

NONALCOHOLIC FATTY LIVER DISEASE IS A CORNERSTONE OF THE CARDIOVASCULAR CONTINUUM

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Abstract: Cardiovascular diseases (CVD) are the leading cause of mortality in most countries worldwide, including Uzbekistan. The main direction in preventing diseases and complications of the cardiovascular system (CVS) is the timely detection and correction of risk factors (RF). Non-alcoholic fatty liver disease (NAFLD) is considered one of the RFs of CVD development, including coronary artery disease (CAD). Data from numerous studies demonstrate increased cardiovascular risks and accelerated progression of liver pathology in the combination of NAFLD and CAD, however, some studies have not confirmed the worsening of outcomes. An association between NAFLD and CAD, atherosclerosis, cardiac rhythm disturbances, arterial hypertension, chronic heart failure and other CVDs has been identified. However, data from meta-analyses should be interpreted with caution due to the use of different diagnostic methods and the heterogeneity of studies included in them. Further studies are needed to clarify the relationship between CVDs and NAFLD further..

Keywords: cardiovascular diseases, non-alcoholic fatty liver disease, atherosclerosis, hepatocardiac continuum



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Introduction

Cardiovascular diseases (CVD) are the leading cause of death in most countries of the world, including Uzbekistan. According to the World Health Organization (WHO), more than 17 million people die annually from diseases of the circulatory system in the world, with the most common cause of death being coronary artery disease (CAD) [1]. In Uzbekistan, CVD is also the main cause of death among the adult population. The analysis shows that 53% of deaths among the population of the Republic of Uzbekistan aged 30-70 years are associated with CVD. They are diagnosed in about 4 million people, which is 12% of the total population [2].

The main direction in preventing diseases and complications from the cardiovascular system (CVS) is the timely identification and correction of risk factors (RF). The importance of such well-known factors for the development of CVD as a family history of early CVD development, age, male sex, smoking, overweight, dyslipidemia (DLP), arterial hypertension (AH), type 2 diabetes mellitus (DM) has been convincingly proven, but even in the absence of these factors, acute myocardial infarction (AMI) and angina pectoris may occur for the first time. Therefore, in order to improve the prediction of the incidence of CVD and determine indications for active primary prevention, it is necessary to study additional criteria that allow a more accurate assessment of the individual risk of the patient. Nonalcoholic fatty liver disease (NAFLD) is considered one of the causes of the development of CVD, including CAD [3]. Data from numerous studies demonstrate an increase in cardiovascular risks and accelerated progression of liver pathology in combination with NAFLD and CVD [4-6], however, some studies have not confirmed a deterioration in outcomes [7].

NAFLD: definition, epidemiology, aetiology, diagnostic criteria. According to the definition of the European Association for the Study of the Liver, NAFLD is characterised by excessive accumulation of fat in the liver, is associated with insulin resistance (IR) and is determined in the presence of steatosis in more than 5% of hepatocytes according to histological examination results or with a proton density of the fat fraction >5.6% according to positron magnetic resonance spectroscopy (PMRS) or quantitative assessment of the ratio fat and water according to magnetic resonance imaging (MRI) [8]. The American Association for the Study of the Liver, the American Gastroenterological Association and the American College of Gastroenterology offer the following definition of NAFLD: the presence of signs of liver steatosis diagnosed by available imaging methods, excluding chronic alcohol intoxication (alcohol-containing products in terms of pure ethanol more than 20 g/day for women and 40 g/day for men), as well as in the absence of reasons for secondary fat accumulation [9]. NAFLD is an independent nosological unit, including fatty degeneration (steatosis), non-alcoholic steatohepatitis (NASH) and cirrhosis of the liver [10].

