifications, are foundational in managing both HFpEF and NAFLD. Dietary changes aimed at weight reduction and improving metabolic health are essential. A Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, has shown beneficial effects on both cardiac and liver health. Regular physical activity, tailored to the patient's abilities, helps improve cardiovascular fitness, insulin sensitivity, and reduce liver fat accumulation [25]. These interventions not only help manage HFpEF symptoms but also mitigate the progression of NAFLD.

Pharmacological treatments targeting both HFpEF and NAFLD are being explored, given the shared pathophysiological mechanisms. Medications such as GLP-1 receptor agonists and SGLT2 inhibitors, initially developed for diabetes, have shown promise in managing both conditions. These drugs help improve insulin sensitivity, promote weight loss, and have cardiovascular benefits, which can be crucial for patients with HFpEF and NAFLD [26]. Additionally, statins and ACE inhibitors, commonly used in cardiovascular disease management, may have beneficial effects on liver enzymes and fibrosis markers, providing dual benefits for these patients [27].

Emerging therapies in clinical trials offer hope for more effective management of HFpEF and NAFLD. Novel agents targeting specific pathways such as fibrosis, inflammation, and metabolic dysregulation are under investigation. For example, antifibrotic agents like lanifibranor and inhibitors of galectin-3 are being studied for their potential to reduce fibrosis in both the heart and liver [28]. Additionally, therapies targeting gut microbiota to reduce systemic inflammation and metabolic endotoxemia are promising avenues for treating NAFLD and potentially improving HFpEF outcomes. These emerging therapies highlight the importance of ongoing research to develop targeted treatments that address the complex interplay between these two conditions.

Future Directions and Reseach Gaps

There are several unexplored mechanisms linking HFpEF and NAFLD that warrant further investigation. One area needing more research is the role of gut microbiota in the pathogenesis of both conditions. Alterations in the gut microbiome have been implicated in systemic inflammation and metabolic dysregulation, which are key features of both HFpEF and NAFLD. Investigating how changes in gut microbiota influence these diseases could uncover novel therapeutic targets. Additionally, the impact of genetic predispositions and epigenetic modifications on the development and progression of HFpEF and NAFLD remains poorly understood and represents a critical research gap.

Innovations in treatment strategies for HFpEF and NAFLD are essential to improve patient outcomes. Emerging

therapies that target specific pathophysiological pathways, such as inflammation, fibrosis, and metabolic dysregulation, hold promise. For instance, agents like lanifibranor, a pan-PPAR agonist, have shown efficacy in reducing fibrosis and improving liver function in NAFLD and could potentially benefit HFpEF patients. Furthermore, therapies that modulate gut microbiota, such as probiotics and prebiotics, may offer new avenues for managing both conditions by reducing systemic inflammation and improving metabolic health. The development of multi-targeted therapies that address the interconnected mechanisms of HFpEF and NAFLD is a promising area for future research. Additionally, longitudinal studies are needed to better understand the long-term outcomes of patients with coexisting HFpEF and NAFLD, as most current studies focus on short-term outcomes and do not provide insights into the chronic progression and long-term prognosis of these patients.

Conclusion

This review emphasizes the complex link between HFpEF and NAFLD, with up to 70% of HFpEF patients also having NAFLD. Both conditions share pathophysiological mechanisms like chronic inflammation, metabolic dysregulation, oxidative stress, and fibrosis, which worsen disease progression and complicate clinical management. Studies show that NAFLD negatively impacts HFpEF outcomes, leading to higher hospitalization and mortality rates. Emerging therapies targeting these shared mechanisms are promising for improving patient outcomes.

For healthcare providers, it is crucial to recognize the coexistence of HFpEF and NAFLD for comprehensive patient management. Screening for NAFLD in HFpEF patients and vice versa should be routine, using non-invasive tools like liver ultrasound and transient elastography. Pharmacological treatments that address both heart and liver issues, such as GLP-1 receptor agonists and SGLT2 inhibitors, should be considered. Lifestyle interventions, including dietary changes and regular exercise, are essential and should be strongly encouraged. Integrated care approaches and ongoing research into the mechanisms linking these conditions are vital for developing effective therapies and improving long-term health outcomes.

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