# CARDIOVASCULAR COMORBIDITY IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide. It is characterized by hepatic steatosis and stetohepatitis and in some cases can progress to cirrhosis with or without hepatic failure and hepatocellular carcinoma. At present, NAFLD is deemed a predictor of cardiovascular risk. Besides, it can aggravate pre-existing cardiovascular conditions. Structural and functional changes in the heart, liver and blood vessels are interdependent and mutually aggravating. Metabolic factors (dyslipidemia, hyperglycemia and insulin resistance) contribute to hepatic, cardiac and vascular damage, and NAFLD and comorbid cardiovascular disorders together can activate fibrogenesis in the heart, blood vessels and liver.

**Keywords:** nonalcoholic fatty liver disease, fatty steatosis, nonalcoholic steatohepatitis, liver fibrosis, endothelial dysfunction

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# КАРДИОВАСКУЛЯРНАЯ КОМОРБИДНОСТЬ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Неалкогольная жировая болезнь печени (НАЖБП) занимает первое место в мире среди болезней печени. Заболевание характеризуется развитием стеатоза и стеатогепатита, в некоторых случаях прогрессирует до цирроза с или без развития печеночной недостаточности и гепатоцеллюлярной карциномы у части пациентов. В настоящее время НАЖБП рассматривают как маркер сердечно-сосудистого риска. Кроме того, она может усугублять течение уже имеющихся сердечно-сосудистых заболеваний. Известно, что развитие структурно-функциональных изменений сердца, печени и сосудов взаимообусловлены и носят взаимоотягощающий характер. Изучено и отрицательное влияние метаболических факторов (дислипидемии, гипергликемии, инсулинорезистентности) на формирование поражения печени, сердца и сосудов, а сочетание НАЖБП и сердечно-сосудистых заболеваний может оказывать влияние на активацию фиброгенеза как в сердце и сосудах, так и в печени.

**Ключевые слова:** неалкогольная жировая болезнь печени, жировой стеатоз, неалкогольный стеатогепатит, фиброз печени, эндотелиальная дисфункция

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Nonalcoholic fatty liver disease (NAFLD) is a chronic metabolic disorder developing in the absence of exogenous hepatotoxicity-inducing factors (e.g. exogenous ethanol) and characterized by excess accumulation of lipids in the cells constituting the hepatic lobule. Morphological findings confirming NAFLD include steatosis, steatohepatitis, fibrosis, cirrhosis, and adenocarcinoma. The diagnosis is considered verified if triglycerides (TG, a type of lipids) make up over 5–10% of the liver's weight or if lipid deposits are observed in over 5% of hepatocytes [1].

At present, NAFLD is the most common chronic liver condition worldwide, affecting on average 25% of the population in high-income countries [2]. Although the majority of patients with NAFLD have moderate steatosis, 20 to 30% develop steatohepatitis with progressive fibrosis. Of them, about 20% will eventually progress to liver cirrhosis and thus be at increased risk for hepatocellular carcinoma [3, 4]

In 2007, the DIREG-1 screening study was conducted to estimate the prevalence of NAFLD in the Russian population. Of 30,750 participants included in the study 27% were diagnosed with NAFLD. Of them, 80.3% had steatosis, 16.8% had steatohepatitis and 2.9% had liver cirrhosis [5]. According to DIREG-2 estimates, the prevalence of NAFLD in the Russian population has been growing steadily in the past years, reaching 37% in 2015 [6]. In the majority of patients, NAFLD is associated with such metabolic comorbidities as obesity, type 2 diabetes mellitus and/or dyslipidemia [7].

