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Review Article

Liver Fibrosis as an Independent Cardiovascular Risk Factor in Non-alcoholic Fatty Liver Disease

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Abstract

This review summarizes the current investigations that confirm the significance of liver fibrosis (LF) as an independent cardiovascular risk factor in non-alcoholic fatty liver disease (NAFLD). PubMed, Google Scholar, Web of Science platform, Reference Citation Analysis, and Cochrane Systematic Reviews were searched for articles published between 2008 and 2023. Relevant articles were identified using the following keywords: "cardiovascular diseases", "cardiovascular risk factors", "non-alcoholic fatty liver disease", "nonalcoholic steatohepatitis", and "liver fibrosis". The reference lists of the identified articles were also searched for other relevant publications. The investigations that described LF as a cardiovascular risk factor in NAFLD met the inclusion criteria. NAFLD occupies a leading position among liver diseases worldwide. Cardiovascular disorders are the most significant cause of unfavorable outcomes in NAFLD patients. Currently, the relationship between them is well established. The pathophysiological mechanisms predisposing to the development of cardiovascular disorders in NAFLD include atherogenic dyslipidemia, impaired glucose metabolism and liver insulin resistance, low-grade systemic inflammation, endothelial dysfunction, cardiovascular remodeling, as well as gut dysbiosis, which are influenced by numerous genetic and epigenetic factors. Identification of cardiovascular risk factors in NAFLD is an important public health issue. At present, there is evidence that the presence of advanced LF may be a strong independent predictor and risk factor for cardiovascular disorders in NAFLD. It is obvious that early diagnosis of LF will allow to stratify NAFLD patients by cardiovascular risk groups and thereby determine the most optimal therapeutic interventions.

Introduction

Non-alcoholic fatty liver disease (NAFLD) occupies a leading position among liver diseases worldwide. The ubiquitous NAFLD incidence increased from 25.26% in 1990–2006 to 38.00% in 2016–2019.[1] NAFLD is described as a condition in which ≥5% of hepatocytes accumulate fat in patients who do not abuse alcohol. There are two main manifestations: simple steatosis without liver fibrosis (LF) (nonalcoholic fatty liver) and nonalcoholic steatohepatitis (NASH). NASH, in addition to steatosis, is characterized by lobular inflammation, hepatocyte ballooning, and various LF stages.[2]

The correlation between NAFLD and cardiovascular diseases (CVDs) is established by numerous clinical studies.[3] NAFLD and NASH are accompanied by an increase in the frequency of cardiovascular events, particularly coronary artery disease, hypertension, atherosclerosis,[4] myocardial infarction, ischemic stroke, atrial fibrillation, and heart failure.[5] The risk of these events escalates with the progression of NAFLD, especially in advanced LF.[6,7] As a result, CVDs are currently the predominant cause of death in NAFLD patients.[8] This problem is compounded by an increase in the number of NAFLD patients with CVDs, who may have cardiovascular risk factors.[9] Therefore, the most commonly used assessment systems, such as the Framingham risk score for hard coronary heart disease, may underestimate the cardiovascular risk associated with NAFLD.[10] Nevertheless, serious cardiovascular disorders can occur in all clinical forms of NAFLD regardless of established cardiovascular risk factors.[11] For example, the relationships between NAFLD, insulin resistance, metabolic syndrome, and CVDs have been well established.[12] It is known that the metabolic syndrome is characterized by a combination of signs such as abdominal obesity, dyslipidemia,

Keywords: Cardiovascular diseases; Cardiovascular risk factors; Non-alcoholic fatty liver disease; Nonalcoholic steatohepatitis; Liver fibrosis.

Abbreviations: ALT, alanine aminotransferase; APRI, AST to Platelet Ratio; AST, aspartate aminotransferase; CRN, Clinical Research Network; CVDs, cardiovascular diseases; FIB-4, fibrosis-4; GLS, global longitudinal strain; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; RV, right ventricular; T2DM, type 2 diabetes mellitus.

