NEUROHUMORAL MECHANISMS IN PATIENTS WITH HEART FAILURE ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

Nargiza Bakhtiyorovna Khaydarova
Assistant, Department of ICP, Faculty of Pediatrics,
Andijan State Medical Institute
ORCID: 0009-0006-4976-7554

Abstract

The coexistence of heart failure (HF) and metabolic dysfunction-associated steatotic liver disease (MASLD) represents an important interdisciplinary problem in contemporary cardiology and hepatology. These conditions share several metabolic, inflammatory, hemodynamic, and neurohumoral mechanisms. Particular importance is attributed to activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), increased circulating catecholamines, vasopressin and endothelin-1, and alterations in the natriuretic peptide system.

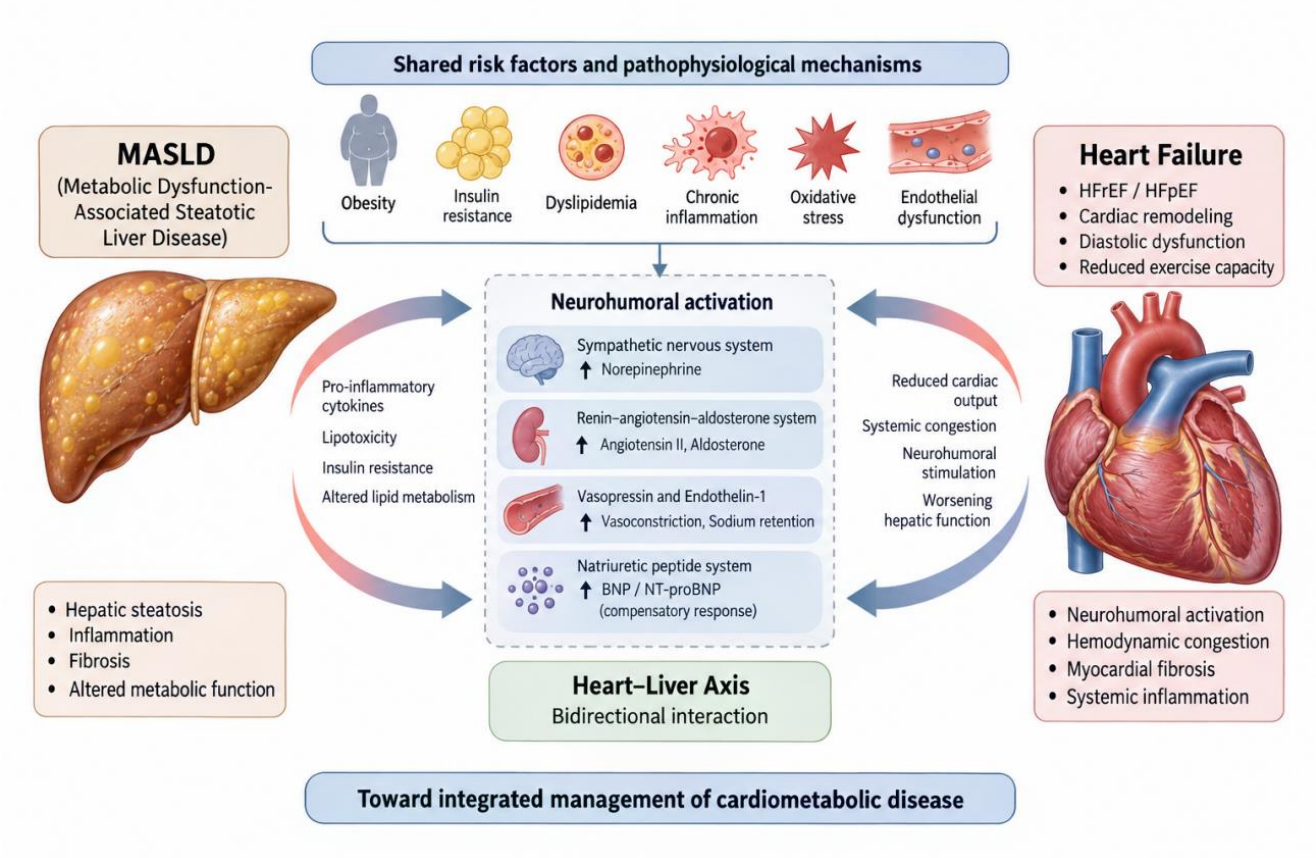
MASLD should not be considered solely a hepatic disorder. It is increasingly recognized as a systemic cardiometabolic condition associated with insulin resistance, visceral adiposity, dyslipidemia, chronic low-grade inflammation, endothelial dysfunction, oxidative stress, and cardiovascular remodeling. Current evidence indicates a close relationship between MASLD and heart failure, particularly heart failure with preserved ejection fraction (HFpEF). The cardiovascular risk appears to increase with progression of hepatic fibrosis.