NAFLD is deemed a predictor of cardiovascular diseases (CVD). The risk of CVD in patients with NAFLD is 4.12 times higher than in those without NAFLD; notably, women with NAFLD are at higher risk for CVD than men [8]. Insulin resistance, dyslipidemia and obesity contribute to NAFLD progression, extrahepatic complications and overall poor prognosis. NAFLD is recognized as a hepatic manifestation of metabolic syndrome. Metabolic risk factors like overeating, a sedentary lifestyle and genetic predisposition cause visceral adipose dysfunction, i.e. overproduction of free fatty acids (FFA) and proinflammatory

cytokines and underproduction of adiponectin. This leads to insulin resistance, dyslipidemia, thrombophilia, and progressive liver cirrhosis. NAFLD causes systemic buildup of TG in various organs, including the myocardium, and induces oxidative stress, which in turn results in cardiomyocyte dysmetabolism and dysfunction provoking ventricular and supraventricular arrhythmias, coronary artery disease and aortic valve sclerosis. Inflammation and metabolic disorders lead to hepatic steatosis, steatohepatitis, liver fibrosis, and heart pathology (atherosclerosis and myocardial dysmetabolism); the latter manifests as subclinical atherosclerosis, arterial hypertension, coronary artery disease (CAD), arrythmias, myocardial infarction, chronic heart failure and eventually death [9].

Notably, patients with progressive fibrosis and advanced steatosis (F > 3) are at the highest risk for death from liver disease, and CVD are very common in patients with early-stage fibrosis (F < 3) associated with NAFLD [10–12].

Possible mechanisms underlying cardiac complications in patients with NAFLD [13] are shown in the Figure.

Patients with NAFLD present with pronounced cardiac remodeling: heart chambers are significantly enlarged and their walls are thickened, epicardial fat thickness and myocardial mass are increased [14]. Myocardial fibrosis during myocardial remodeling leads to electrophysiological disorders and secondary ischemia. The loss of cardiomyocytes is accompanied by an increase in adipocytes. Adipose tissue is an active endocrine organ that synthesizes and secretes large amounts of bioactive substances, including interleukin 6, renin, angiotensin I and II, tumor necrosis factor α, resistin, adiponectin, and leptin [15–17]. Visceral adipose tissue lipolysis results in increased secretion of FFA, which, on the one hand, become a substrate for atherogenic lipoproteins and, on the other hand, potentiate IR at the liver level, reducing plasma membrane permeability to glucose [16]. The severity of visceral obesity and adipose tissue dysfunction in patients with NAFLD has been shown to reliably correlate with the severity of the cytolysis syndrome and cholestasis [18]. Thus, progression of visceral obesity in patients with NAFLD is accompanied by progressive structural and functional liver damage [18]. Notably, secretion of proinflammatory cytokines by epicardial adipose tissue into the bloodstream enhances systemic inflammation, which in turn aggravates cardiometabolic dysfunction promoting buildup of epicardial fat [19]. The latter is a source of FFA, especially in the setting of increased myocardial energy demand observed in many conditions, including ischemia [20, 21]. FFA produced by epicardial adipose tissue are taken up by the myocardium, where they fuel myocardial steatosis, inducing structural and functional changes in the heart (heart enlargement, left ventricular hypertrophy and left ventricular diastolic disfunction) [22].

In patients with NAFLD, the risk of death from CVD is determined by the stage of NAFLD and other cardiometabolic risk factors [23]. As a rule, the severity of fibrosis becomes the defining factor for CVD development and death from CVD in patients with NAFLD. Non-alcoholic steatohepatitis increases mortality by 70%, mostly due to an increase in CVD-related mortality [24]. Patients with steatohepatitis and patients with NAFLD and co-existing type 2 DM constitute a special risk group for CVD and cardiovascular events.

It has been demonstrated that patients with NAFLD are at higher risk for cardiovascular pathology on the SCORE scale than those without NAFLD [25]. Moreover, the study has established an association between the severity of NAFLD and the high risk of poor cardiovascular outcomes. These findings are consistent with the results of another study in which NAFLD confirmed by ultrasonography was strongly associated with non-fatal cardiovascular events [26].

Arterial hypertension is the most common risk factor for CVD. According to WHO's estimates, 54% of all strokes and 47% of all CAD cases are direct consequences of elevated blood pressure [27, 28]. Patients with NAFLD and arterial hypertension make up 40–70% of the general population. NAFLD is also associated with heightened risk of prehypertension [29].