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glucose metabolism disorders and hypertension.[13] However, even normoponderal NAFLD patients have an increased risk of CVDs.[14] This is likely due to the presence of other independent cardiovascular risk factors in NAFLD patients. At present, there is evidence that the presence of advanced LF may be a strong independent predictor and risk factor for cardiovascular disorders in NAFLD.[15,16]

This review summarizes the current investigations that confirm the significance of LF as an independent cardiovascular risk factor in NAFLD.

Literature search

PubMed, Google Scholar, Web of Science platform, Reference Citation Analysis, and Cochrane Systematic Reviews were searched for articles published between 2008 and 2023. Relevant articles were identified using the following keywords: "cardiovascular diseases", "cardiovascular risk factors", "non-alcoholic fatty liver disease", "nonalcoholic steatohepatitis", and "liver fibrosis". The reference lists of the identified articles were also searched for other relevant publications. The investigations that described LF as a cardiovascular risk factor in NAFLD met the inclusion criteria.

Pathophysiological mechanisms of cardiovascular disorders in NAFLD

The pathophysiological mechanisms predisposing to the development of cardiovascular disorders in NAFLD are complex and multifactorial.[17] These mechanisms include atherogenic dyslipidemia, impaired glucose metabolism, liver insulin resistance, low-grade systemic inflammation, endothelial dysfunction, as well as gut dysbiosis, all of which are influenced by numerous genetic and epigenetic factors.[18] In addition, advanced LF/cirrhosis in NASH may contribute to cardiovascular disorders as a result of cardiovascular remodeling in response to the hyperdynamic circulatory state associated with portal hypertension. The term "remodeling" began to be used in cardiology in the 1980s, and in strict interpretation, means the process of reorganization of the existing structure, during which new material is attached to it, or it is completely changed (Fig. 1).[19] In particular, left ventricular concentric remodeling, which was an unfavorable prognostic sign, was revealed in NASH patients.[20] LF in NASH may also be associated with CVDs by a more expressed profile of systemic inflammation affecting various organs and systems and the interactions between them, leading to further inflammation and immune response activation.[21]

Noninvasive tests of liver fibrosis to assess cardiovascular risk in NAFLD

Given the known limitations of performing a liver biopsy, noninvasive tests of LF have been used in most investigations to assess cardiovascular risk in NAFLD (Table 1).[22,23,24–44] The Fibrosis-4 (FIB-4) score is an index based on aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, platelet count, and age to evaluate LF. When evaluating LF in NAFLD patients, a FIB-4 score <1.3 is categorized as low risk, while a FIB-4 score ≥2.67 is categorized as high risk of LF.[45] The NAFLD fibrosis score (NFS) is a combined assessment of age, hyperglycemia, body mass index, platelet count, albumin, and the AST/ALT ratio to evaluate LF. The following NFS thresholds for evaluating LF are proposed: <−1.455 - predictor of absence of significant LF (F0-F2); ≤−1.455 to ≤0.675 - indeterminate score; >0.675 - predictor of presence of significant LF (F3-F4).[46] The BARD score includes three variables: AST/ALT ratio ≥0.8–2 points; a body mass index ≥28—1 point; and the presence of type 2 diabetes mellitus (T2DM)—1 point. The possible score ranges from 0 to 4 points. A total score of ≥2 is associated with advanced LF.[47] The APRI index is calculated by using the formula AST/upper limit of normal × 100/platelet count. APRI index values of ≤0.3 and ≤0.5 rule out significant LF and cirrhosis, respectively, and a value of ≥ 1.5 rules out significant LF.[48] The Forns index, calculated based on the following four parameters: patient age, total cholesterol, gamma-glutamyl transferase, and platelet count, has the cut-off points for the LF assessment <4.2 and >6.9.[49] Transient elastography is the most commonly used imaging-based LF assessment method. To exclude advanced LF in NAFLD patients, the recommended values of liver stiffness measured by transient elastography are <8 kPa. The general limitations of noninvasive tests include insufficient verification accuracy for mild and moderate LF and inadequate differences in adjacent LF stages; in addition, there are not enough noninvasive tests to diagnose subclinical hepatic inflammation and ballooning, as well as to accurately determine the severity of portal hypertension in compensated advanced chronic liver disease. There are also specific advantages and limitations of individual noninvasive tests. Finally, the test-retest reliability of noninvasive tests has not been fully studied, warranting future research. Nevertheless, the use of noninvasive tests in scientific research for evaluating liver disease severity and prognosis is supported by the current guidelines.[50]