According to WHO, there is a clear trend towards an increase in the number of liver diseases worldwide. NAFLD is the subject of close attention of doctors of various specialities and, according to the results of epidemiological studies, is currently considered one of the most common diffuse liver diseases [11]. The global prevalence of NAFLD is about 25% [12] with wide geographical, age, gender and ethnic differences. Depending on the diagnostic method, age, gender and ethnicity [4], the incidence of NAFLD among the adult population ranges from 17 to 46%. The highest prevalence rates of NAFLD diagnosed by ultrasound were reported in the Middle East (31.79%) and South America (30.45%) [13], while a limited number of studies from Africa report a much lower prevalence (13.48%) [14]. The study of the incidence of NAFLD in patients with CAD in the Aral Sea region revealed that the largest number of patients with CAD who had NAFLD occurs in the age group from 45 to 59 years (51.5%), that is, the most active and able-bodied age; the risk of developing NAFLD among patients with CAD is the same in both women and men; there were no significant differences between urban and rural populations in this study [15].

Primary NAFLD is established when the following causes of secondary pathology are excluded:

1. Toxic liver damage due to taking medications (glucocorticoids, amiodarone, nonsteroidal anti-inflammatory drugs, methotrexate, somatostatin, rifampicin, amitriptyline, nifedipine, antiretroviral therapy; effects of chemicals (arsenic, chloroform, lead, phosphorus, tetrachloroethane, pentachloroethane).
2. Rapid weight loss when inadequate treatment of obesity, during starvation.
3. Malabsorption syndrome due to surgical interventions.
4. Viral hepatitis B, C.
5. Congenital metabolic disorders (familial combined hyperlipidemia, Wilson-Konovalov disease, celiac disease) [16].

Early diagnosis of NAFLD is difficult and is often diagnosed accidentally when examining a patient for another reason. Routine screening of NAFLD in high-risk patients is controversial, mainly

due to the lack of effective treatment and a cost-effective screening method. The American Association for the Study of the Liver does not recommend routine screening of NAFLD, even in high-risk groups due to uncertainty in diagnostic work and limited treatment options. On the contrary, according to the international consensus and clinical practical recommendations of the European Association for the Study of the Liver, active screening of NAFLD is primarily necessary for obesity – the main cause of the development and progression of NAFLD and IR. Screening examination for the detection of NAFLD is indicated in patients with obesity, type 2 DM, and DLP [7].

According to the recommendations of the American Association for the Study of the Liver, the diagnostic criteria for the diagnosis of NAFLD are the following: liver steatosis according to imaging diagnostic methods or histological picture; absence of a clinically significant amount of alcohol in the anamnesis; exclusion of hereditary and viral liver diseases [3]. Diagnosis of NAFLD requires a comprehensive assessment of anamnesis, laboratory and instrumental data, which makes it possible to exclude other liver diseases. In laboratory tests, patients with NAFLD may experience an increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gammaglutaryltranspeptidase (GGTP). At the same time, the rise of these enzymes often correlates with the severity of NAFLD. Imaging research methods (ultrasound, computed tomography (CT), MRI, PMRS) make it possible to reliably diagnose diseases of the hepatobiliary system. Liver ultrasound is recommended as a first-line diagnostic method and is characterized by high diagnostic accuracy in detecting NAFLD with a sensitivity of 60-94% and specificity of 66-97% [6], however, in obese patients, the sensitivity of this method is 49.1%, specificity is 75% [7].

NAFLD and cardiovascular risks. The need for timely diagnosis and monitoring of NAFLD is because this disease is associated with the risk of developing cardiovascular pathology, given the fact of their common mechanisms of development. The opinion of scientists is correct, considering NAFLD as a disease that harms the progression of CVD and represents a modifiable RF [15]. The results of clinical studies allow us to discuss NAFLD as a comorbid condition for CVD. The mortality of patients with NAFLD is mainly due to the development of complications of CVD. The question of whether NAFLD is an independent RF for cardiovascular mortality and other cardiovascular events has been studied, but remains controversial. A number of cohort studies have demonstrated increased cardiovascular mortality in patients with NAFLD, although studies have been conducted that have not confirmed this relationship [16,17]. The meta-analysis which included 34,043 people from 16 prospective and retrospective studies assessing cardiovascular events (death, MI, stroke or coronary revascularization) demonstrated that patients with NAFLD had a 65% higher risk of fatal and/or nonfatal cardiovascular events than patients without NAFLD during 7 years of follow-up [18]. However, when the analysis was limited to studies with CVD mortality as the main result, the association between NAFLD and CVD deaths was not statistically significant. Meta-analyses should be interpreted with caution due to the use of various diagnostic methods and the heterogeneity of the studies included in them. Further research is needed to further clarify the relationship between CVD and NAFLD. The relationship of NAFLD with various CVDs will be discussed below.