The Finnish OPERA study conducted in hypertensive patients revealed that the average diurnal blood pressure values were higher in patients diagnosed with liver steatosis (30.9% vs 24.6%; $p$ = 0,057) [30]. In another study, blood pressure variability was greater in patients with arterial hypertension and NAFLD than in those with isolated hypertension [31]. It is reported that the high 10-year risk of cardiovascular events is more frequent among patients with hypertension and NAFLD than among patients with isolated hypertension [32].

Systemic inflammation associated with NAFLD can stimulate activation of the sympathetic nervous system, promoting hypertension. Another mechanism implicated in elevated blood pressure is IR: it leads to overproduction of free fatty acids and increased oxidative stress [33].

NAFLD is associated with a high risk of coronary atherosclerosis [34, 35], impaired myocardial perfusion and poor outcomes of coronary artery stenting due to the high risk of restenosis [36, 37]. These impairments are predominantly associated with abnormal vasodilatory response, increased coronary intima-media thickness and atherosclerosis. According to the meta-analysis of 6 studies with a total sample of 25,837 participants, patients with NAFLD were at higher risk of clinical CAD than patients without NAFLD (CI 1.04–4.92; $p$ < 0.001) [38]. Another study conducted in 360 patients with a past history of ST-segment elevation myocardial infarction found that nonalcoholic liver steatosis was an independent predictor of plaque formation in coronary arteries, revealing higher hospitalization and 3-year mortality rates among patients with NAFLD than in the control group [39].

Atrial fibrillation (AF) is a common type of arrythmia; due to the global population ageing, its incidence has been on the rise over the past decades [40]. According to the study of NAFLD effects on the risk of paroxysmal AF, patients with type 2 DM and co-existing NAFLD have more frequent episodes of paroxysmal or permanent AF than those without NAFLD [41, 42]. It is known that intra-atrial conduction delay underlies the pathophysiology of AF. It is reported that NAFLD patients without DM, clinically confirmed hypertension or CVD have significantly longer inter-atrial and intra-atrial electromechanical delay intervals than the control group. This is associated with reduced electrophysiological potential of the myocardium, when cardiac conduction velocity is reduced due to fibrosis, causing cardiac rhythm disturbances and especially high-risk arrythmias. It has been demonstrated that NAFLD is an independent predictor of such electrophysiological disorders of the heart [43].

Being the risk markers of ventricular arrythmia, heart rate variability and prolonged QT intervals are associated with a higher risk of death from cardiovascular disorders [33]. In a study conducted in NAFLD patients with type 2 DM without preexisting heart conditions, NAFLD severity was associated with prolonged QT intervals regardless of the patient's age, sex, the presence of hypertension or type 2 DM. The analysis confirmed the association between the severity of NAFLD and the probability of prolonged QT regardless of the presence of cardiometabolic risk factors [44]. Indeed, the role of NAFLD in the development of ventricular arrythmia still remains understudied