Impact of liver fibrosis on cardiovascular risk in NAFLD

It has been shown that patients with NASH or advanced LF are at a higher risk of atherosclerotic CVDs compared to non-LF NAFLD patients, independent of established cardiovascular metabolic risk factors.[22] In a study by Labenz *et al.*,[51] the overall 10-year CVDs risk, according to the Framingham risk scale, was high among patients with histologically confirmed NAFLD, with the highest risk observed in those with advanced LF. Noninvasive LF markers in NAFLD patients may be predictors of an increased risk of cardiovascular events, regardless of metabolic syndrome.[23] For example, a FIB-4 score ≥2.67 was found to be a strong independent prognostic criterion for major adverse cardiovascular events in NAFLD and was invariably associated with unstable angina, myocardial infarction, heart failure, percutaneous coronary intervention, and coronary artery bypass grafting in addition to known cardiovascular risk factors.[24] In a study by Hanson *et al.*,[52] the NFS in NAFLD patients with advanced LF without prior CVDs was found to be an independent predictor of cardiovascular events, even after adjusting for the relevant covariates, which included cardiovascular risk indicators such as the Framingham risk score and atherosclerotic CVDs indicators. In the Alimentazione, Benessere Cardiovascolare e Diabete study, the LF severity assessed by transient elastography was an independent factor for a higher atherosclerotic CVDs risk in addition to steatosis after adjusting for obesity.[25] Multivariate adjusted logistic regression models that were used in 3,276 adult participants of the Framingham Heart Study showed a significant association between advanced LF assessed by transient elastography and obesity-related signs, namely, hypertension, low high-density lipoprotein cholesterol and most notably, T2DM. This association persisted with a 2.5-fold increase even after accounting for controlled attenuation parameters. This suggests a link between LF and cardiometabolic

