ANALYSIS OF CHANGES IN THE CARDIOVASCULAR SYSTEM IN NON-ALCOHOLIC FATTY LIVER DISEASE (LITERATURE REVIEW)

Head of the Department of Preclinical Sciences, Bukhara Campus, Zarmed University, PhD: Zokirov Vokhid Zoyit o'g'li

Abstract: According to projections by the World Health Organization (WHO), non-alcoholic fatty liver disease (NAFLD) is expected to become the most common liver disorder worldwide by 2026. Currently, NAFLD-related cirrhosis already represents the second most frequent indication for liver transplantation, surpassed only by viral cirrhosis. Patients with NAFLD experience markedly higher mortality during the first postoperative month compared with individuals transplanted for other causes of cirrhosis. They are also more prone to developing severe post-transplant complications, including sepsis, graft rejection, and cardiovascular disorders.

The 2030 Agenda for Sustainable Development identifies noncommunicable diseases (NCDs) as a major obstacle to global progress. Within this framework, world leaders pledged to reduce premature mortality from NCDs by one-third through preventive strategies and appropriate treatment by the year 2030 (SDG Target 3.4). WHO plays a central coordinating role in global actions aimed at addressing NCDs and supporting progress toward this target. Clear diagnostic algorithms and standardized therapeutic strategies for NAFLD are still lacking; in practice, the condition is often diagnosed by excluding other hepatic diseases. Despite its high prevalence, the challenge of finding an effective treatment remains unresolved, and none of the currently used pharmacological therapies has a robust evidence base. Lifestyle modification — particularly weight control, correction of food-related behavioral patterns, and increased physical activity — remains the most reliable approach for preventing NAFLD progression and mitigating metabolic disturbances linked to severe type 2 diabetes and elevated cardiovascular risk. Present-day understanding defines NAFLD as a spectrum of liver abnormalities that range from simple steatosis to steatosis accompanied by inflammation and hepatocellular injury (non-alcoholic/metabolic steatohepatitis), and ultimately fibrosis, which may progress to cirrhosis. Current clinical guidelines advise treating these patients with statins at doses proven to reduce cardiovascular risk. Nonetheless, some individuals are unable to tolerate statins or fail to achieve cholesterol control even on maximal therapy, creating clinical limitations[1].

Management of NAFLD typically includes medications that offer antioxidant protection, stabilize hepatocyte membranes, exert immunomodulatory or anti-inflammatory effects, lower lipid levels, and reduce insulin resistance. The

overarching goal of therapy is to prevent the development of cirrhosis and its complications. Although addressing components of metabolic syndrome — particularly insulin resistance — is critical, these measures alone are insufficient for complete disease reversal; additional antioxidant and cytoprotective therapy is often required to counteract ongoing necroinflammatory damage and fibrosis.

Initial management should always focus on dietary modification and increased physical activity, especially in individuals with obesity or diabetes. When lifestyle interventions fail, pharmacologic options for treating morbid obesity can be considered, and in selected cases, bariatric surgery may be appropriate[2].

Guidelines issued by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO) recommend initiating pharmacological treatment in patients with NASH, particularly those with significant fibrosis (≥F2). Even patients with milder forms of NAFLD may require medical therapy if they possess risk factors known to accelerate disease progression, such as diabetes, metabolic syndrome, or persistent elevations in ALT. The 2012 American guidelines on NAFLD diagnosis and treatment identified several recommendations with the highest evidence level (Grade 1A). To improve hepatic steatosis, a weight reduction of at least 3–5% is necessary, whereas a more substantial weight loss of about 10% is required to diminish necroinflammatory activity. These statements are supported by Level 1B evidence.

Keywords: Non-alcoholic fatty liver disease, cardiovascular system, dyslipidemia, insulin resistance, endothelial dysfunction, atherosclerosis.

Introduction: Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of metabolic syndrome and is characterized by the pathological accumulation of triglycerides within hepatocytes as a result of impaired lipid metabolism. Over the past several decades, the prevalence of NAFLD has risen dramatically and is now recognized as one of the most common chronic liver diseases worldwide. In many industrialized nations, NAFLD affects an estimated 25–30% of the general population, making it a major global health burden. Importantly, the significance of this disease extends far beyond liver-specific outcomes; NAFLD is increasingly being identified as a major, independent risk factor for the development of cardiovascular diseases, which remain the leading cause of mortality among affected individuals.