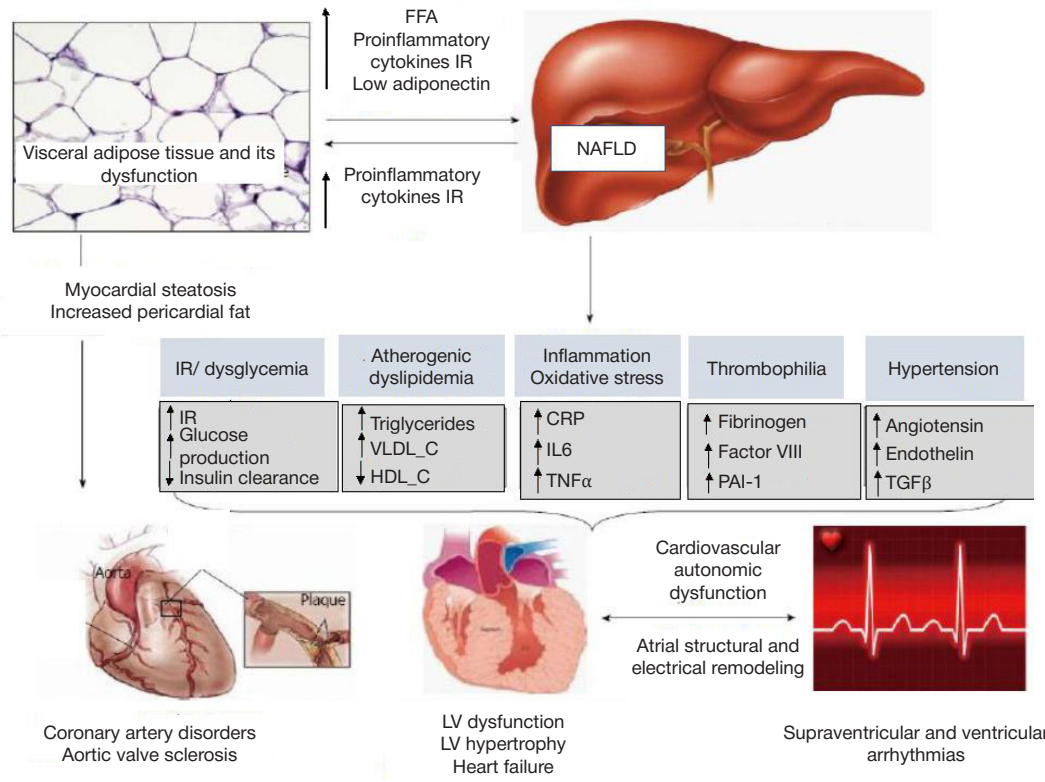


**Fig.** Possible mechanisms underlying cardiovascular complications in patients with NAFLD. PAI-1 — plasminogen activator inhibitor-1; TGFβ — transforming growth factor β; IL6 — interleukin 6; IR — insulin resistance; FFA — free fatty acids; LV — left ventricle; VLDL_C — very-low-density lipoprotein cholesterol, HDL_C — high-density lipoprotein cholesterol, CRP — C-reactive protein

but the implication of pathophysiological mechanisms typically underlying NAFLD (chronic inflammation and insulin resistance) in electrophysiological myocardial dysfunction is undeniable.

Chronic heart failure (CHF) is an extremely severe complication of CVD characterized by poor outcomes. In addition, it poses a diagnostic difficulty and its therapy and prevention required special approaches. It has been established that NAFLD aggravates the course of CHF. One of CHF manifestations is left ventricular diastolic dysfunction. NAFLD is associated with left ventricular diastolic dysfunction regardless of the presence of other cardiovascular risk factors and metabolic syndrome [45, 46]. In a multicenter study conducted in 2,713 patients with cardiovascular pathology, NAFLD patients had elevated left ventricular filling pressure, increased left atrial volume, reduced ejection fraction, and reduced diastolic function in comparison with patients who had no history of NAFLD [47]. Other studies report an association between NAFLD and diastolic dysfunction of the left ventricle in patients with type 2 DM [48, 49].

Moreover, patients with NAFLD develop early left ventricular diastolic dysfunction more frequently [50]. Diastolic dysfunction is indicative of myocardial stiffness and fibrosis. These changes are manifestations of systemic fibrosis. In addition, our study conducted in patients with chronic heart failure and nonalcoholic fatty liver disease revealed that changes in vascular wall stiffness and microcirculation disorders (pathological hemodynamic types of microcirculation with predominance of shunt blood flow, nutritional insufficiency) correlated with changes in the structural and functional state of the liver [51].

## CONCLUSION

Patients with NAFLD can progress from steatosis (fatty infiltration of over 5% of hepatocytes) to nonalcoholic steatohepatitis (fatty infiltration with necroinflammation) to liver fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD is a risk factor for cardiovascular comorbidities, predictor of CVD and death. Patients with NAFLD should undergo screening for cardiovascular pathology and NAFLD-associated risk factors without delay. Timely therapy commenced at the stage of liver steatosis will prevent progression of the disease and poor cardiovascular outcomes in NAFLD patients.

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