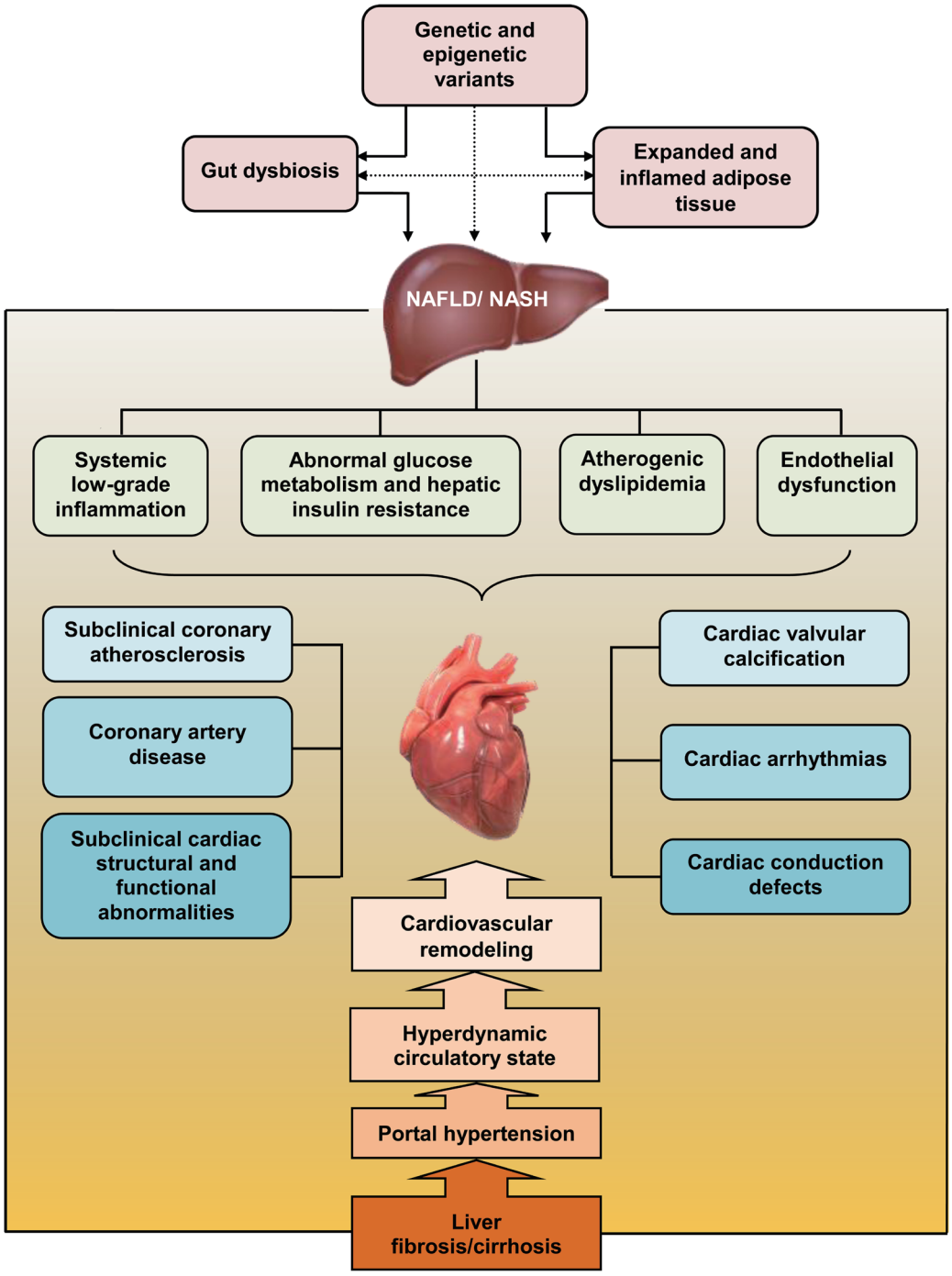

Fig. 1. Potential pathophysiological mechanisms of cardiovascular disorders in non-alcoholic fatty liver disease. NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

diseases in addition to an association with liver steatosis.[26]

Impact of liver fibrosis on the cardiovascular outcome in NAFLD

Although liver-related complications are a significant cause of mortality in NAFLD, CVDs accounts for at least 40% of the total number of deaths in NAFLD, making it the predominant cause of mortality.[53] According to a meta-analysis by Younossi *et al.*,[1] the pooled CVDs-related mortality rate in NAFLD patients was 4.2 per 1,000 person-years. The NAFLD severity is the main factor determining the increased risk of CVDs. Therefore, patients with NASH and progressive LF can be classified as a special risk group.[54] In a large study involving 11,154 patients, 34% of whom

Table 1. Main characteristics of investigations on the significance of liver fibrosis as an independent cardiovascular risk factor in non-alcoholic fatty liver disease