NAFLD and atherosclerosis. A number of studies have been conducted to quantify the relationship between atherosclerosis and NAFLD. With NAFLD, the serum lipid profile changes in the form of abnormally elevated levels of triglycerides (TG), very low density lipoproteins (VLDL) and low-density lipoproteins (LDL), as well as reduced levels of high-density lipoproteins (HDL) [19-22]. Further investigation of lipoprotein subclasses revealed that patients with NAFLD have significantly smaller particle size and higher concentrations of LDL particles, higher LDL-IVB levels and reduced HDL-2b levels, indicating a mechanism for potentially higher risk of CAD in individuals with more severe NAFLD [23]. Patients with NAFLD may also be at increased risk of developing atherosclerosis due to an increase in prothrombotic factors [24]. A connection was found between NAFLD and markers of atherosclerosis, such as increased calcification of the coronary arteries (CA), and an increase in the carotid intima-media thickness (IMT) [25]. A meta-analysis of 27 cross-sectional studies, regardless of the classical predictors of CVD and metabolic syndrome (MS), established a link between NAFLD and markers of the subclinical course of atherosclerosis: increased

carotid IMT – 16 studies; increased calcification of CA – 7 studies; impaired vasodilation (endothelial dysfunction) – 7 studies; reduction of arterial elasticity – 6 studies [26]. NAFLD is independently associated with an increase in IMT and coronary calcium (CC) score. In patients with NAFLD, compared with patients without steatosis, a higher percentage of atherosclerotic stenosis in the carotid arteries is visualised. In a meta-analysis of 7 studies involving 3,497 participants, patients with NAFLD showed a 13% increase in IMT [27]. Another meta-analysis of 16 studies evaluating the CC score in 16,433 patients with NAFLD (and 41,717 participants in the control group) showed that NAFLD is associated with both a CC score >0 and a CC score >100 [28]. A larger meta-analysis involving 85,395 participants, 29,493 of whom had NAFLD, also showed an increased risk of subclinical atherosclerosis compared to individuals without NAFLD, while subgroup analysis showed an increase in IMT, arterial stiffness, and endothelial dysfunction. NAFLD increased the risk of detection of asymptomatic atherosclerotic plaques by 85% [29].

NAFLD is also associated with an increase in arterial stiffness. Thus, a study conducted in Baltimore showed a 42% increase in the risk of increased pulse wave velocity (PWV) in patients with NAFLD, regardless of body mass index (BMI), waist coverage, smoking, type 2 DM and hypertension [30]. A decrease in the magnitude of flow-dependent dilation in patients with NAFLD compared with the control group indicated a violation of endothelial function. The risk of developing atherosclerosis depends not only on the presence of NAFLD in the patient but also on the activity and severity of the process. Thus, PWV and IMT are higher in patients with confirmed liver fibrosis than in patients with NAFLD without fibrosis. The presence of fibrosis is an independent predictor of an increase in IMT, the formation of atherosclerotic plaques in the brachiocephalic arteries, and an increase in PWV [31].

In addition to subclinical atherosclerosis, patients with NAFLD are at increased risk of clinically significant atherosclerosis requiring percutaneous coronary intervention (PCI). Signs of high-risk atherosclerotic plaques according to CT angiography were more common in patients with NAFLD than in patients without NAFLD (59.3% vs. 19.0%, respectively) [32]. It was noted that NAFLD increases the risk of carotid atherosclerosis by 1.85 times [33].

NAFLD and CAD. As noted above, a close relationship between atherosclerosis and NAFLD has been revealed. Therefore, a similar trend should be expected with the occurrence of CAD in patients with NAFLD, given that the cause of CAD in 95% of cases is atherosclerosis.