The aim of this review is to summarize current concepts regarding the neurohumoral mechanisms involved in the development and progression of heart failure in patients with MASLD and to discuss potential approaches to the integrated diagnosis and management of this comorbid condition.

Keywords: heart failure, MASLD, metabolic dysfunction-associated steatotic liver disease, neurohumoral activation, sympathetic nervous system, renin–angiotensin–aldosterone system, natriuretic peptides, insulin resistance, inflammation, hepatic fibrosis.

Introduction

Heart failure is one of the most complex and clinically significant syndromes in modern medicine. Despite substantial advances in diagnostic methods and pharmacological treatment, the burden of HF continues to increase. This trend is largely associated with the growing prevalence of arterial hypertension, type 2 diabetes mellitus, obesity, and other cardiometabolic disorders.



At the same time, the global prevalence of metabolic dysfunction-associated steatotic liver disease has increased considerably. In 2023, an international multidisciplinary consensus introduced the term MASLD to replace the previously used

term non-alcoholic fatty liver disease (NAFLD), emphasizing the central role of metabolic dysfunction in disease development. MASLD is characterized by hepatic steatosis accompanied by at least one cardiometabolic risk factor.

The coexistence of MASLD and HF is of particular clinical interest because both disorders share multiple pathogenic pathways, including insulin resistance, obesity, dyslipidemia, chronic inflammation, oxidative stress, endothelial dysfunction, fibrosis, and neurohumoral activation. These mechanisms may establish a bidirectional heart–liver interaction in which dysfunction of one organ contributes to progression of the other.

Neurohumoral Activation in Heart Failure

Chronic neurohumoral activation is a major mechanism underlying the progression of heart failure. A reduction in cardiac output and effective arterial blood volume stimulates compensatory mechanisms initially intended to maintain adequate perfusion of vital organs.

The sympathetic nervous system plays a central role in this response. Increased sympathetic activity leads to enhanced release of norepinephrine and epinephrine. In the short term, this increases heart rate, myocardial contractility, and vascular tone. However, persistent sympathetic activation becomes maladaptive and contributes to disease progression.

Prolonged elevation of circulating catecholamines may result in tachycardia, peripheral vasoconstriction, increased myocardial oxygen demand, and progressive cardiac remodeling. At the same time, β-adrenergic receptor responsiveness may decrease, leading to impaired adrenergic regulation. Consequently, an initially compensatory mechanism becomes an important contributor to chronic HF.

Another major pathway is activation of the renin–angiotensin–aldosterone system. Reduced renal perfusion and effective arterial filling stimulate renin release and subsequent formation of angiotensin II. Angiotensin II induces vasoconstriction,

promotes aldosterone secretion, enhances sodium and water retention, increases afterload, and stimulates fibrotic processes.

Aldosterone also contributes to inflammation, oxidative stress, and myocardial remodeling. Therefore, persistent RAAS activation has both hemodynamic and structural-metabolic consequences in patients with HF.

Interaction Between MASLD and Neurohumoral Activation

Patients with MASLD may develop conditions favoring chronic neurohumoral activation even during relatively early stages of the disease. Insulin resistance is considered one of the central mechanisms.