First author, year, ref.	Design	Liver fibrosis assessment	Main findings*
Impact of liver fibrosis on the cardiovascular risk in NAFLD			
Park, 2021[22]	A prospective cross-sectional study	Liver biopsy	NASH or advanced LF was independently associated with a higher risk of atherosclerotic CVDs.
Baratta, 2020[23]	A prospective cohort study	FIB-4 score, NFS	FIB-4 score >2.67, and NFS >0.676 in NAFLD patients were independently associated with risk of incident cardiovascular events.
Vieira Barbosa, 2022[24]	A prospective cohort study	FIB-4 score	FIB-4 score ≥2.67 in NAFLD patients was the strongest predictor of major adverse cardiovascular events overall and was consistently associated with myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary artery bypass graft, and percutaneous coronary intervention.
Pennisi, 2021[25]	A prospective cohort study	Transient elastography	LF severity in NAFLD patients were independent factors for a higher atherosclerotic cardiovascular risk after adjusting for obesity.
Long, 2021[26]	A prospective cohort study	Transient elastography	LF in NAFLD patients was associated with multiple cardiovascular risk factors, including increased odds of obesity, metabolic syndrome, T2DM, hypertension, and low high-density lipoprotein cholesterol.
Impact of liver fibrosis on the cardiovascular outcome in NAFLD			
Kim, 2013[27]	A retrospective cohort study	NFS, APRI index, FIB-4 score	Compared to NAFLD patients without LF, those with a high probability of advanced LF had a 69% increase in mortality after adjustment for other known predictors of mortality. These increases in mortality were almost entirely from cardiovascular causes.
Park, 2021[28]	A prospective cohort study	BARD score	NAFLD patients with advanced LF demonstrated a significantly higher incidence of heart failure, hospitalized heart failure, all–cause mortality and cardiovascular mortality compared to NAFLD patients without advanced LF.
Impact of liver fibrosis on the cardiovascular comorbidities in NAFLD Subclinical coronary atherosclerosis			
Jamalinia, 2023[29]	Systematic review and meta-analysis	No data available	A significant association of subclinical atherosclerosis with LF in NAFLD patients was revealed, as well as its correlation with LF stages.
Song, 2019[30]	A retrospective, cross-sectional study	NFS, FIB-4 score, Forns index, APRI index	An association of coronary atherosclerosis with LF in NAFLD patients was revealed.
Tsai, 2022[31]	A retrospective cohort study	NFS, FIB-4 score, Forns index, APRI index	The male gender, diastolic blood pressure, and NFS in NAFLD patients were independently associated with coronary segment stenosis score progression.
Chen, 2015[32]	A prospective cross-sectional study	NFS	Compared to NAFLD patients without advanced LF, presence of advanced LF associated with a 303% increased risk for elevated carotid intima-media thickness, a 398% increased risk of prevalence of carotid plaque, and a 456% increased risk for prevalence of arterial stiffness.
Kim, 2022[33]	A retrospective, cross-sectional study	NFS, BARD score	Patients with lean NAFLD and advanced LF had a significantly higher risk for atherosclerotic CVDs than those with obese NAFLD with or without advanced LF.
Coronary artery disease			
Sinn, 2020[34]	A retrospective cohort study	NFS, FIB-4 score	NAFLD patients with advanced LF may have an increased risk of myocardial infarction.

(continued)

Table 1. - *(continued)*

First author, year, ref.	Design	Liver fibrosis assessment	Main findings*
Higashiura, 2022[35]	A prospective cohort study	FIB-4 score	LF stage in NAFLD patients correlated with new onset of ischemic heart disease in the group with "fatty liver", but not in the group without "fatty liver".
Subclinical cardiac structural and functional abnormalities			
Lee, 2018[36]	A prospective cohort study	Transient elastography, NFS	Compared to those without NAFLD, NAFLD patients had alterations in cardiac remodeling, manifested by increased left ventricular mass index, left ventricular end-diastolic diameter, and left atrial volume index. NAFLD patients with advanced LF demonstrated higher values of left ventricular filling pressure and tended to increase it.
Chung, 2018[37]	A prospective cross-sectional study	NFS	The risk of diastolic dysfunction in NAFLD patients gradually increases according to the LF severity.
Canada, 2019[38]	A prospective cross-sectional study	Liver biopsy	On stress echocardiography in NAFLD patients a significant stepwise increase in stress left ventricular filling pressure with increasing LF stage was noted. A trend between impaired left ventricular relaxation with exercise and increasing LF stages was also noted.
Lee, 2020[39]	A retrospective cohort study	NFS	LF in NAFLD patients was independently associated with diastolic dysfunction after adjusting for insulin resistance and cardiometabolic risk factors.
Sunbul, 2015[40]	A prospective cohort study	Liver biopsy	NAFLD patients with LF had significantly lower RV function assessed by GLS compared to patients without LF. NASH CRN score ≥5 was associated with lower RV-GLS. NASH CRN score inversely correlated with RV-GLS such as patients with impaired RV-GLS (<19%) showed significantly higher NASH CRN score compared to normal RV-GLS group.
Cardiac arrhythmias			
Käräjämäki, 2017[41]	A prospective cross-sectional study	Transient elastography, NFS	LF severity was highest in NAFLD patients with atrial fibrillation.
Park, 2020[42]	A retrospective cohort study	FIB-4 score	LF severity in NAFLD patients had a significant correlation with atrial fibrillation.
Kang, 2020[43]	A retrospective, cross-sectional study	NFS, FIB-4 score	LF severity in NAFLD patients was associated with atrial fibrillation.
Cardiac conduction defects			
Mantovani, 2017[44]	A retrospective cross-sectional study	FIB-4 score, APRI index	NAFLD patients with advanced LF had a substantially greater prevalence of heart block as compared to NAFLD patients with mild and moderate LF or persons without NAFLD.