Compared with non-NAFLD sufferers, patients with NAFLD are associated with a significant risk of fatal and non-fatal cardiovascular events such as angina pectoris, MI, coronary revascularization or stroke [28]. An extensive meta-analysis of 6 studies, including 25,837 adults, showed that patients with NAFLD had an increased risk of clinical cardiovascular events compared with patients without NAFLD (14.9% vs. 6.3%) [29].

Fatty liver dystrophy also appears to be a risk factor for CAD, regardless of common RF such as age, gender, family history of CVD, DLP, obesity, hypertension and diabetes [23]. A cohort study of 3,756 North Americans who were diagnosed with NAFLD by CT and CAD by coronary angiography (CAG) demonstrated that liver steatosis is associated with serious adverse cardiovascular events (MACE) independently of other cardiovascular RF [33]. According to Choi et al., the intensity of NAFLD was closely related to the severity of CA stenosis, confirmed by CAG in the Asian population. In the meta-analysis, the prevalence of subclinical CAD in 67,070 patients with NAFLD reached 38.7%, and clinical CAD was present in 55.4% of patients with symptoms. An example confirming the existence of high-risk coronary plaques in patients with NAFLD is a cohort study conducted as part of the ROMICAT II study. A more frequent prevalence of high-risk plaques in patients with NAFLD has been demonstrated, compared with patients without NAFLD, regardless of cardiovascular RF and the severity of CAD. Asymptomatic patients with NAFLD who have undergone CAG have a higher risk of needing PCI or bypass surgery with an increased risk of fatal and non-fatal outcomes [34].

Agaç et al. studied 80 patients admitted with acute coronary syndrome (ACS) and found that the presence of NAFLD is associated with a higher SYNTAX Score [6]. It was also demonstrated

that NAFLD independently increased the risk of multivessel damage in CAD associated with cardiovascular complications in patients without diabetes admitted with ACS with ST elevation [17]. A meta-analysis conducted in 2016 involving 25,837 patients with NAFLD revealed a higher risk of CAD compared to the control group [37]. A similar study was conducted in Japan, where, after 5 years of follow-up, it was found that out of 1,637 people diagnosed with NAFLD, 1,221 of them had manifestations of CAD [38].

A survey of 471,849 patients performed in 2019 did not reveal a link between NAFLD and CVD. This analysis showed that with NAFLD, the risk of mortality from all causes increases, especially from liver complications, and not from cardiovascular pathology. An increased risk of mortality in women with NAFLD has also been shown, which requires further research to clarify gender differences and identify their mechanisms [23]. Nevertheless, it is known that compared with patients without liver damage, patients with NAFLD have a higher mortality rate from ACS (3.1% vs 21.4%) [20, 33, 39].

NAFLD and arterial hypertension (AH). NAFLD is an independent predictor of increased arterial wall stiffness, including in people who do not suffer from DM, hypertension or obesity [27]. A study of 8632 patients over 40 years of age demonstrated an increase in the ankle-brachial index in patients with NAFLD, regardless of the presence of CVD RF [25]. There is also evidence that NAFLD increases the risk of increased arterial stiffness in postmenopausal women [8]. In patients with non-alcoholic liver damage, hypertension occurs in 49.5% of cases, while in people with healthy liver, the frequency is 38.5% [25]. It is known that in patients with NAFLD, an increase in systolic blood pressure, a violation of the daily blood pressure profile, and an increase in pulse pressure are more common [27].