Reduced insulin sensitivity impairs glucose utilization, promotes adipose tissue lipolysis, and increases the delivery of free fatty acids to the liver. Excessive lipid accumulation may lead to lipotoxicity, mitochondrial dysfunction, and increased generation of reactive oxygen species.

In the liver, these processes activate pro-inflammatory signaling pathways and increase the production of cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This contributes to chronic low-grade systemic inflammation. The combination of insulin resistance, dyslipidemia, inflammation, and oxidative stress may adversely affect vascular function and myocardial structure.

MASLD is therefore increasingly viewed as a systemic cardiometabolic disorder rather than an isolated hepatic disease. Patients with MASLD have an increased risk of cardiovascular complications, including heart failure, particularly when advanced hepatic fibrosis is present.

Role of the Sympathetic Nervous System

The interaction between metabolic abnormalities and sympathetic nervous system activity is particularly relevant in patients with concomitant HF and MASLD.

Hyperinsulinemia and insulin resistance may contribute to increased sympathetic activity. Conversely, chronic sympathetic stimulation can aggravate lipid metabolism,

promote vasoconstriction, and impair microcirculation. This creates a potentially self-perpetuating cycle in which metabolic disturbances enhance neurohumoral activation, while sustained neurohumoral activation further contributes to metabolic and cardiovascular dysfunction.

Increased sympathetic activity may be reflected by elevated norepinephrine concentrations. Measurement of catecholamines, including norepinephrine, may therefore provide information about sympathetic neurohumoral activity. However, these biomarkers should be interpreted in conjunction with clinical status, renal function, current medications, and other relevant factors.

Renin–Angiotensin–Aldosterone System and Fibrosis

RAAS activation represents another important link between HF and MASLD. Angiotensin II not only increases vascular resistance but also promotes fibrogenic signaling.

In the myocardium, persistent RAAS stimulation contributes to cardiomyocyte hypertrophy, interstitial fibrosis, and structural remodeling. Similar signaling pathways in the liver may participate in the development and progression of hepatic inflammation and fibrosis.

Thus, RAAS may represent one of the central molecular pathways connecting cardiac and hepatic pathology. Progressive liver fibrosis may further alter vascular and metabolic regulation, potentially increasing cardiovascular burden.

Importantly, the risk of HF appears to increase with greater severity of hepatic fibrosis. Current evidence also suggests a particularly close association between MASLD and the HFpEF phenotype.

Natriuretic Peptides and Neurohumoral Imbalance

The natriuretic peptide system represents an important counter-regulatory mechanism in heart failure. Increased myocardial wall stress stimulates the release of

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Natriuretic peptides exert vasodilatory, natriuretic, and diuretic effects and counteract both RAAS and sympathetic nervous system activity. However, during chronic HF, these protective mechanisms may become insufficient because of persistent neurohumoral activation and reduced tissue responsiveness.

NT-proBNP is widely used as a diagnostic and prognostic biomarker of HF. Its interpretation requires consideration of age, renal function, body mass, cardiac rhythm, and other clinical variables. In patients with MASLD, NT-proBNP should therefore be interpreted within the broader cardiometabolic context.

Current HF treatment targets several neurohumoral pathways. Pharmacological modulation of RAAS and neprilysin, including sacubitril/valsartan therapy, can enhance the activity of endogenous natriuretic peptides and modify maladaptive neurohumoral signaling.

Inflammation, Oxidative Stress, and Endothelial Dysfunction

Chronic inflammation represents another important mechanism linking MASLD and heart failure.

Excessive hepatic lipid accumulation is associated with activation of Kupffer cells, increased production of pro-inflammatory cytokines, and development of a systemic inflammatory response. These inflammatory mediators can affect vascular endothelial cells, cardiomyocytes, and immune cells.