*The research results are statistically significant. APRI, AST to Platelet Ratio; CRN, Clinical Research Network; CVDs, cardiovascular diseases; FIB-4, fibrosis-4; GLS, global longitudinal strain; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; RV, right ventricular; T2DM, Type 2 Diabetes Mellitus.

were diagnosed with NAFLD, higher values of noninvasive LF tests, such as the APRI index, FIB-4 score, and NFS, were associated with a progressive increase in CVDs mortality after correction for other predictors of death.[27] In a study by Mann *et al.*,[55] NAFLD patients with liver cirrhosis had higher mortality regardless of known cardiovascular risk factors. Additionally, liver steatosis and/or advanced LF in NAFLD patients assessed by the fatty liver index as well as the BARD score and NFS significantly correlated with the risk of heart failure and mortality.[28,56]

Impact of liver fibrosis on cardiovascular comorbidities in NAFLD

NAFLD can negatively affect both the coronary arteries and other heart anatomical structures, contributing to an increase in morbidity and mortality from CVDs among NAFLD patients.[57] In particular, there is strong evidence linking NAFLD with the risk of developing coronary atherosclerosis and coronary artery disease, cardiac structural and functional abnormalities, cardiac valvular calcification, cardiac arrhythmias, and conduction defects.[58]

Subclinical coronary atherosclerosis

For a long time, NAFLD was not considered a probable cause of atherosclerosis but was recognized as a valuable indicator of the early stages of its development.[59] Moreover, well-planned and controlled studies conducted in recent years have provided very valuable information that allows one to take a fresh look at the relationships among these pathological conditions.[60] In particular, the association of LF in NAFLD with subclinical atherosclerosis was shown, and LF severity aggravated this relationship.[29]

Coronary artery calcium scoring via computerized tomography is usually used to determine the degree of coronary atherosclerosis. In a study involving 665 NAFLD patients, noninvasive LF markers, such as APRI index, NFS, and FIB-4 score, made it possible to reliably predict the values of the coronary calcium index >100 via computerized tomography.[30] In a study by Tsai *et al.*,[31] NAFLD patients with basal coronary plaques had higher NFSs, FIB-4 scores and Forns index, suggesting the possibility of their use for early identification of coronary plaques and prediction of the risk of adverse cardiovascular events. According to a study by Chen *et al.*,[32] NAFLD patients with advanced LF assessed by the NFS had a higher probability of carotid artery intima-media thickening, the presence of carotid plaque and arterial stiffness, regardless of known metabolic factors, prior cardiovascular events, or insulin resistance. It was found that NASH patients have higher carotid artery intima-media thickness than nonalcoholic fatty liver patients. In addition, NASH patients had high levels of high-sensitivity C-reactive protein, and the levels of high-sensitivity C-reactive protein were significantly correlated with LF. It is known that high levels of highly sensitive C-reactive protein are associated with an increased risk of heart attack.[61] Interestingly, lean NAFLD patients with advanced LF are more likely to have atherosclerotic CVDs than obese subjects.[33]

Coronary artery disease

The presence, severity and prevalence of coronary artery disease may be associated with NAFLD, regardless of well-known risk factors. In addition, the relationship between coronary artery disease and NAFLD may be attributed to the formation of atherosclerotic coronary plaques characteristic of both diseases. Their calcium content according to computerized tomography data is a clinically significant sign of subclinical coronary artery disease.[62] In a study by Wong *et al.*,[63] NAFLD patients prevailed among those with significant coronary artery stenosis. An association between NAFLD and an increased risk of acute myocardial infarction has also been shown, regardless of known risk factors.[34] An independent correlation was shown between the FIB-4 score in NAFLD patients and the risk of coronary artery disease.[35] In a study by Ghoneim *et al.*,[64] it was found that NASH is associated with acute myocardial infarction regardless of the established risk factors. The probability of acute myocardial infarction in young NASH patients was higher than that in older subjects. Acute myocardial infarction is a frequent outcome in NASH patients.