NAFLD and chronic heart failure (CHF). NAFLD exacerbates the course of CHF [11, 23]. In turn, patients with heart failure have a higher (up to 77%) incidence of non-alcoholic liver damage than those without CHF [11]. To maintain homeostasis in CHF, there is a redistribution of normally balanced blood flows in the arterial and venous systems of the liver. The liver becomes the most voluminous blood depot in case of a violation of the contractile function of the heart, thereby protecting it from excessive stress. Against the background of CHF, a violation of angioarchitectonics and liver dysfunction are naturally formed. It has been demonstrated that a decrease in the stroke volume and ejection fraction (EF) of the left ventricle (LV) leads to an increase in the time of early filling of the atria, an increase in the size of the right atrium (RA), an increase in pressure in the inferior vena cava and an increase in the size of the liver. With the progression of CHF, patients experience thickening and stagnation of bile, impaired concentration function of the gallbladder and impaired pigment metabolism in the liver. As a result, CHF can be considered an additional RF for the development of diseases of the gastrointestinal tract and biliary tract [40]. This confirms the existence of a bidirectional relationship between NAFLD and CVD, in particular, CHF.

A study of 102 patients with heart failure was conducted in Beijing, in which 36% had NAFLD and patients with NAFLD were younger, and had a higher BMI and LV mass index [22]. NAFLD also correlates independently with the degree of LV fibrosis and possibly exacerbates the progression of CHF [29]. However, further research is needed on this issue to identify the mechanisms of interaction between NAFLD and CHF.

NAFLD and cardiac arrhythmias. There is evidence of the association of NAFLD with the development of cardiac arrhythmias [14]. It was noted that in patients with NAFLD, atrial fibrillation (AF) is 2.5 times more common than in people without liver pathology [27]. It has been demonstrated that NAFLD is an independent RF for the development of AF [33]. During the ten-year follow-up period in patients with NAFLD, the incidence of AF was higher than in patients with a healthy liver [14]. The mechanism of AF in NAFLD has not been fully elucidated, but there are suggestions that the accumulation of fat in hepatocytes and oxidative stress leads to an increase in the synthesis of proinflammatory cytokines, which is a factor in the development of AF [41]. According to other data, autonomic dysfunction developing against the background of NAFLD disrupts the sympathetic nervous system and can provoke the occurrence of AF [33]. The presence of NAFLD is associated

with an increase in the QT interval, which in turn leads to the development of ventricular arrhythmias and an increased risk of sudden cardiac death [14, 26, 31]. However, the mechanisms of influence on the QT interval are not known. There is also evidence that patients with left bundle branch block are more susceptible to the development of NAFLD, but this issue has not been studied in more detail [18, 26].

Conclusion

The concept of "hepatocardiac continuum" plays an important role in the diagnosis of CVD. Hepatocardiac events progress up to the development of inflammatory reactions, apoptosis and fibrosis. All this affects the aggravation of both hepatic pathology in the form of NAFLD with progression to cirrhosis, accompanied by both atherosclerotic and dysmetabolic processes [37] and CVD.

The close relationship between NAFLD and CVD requires an integrated approach to the treatment of such patients since CVD complications often determine the prognosis of NAFLD patients. In this regard, it is necessary to conduct an early assessment of CVD in patients with NAFLD and their prevention [9]. Primary prevention of NAFLD coincides with the prevention of CVD. Lifestyle modification, including weight loss, improved diet and increased physical activity, are essential components of CVD prevention. Thus, for patients with CVD and NAFLD, lifestyle modification and drug treatment of NAFLD may be recommended to improve long-term clinical prognosis. In the Republic of Uzbekistan, special attention is paid to the primary prevention and early diagnosis of both CVD and liver diseases [38]. Within the framework of the Decree of the President of the Republic of Uzbekistan №103 "On measures to prevent and improve the quality of treatment of cardiovascular diseases", large-scale work is being carried out on the prevention, early detection and effective treatment of CVD in all regions of the country.

Given that NAFLD is an RF of CVD, a comorbid condition for CVD, the search for links between NAFLD and CVD remains an urgent problem in modern medicine. Due to the presence of bilateral multiple causal relationships, predicting the development of NAFLD at an early stage of fatty liver infiltration will likely prevent (slow down) the risk of cardiometabolic complications. Interestingly, a new term "Metabolic associated fatty liver disease (MAFLD) was suggested over the term NAFLD because of the close relations between fatty liver dysfunction and metabolic and cardiovascular disorders [42]. Real clinical practice needs to deepen knowledge about the mutual influence of these pathologies and develop algorithms for the management of such comorbid patients.

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