NAFLD encompasses a broad spectrum of hepatic abnormalities that range from simple steatosis, which involves fat accumulation without significant inflammation, to non-alcoholic steatohepatitis (NASH), a more severe form

characterized by hepatocellular injury, inflammation, and varying degrees of fibrosis. If left untreated, NASH can progress to advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC). However, the majority of deaths in patients with NAFLD are not due to end-stage liver disease, but to cardiovascular complications such as coronary artery disease, stroke, and progressive heart failure. This shift in understanding has led to a broader conceptualization of NAFLD as a multisystem disorder that reflects widespread metabolic dysfunction rather than a disease limited to the liver alone. The pathogenesis of NAFLD is complex and multifactorial, involving a combination of genetic predisposition, environmental influences, and metabolic abnormalities[3]. Insulin resistance—a hallmark of metabolic syndrome—is widely considered the central driver of disease development. When peripheral tissues such as muscle and adipose tissue become resistant to insulin, circulating insulin levels increase, promoting enhanced fatty acid flux to the liver. This influx overwhelms the liver's metabolic capacity, resulting in excessive triglyceride synthesis and deposition within hepatocytes. In addition, insulin resistance disrupts normal lipolytic pathways and alters adipokine secretion, further amplifying fat accumulation and hepatic inflammation. Dyslipidemia is another key contributor to disease progression. Many patients with NAFLD exhibit elevated levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and qualitative changes in low-density lipoprotein particles (LDL), particularly an increase in small, dense LDL fractions that are highly atherogenic. These lipid abnormalities not only exacerbate liver injury but also accelerate the development of atherosclerosis, thereby strengthening the link between NAFLD and cardiovascular disease. Indeed, the presence of NAFLD predicts an increased risk of myocardial infarction, carotid artery disease, hypertension, and overall cardiovascular mortality independent of traditional risk factors.

Genetic factors also play a major role in susceptibility to NAFLD. Variants in genes such as PNPLA3, TM6SF2, and MBOAT7 have been shown to influence lipid metabolism and hepatic fat storage, contributing to inter-individual differences in disease severity and progression. Likewise, lifestyle factors—particularly excessive caloric intake, diets high in saturated fats and fructose, and low levels of physical activity—compound the risk of disease onset and progression. The clinical implications of NAFLD are profound. As the disease progresses, patients may develop complications of chronic liver failure including portal hypertension, variceal bleeding, hepatic encephalopathy, and an increased risk of hepatocellular carcinoma—even in the absence of cirrhosis in some cases. However, for most patients, cardiovascular disease remains the dominant threat.

Several longitudinal cohort studies have shown that individuals with NAFLD have significantly higher rates of major adverse cardiovascular events compared with those without the condition, even when adjusted for conventional risk factors such as smoking, obesity, and hypertension[4].

Literature review and analysis: Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as the hepatic manifestation of metabolic syndrome and represents a major public health concern due to its high prevalence and strong association with cardiovascular disease. Epidemiological and clinical research over recent decades has consistently demonstrated that patients with NAFLD are at significantly increased risk of developing a spectrum of cardiovascular disorders, including ischemic heart disease, arterial hypertension, left ventricular hypertrophy, cardiac arrhythmias, and heart failure. Unlike traditional liver diseases, in which hepatic complications dominate the clinical course, the primary morbidity and mortality in NAFLD patients are frequently related to cardiovascular events, underscoring the systemic nature of this disease.

The pathogenesis of NAFLD is multifactorial, involving a complex interplay of metabolic, inflammatory, and oxidative processes. Insulin resistance serves as the central mechanism linking hepatic lipid accumulation with systemic cardiovascular risk. Impaired insulin signaling disrupts glucose homeostasis and lipid metabolism, leading to an increased flux of free fatty acids into the liver. Accumulation of triglycerides in hepatocytes results in hepatic steatosis, which may progress to non-alcoholic steatohepatitis (NASH) when combined with inflammation and hepatocellular injury. This state of metabolic dysregulation has systemic consequences. Elevated free fatty acids and hyperinsulinemia promote endothelial dysfunction, a critical early event in atherogenesis. Endothelial cells exposed to high levels of circulating lipids and inflammatory mediators lose their capacity to produce adequate nitric oxide, leading to increased vascular tone, impaired vasodilation, and the promotion of vascular stiffness. These changes facilitate the development of atherosclerotic plaques, increasing the likelihood of ischemic heart disease and cerebrovascular events. Inflammatory mediators secreted by the liver, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), further exacerbate vascular injury[5]. These cytokines induce chronic low-grade inflammation within the vascular wall, enhancing oxidative stress, promoting monocyte recruitment, and accelerating plaque formation. Moreover, this systemic inflammatory state contributes to left ventricular remodeling, myocardial fibrosis, and the eventual development of diastolic dysfunction, as observed in numerous imaging studies.