Subclinical cardiac structural and functional abnormalities

Recent studies have identified NAFLD as a risk factor not only for premature coronary artery disease and cardiovascular events but also for early cardiac structural and functional abnormalities. For example, in a study by Lee *et al.*,[36] it was demonstrated that advanced LF in NAFLD patients without a history of CVDs correlates with an increase in left ventricular filling pressure, which is associated with diastolic dysfunction associated with impaired myocardial glucose uptake. It was noted that left ventricular diastolic dysfunction in advanced LF was significant only in NAFLD patients without obesity.[37] Alterations in myocardial structure and in the load dependence of left ventricular diastolic function parameters were also observed in NASH patients without a history of CVDs.[65] Another study revealed that NASH patients with liver cirrhosis had an increased prevalence of diastolic dysfunction compared with patients with other causes of liver cirrhosis.[66] Diastolic dysfunction in NASH patients leads to a decrease in physical performance. The severity of these disorders correlates with the LF stage.[38] In a study by Lee *et al.*[39] including T2DM patients aged ≥50 years, participants with NAFLD had changes in left ventricular structure and diastolic dysfunction compared to non-NAFLD patients. Advanced LF significantly correlated with left ventricular diastolic dysfunction after correction for cardiovascular risk factors, especially in patients without insulin resistance. Although NASH is accompanied by a higher frequency of left ventricular diastolic dysfunction, this does not affect the immediate post-transplant outcome or 30-day mortality from all causes.[67] Sunbul *et al.*[40] have shown that NAFLD patients with LF have significantly lower right ventricular function compared to patients without LF. They used the NASH CRN histological scoring system as an independent predictor. It turned out that the NASH CRN score ≥5 was associated with lower right ventricular global longitudinal strain. The NASH CRN score inversely correlated with right ventricular global longitudinal strain. Patients with impaired right ventricular global longitudinal strain had a higher NASH CRN score than did those with normal right ventricular global longitudinal strain. Cardiac structural and functional abnormalities contribute to the development of heart failure, which, in NAFLD, occurs with a preserved ejection fraction. The relationship between more advanced heart failure and LF stage was evident in NAFLD patients. Left atrial dilatation and more pronounced diastolic dysfunction were observed in NAFLD patients with advanced LF.[68]

Cardiac arrhythmias

Atrial fibrillation is an extremely important social problem due to its large prevalence and high morbidity and mortality rates.[69] Atrial fibrillation often occurs in NAFLD patients, in whom it usually has a permanent (chronic) form.[70] In a study by Whitsett *et al.*,[71] atrial fibrillation was found to be twice as common in NASH patients than in the general population. An Oulu Project Elucidating

the Risk of Atherosclerosis study revealed a link between atrial fibrillation and liver stiffness measured by transient elastography in elderly NAFLD patients.[41] A number of studies have shown an independent association between atrial fibrillation and advanced LF assessed by NFS and FIB-4 score in NAFLD patients.[42,43]

Cardiac conduction defects

Cardiac conduction defects are a well-established risk factor for general and cardiac mortality in NAFLD patients.[72] In a study by Mantovani *et al.*,[43] persistent heart block was found to be most common in NAFLD patients with T2DM in the presence of advanced LF, assessed by the FIB-4 score.

Conclusions

NAFLD occupies a leading position among liver diseases worldwide. Given that cardiovascular disorders are the most significant cause of unfavorable outcomes in NAFLD patients, identifying cardiovascular risk factors is an important public health issue. There is much evidence that LF can considerably increase morbidity and mortality from CVDs in NAFLD patients. Early diagnosis of LF will allow to stratify NAFLD patients by cardiovascular risk groups and thereby determine the most optimal therapeutic interventions.

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Conflict of interest

The author has no conflict of interests related to this publication.

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