At the same time, oxidative stress increases as a consequence of excessive reactive oxygen species production. Oxidative injury can affect cellular membranes, mitochondria, and proteins and may impair myocardial energy metabolism.

Endothelial dysfunction is characterized by reduced nitric oxide bioavailability, impaired vasodilation, and increased vascular resistance. These changes increase left

ventricular afterload and may contribute to myocardial hypertrophy and diastolic dysfunction.

Thus, inflammation, insulin resistance, lipotoxicity, oxidative stress, endothelial dysfunction, and neurohumoral activation form an interconnected pathogenic network linking MASLD with cardiovascular dysfunction.

Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction represents a particularly important phenotype in the context of MASLD. Although left ventricular ejection fraction may remain within the normal range, patients may develop impaired myocardial relaxation, increased ventricular stiffness, and elevated filling pressures.

MASLD may contribute to the development of HFpEF through insulin resistance, obesity, systemic inflammation, endothelial dysfunction, and hepatic fibrosis. These mechanisms may collectively promote a distinct metabolic phenotype of HFpEF.

Increasing evidence suggests that MASLD may be particularly relevant to the pathogenesis of HFpEF. The degree of hepatic fibrosis may also serve as an indicator of the severity of systemic metabolic dysregulation.

Clinical Significance of Neurohumoral Biomarkers

Understanding neurohumoral mechanisms has both theoretical and practical clinical significance. In patients with concomitant HF and MASLD, an integrated assessment of cardiovascular, hepatic, renal, and metabolic status is appropriate.

Depending on the clinical setting, evaluation may include NT-proBNP or BNP, liver function parameters, lipid profile, fasting glucose and glycated hemoglobin (HbA1c), renal function, inflammatory markers, and instrumental assessment of hepatic steatosis and fibrosis.

Echocardiography is important for evaluating left ventricular ejection fraction, diastolic function, cardiac chamber dimensions, and signs of elevated filling pressures.

Liver assessment may include ultrasonography, elastography, and validated non-invasive fibrosis scores.

Therefore, the diagnostic approach should not be limited to confirming the presence of two separate diseases. It should also assess the degree to which hepatic and cardiovascular abnormalities interact and influence disease progression.

Therapeutic Perspectives

Management of patients with concomitant HF and MASLD should be comprehensive and directed toward shared pathogenic mechanisms. Lifestyle interventions, including appropriate nutrition, weight management, increased physical activity, and control of blood pressure, glycemia, and lipid levels, represent important components of care.

Heart failure should be treated according to the patient's specific HF phenotype and evidence-based therapeutic recommendations. Current approaches target the RAAS, β-adrenergic signaling, natriuretic peptide pathways, and renal-metabolic mechanisms.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become an important component of modern HF therapy and may provide additional metabolic benefits. Incretin-based therapies are also being investigated as a promising strategy for the management of metabolic abnormalities. Selection of treatment should nevertheless be individualized according to the patient's clinical phenotype and established indications.

Because HF and MASLD frequently coexist with renal and metabolic abnormalities, integrated management involving cardiovascular, hepatic, and metabolic assessment may provide a more comprehensive approach to these patients.

Conclusion

The coexistence of heart failure and metabolic dysfunction-associated steatotic liver disease represents a complex cardiometabolic condition characterized by close

interactions between the heart, liver, vascular system, nervous system, and endocrine regulation.

Chronic activation of the sympathetic nervous system, RAAS, and other neurohumoral pathways plays a central role in disease progression, while MASLD may intensify metabolic and inflammatory stress, endothelial dysfunction, lipotoxicity, oxidative stress, and fibrotic remodeling. The association between MASLD and HFpEF is of particular clinical importance.

Assessment of neurohumoral biomarkers, including NT-proBNP and norepinephrine, together with evaluation of hepatic fibrosis, metabolic status, and cardiac function, may contribute to a more comprehensive characterization of patients with this comorbid condition. Further investigation of the heart–liver–metabolism axis may help identify additional prognostic biomarkers and therapeutic targets and support the development of more individualized management strategies.

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