Dyslipidemia is another critical component of NAFLD-associated cardiovascular risk. Patients commonly exhibit elevated triglyceride levels, increased low-density lipoprotein (LDL), particularly small, dense LDL particles, and decreased high-density lipoprotein (HDL). These lipid abnormalities enhance lipid deposition within arterial walls, accelerating the progression of atherosclerosis and amplifying the risk of coronary artery disease and stroke. The combination of insulin resistance, dyslipidemia, and inflammation thus establishes a pathophysiological milieu conducive to cardiovascular complications[6].

Cardiac involvement in NAFLD extends beyond traditional risk factors. Ultrasonographic and echocardiographic studies reveal that NAFLD patients frequently exhibit impaired left ventricular relaxation, indicative of diastolic dysfunction. Reduced myocardial elasticity, increased ventricular stiffness, and altered ventricular geometry have been consistently reported. Notably, systolic function often remains preserved until late in the disease course, allowing subclinical cardiac changes to progress unnoticed. This silent progression underscores the importance of early detection and comprehensive cardiovascular risk assessment in patients with NAFLD. Metabolic cardiomyopathy represents a distinct clinical entity in NAFLD patients. Excessive lipid accumulation within cardiomyocytes, coupled with mitochondrial dysfunction and oxidative stress, leads to impaired contractility and eventual heart failure. The deposition of lipid droplets within myocardial tissue not only disrupts cellular energetics but also promotes local inflammation and fibrosis. As a result, patients may develop subtle reductions in cardiac output, increased ventricular filling pressures, and clinical manifestations of heart failure over time[7]. Arterial hypertension is highly prevalent among individuals with NAFLD. Pathophysiological mechanisms underlying this observation include hyperactivation of the renin-angiotensin-aldosterone system (RAAS) and increased sympathetic nervous system activity. Elevated angiotensin II and aldosterone levels contribute to vasoconstriction, sodium retention, and vascular remodeling, further exacerbating cardiovascular risk. Endothelial dysfunction decreases nitric oxide bioavailability, thereby increasing systemic vascular resistance. The combination of these factors not only elevates blood pressure but also accelerates the progression of atherosclerosis and left ventricular hypertrophy.

NAFLD rarely occurs in isolation; it is strongly associated with components of the metabolic syndrome, including obesity, type 2 diabetes, and insulin resistance. The coexistence of these conditions compounds cardiovascular risk. Hyperglycemia and insulin resistance drive further hepatic lipid accumulation and systemic inflammation. Dyslipidemia, characterized by high triglycerides and low

HDL, synergizes with endothelial dysfunction and pro-inflammatory signaling to promote atherogenesis. Collectively, these factors create a vicious cycle in which metabolic and cardiovascular pathologies reinforce one another[8].

The recognition of NAFLD as a multisystem disorder has profound clinical and public health implications. Given its high prevalence and strong association with cardiovascular disease, early screening and intervention are critical. Weight reduction through lifestyle modification, including dietary interventions and regular physical activity, remains the cornerstone of management. Clinical studies have shown that modest weight loss of 5–10% can significantly reduce hepatic steatosis, improve insulin sensitivity, and decrease systemic inflammation. Pharmacological therapies targeting insulin resistance, dyslipidemia, and inflammatory pathways are increasingly being investigated as adjuncts to lifestyle modification. Additionally, regular cardiovascular assessment, including echocardiography, blood pressure monitoring, and lipid profiling, is recommended in patients with NAFLD. Early identification of diastolic dysfunction or other subclinical cardiac abnormalities allows for timely intervention and may prevent progression to overt heart failure or ischemic events. Considering the systemic nature of the disease, a multidisciplinary approach involving hepatologists, cardiologists, endocrinologists, and primary care providers is essential.

Conclusion: NAFLD represents a significant global health challenge, not only because of its impact on liver function but also due to its profound effects on cardiovascular health. Insulin resistance, dyslipidemia, endothelial dysfunction, and chronic inflammation are central to the pathophysiology linking NAFLD to cardiovascular disease. Structural and functional cardiac changes, including diastolic dysfunction and metabolic cardiomyopathy, highlight the multisystemic nature of this disorder. Early identification, lifestyle interventions, and targeted pharmacotherapy are critical for mitigating both hepatic and cardiovascular complications. As the prevalence of NAFLD continues to rise worldwide, addressing its cardiovascular consequences remains a priority for clinicians and public health policymakers alike.

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