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ASSOCIATION OF CARDIOVASCULAR COMPLICATIONS AND NONALCOHOLIC FATTY LIVER DISEASE

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Abstract

The presented review article analyzes the pathogenetic mechanisms of cardiovascular disease (CVD) formation in patients with nonalcoholic fatty liver disease (NAFLD). The role of insulin resistance, proinflammatory cytokines, adipocytokines, genetic factors of atherosclerosis formation, diastolic left ventricular dysfunction and chronic heart failure was considered. It was noted that ectopic accumulation of adipose tissue can be a key pathogenetic element of CVDs formation, and, therefore, NAFLD patients have a high risk of their development. It has been shown that people with NAFLD and higher levels of C-reactive protein have the highest risk of CVD formation. It was demonstrated that the degree of histological changes in the liver in NAFLD patients correlated with the manifestations of atherosclerotic changes in the carotid arteries. It was shown that the increased level of transaminases in NAFLD patients was an independent risk factor of cardiac insufficiency formation. It was noted that echocardiographic signs of sclerotic changes of aortic valve have a clear association with the presence of NAFLD in patients. It was shown that PNPLA3 GG genotype is associated with the severity of atherosclerotic changes in the carotid arteries in young patients with NAFLD.

Keywords: nonalcoholic fatty liver disease, insulin resistance, risk, cardiovascular disease, atherosclerosis.

Nonalcoholic fatty liver disease (NAFLD) has now become one of the most important public health problems in all countries of the world due to the high prevalence of this disease [1]. The prevalence of NAFLD in Western countries ranges from 20 to 30%, and in Asian countries from 5 to 18%, and the incidence increases with age [2]. Now NAFLD is considered to be a component of metabolic syndrome (MS) [3], which is a significant risk factor for cardiovascular diseases (CVD) [4]. A recent study showed that the presence of NAFLD was associated with the risk of increased arterial stiffness in postmenopausal women, and an interesting feature was that these changes were detected regardless of the presence of MS [5]. Similar results on the detection of a high incidence of CVD risk in NAFLD patients without excessive body weight were obtained in a recent cohort study [6]. The results of this study showed that the risk of CVDs was higher in moderately overweight subjects with NAFLD than in overweight subjects without NAFLD. The results of this study suggested that the presence of NAFLD plays a more significant role in the formation of CVD than the mere presence of excess body weight. Currently, there is an active search for possible pathogenetic mechanisms underlying this phenomenon. It is known that NAFLD is accompanied by the formation of ectopic fat in liver tissue [7]. Epicardial fat, which is the classic ectopic fat, has been shown to be associated with an increased risk of CVD

formation [8]. Thus, ectopic accumulation of adipose tissue may be a key pathogenetic element of CVD formation, and, therefore, patients with NAFLD have a higher risk of their development [4]. In addition, there are studies showing that people with NAFLD have a higher degree of insulin resistance compared with patients without NAFLD, even if there are normal fasting plasma glucose levels and normal values of insulin and serum lipid levels [9].

There are studies explaining the pathogenetic mechanisms of the link between NAFLD and CVD through the accumulation of adipose tissue in the liver, followed by the development of hyperglycemia, dyslipidemia and subclinical inflammation [10]. This hypothesis is supported by the fact that adipokines, such as adiponectin, leptin, resistin, tumor necrosis factor alpha (TNFα) and interleukin-6, produced by fatty liver tissue in steatosis [11, 12], are actively involved in the formation of CVD in subjects with NAFLD [13].

In addition, it is hypothesized that adipose tissue storage capacity differs in different individuals, with ectopic adipose tissue easily increasing in those individuals who have low subcutaneous fat and visceral adipose tissue accumulation and storage capacity [14]. Thus, the individuals with the lowest weight combined with NAFLD represent representatives of the classic phenotype with low ability to store subcutaneous and visceral fat. Thus, the risk of CVD formation in patients with moderate body weight combined with NAFLD is significantly higher than in representatives of other phenotypes [14].

The risk of CVD in NAFLD differed depending on the level of systemic inflammation, which is a known mediator and biomarker of adverse outcomes in patients [15]. Individuals with NAFLD and higher levels of C-reactive protein had the highest risk of CVD, suggesting that the simultaneous existence of NAFLD and systemic inflammation significantly increases the risk of CVD [16]. These results require closer attention to young people with asymptomatic NAFLD and elevated CRP, reflecting the presence of systemic inflammation, with regard to a set of measures on rational diet and physical activity to prevent the progression of NAFLD.

A large number of large population studies using hyperenzyme indicators as surrogate markers of NAFLD have noted a high risk of cardiovascular mortality associated with elevated levels of gammaglutamyl transpeptidase, which is now considered not only a marker of NAFLD, but also an independent, long-term predictor of cardiovascular events in men and women [16]. And in the study of Sung K. C. et al. (2008) including more than 30 000 patients with NAFLD noted 5,3-fold increase of 10-year risk of cardiovascular events 10% (estimated by Framingham scale) in patients with nonalcoholic steatohepatitis and elevated alanine transaminase level. Some works noted that the appearance of ultrasound signs of NAFLD, not yet accompanied by hyperfermentemia, significantly increases the risk of cardiovascular events [13]. The work of Hamaguchi M. et al. is interesting, in which it was shown that when ultrasound signs of NAFLD were diagnosed in a cohort of healthy adults, they correlated with increased risk of nonfatal cardiovascular events regardless of cardiometabolic factors [6]. What are the mechanisms mediating such an undeniable association between NAFLD and the risk of cardiovascular disease development and progression?

To date, there is no clear answer to this question. The close correlations between NAFLD, abdominal obesity, insulin resistance, and their outcomes make the differentiation of causal relationships underlying increased cardiovascular risk among NAFLD patients an extremely difficult task. Indeed, there is a high incidence of traditional cardiovascular disease risk factors in NAFLD patients, as well as the interdependence of these traditional cardiovascular disease risk factors with the formation of NAFLD: it has been proven that all of them with the same degree can lead to metabolic liver damage and the development of NAFLD. Thus, the well-known Dionysos study demonstrated the presence of histologically confirmed hepatic steatosis in 46% of obese patients [11]. Herewith, there is an inverse relationship: in NAFLD patients obesity is revealed in 30-100 % of cases, diabetes type 2 - in 10-75 % of cases, hyperlipidemia - in 20-92 % of cases. More than 50% of patients with arterial hypertension (AH) have NAFLD without other risk factors for liver disease, and AH, especially systolic, is an independent predictor of NAFLD [17]. At present, it is well known that in the formation of NAFLD four main pathogenetic mechanisms play a role: lipotoxicity of free fatty acids (FFAs), insulin resistance

(IR), the formation of a systemic inflammatory response, as well as the activation of oxidative stress and lipid peroxidation (LPO) [3]. Recent studies have shown that NAFLD is associated with a high risk of CVD through endothelial dysfunction [7, 8].

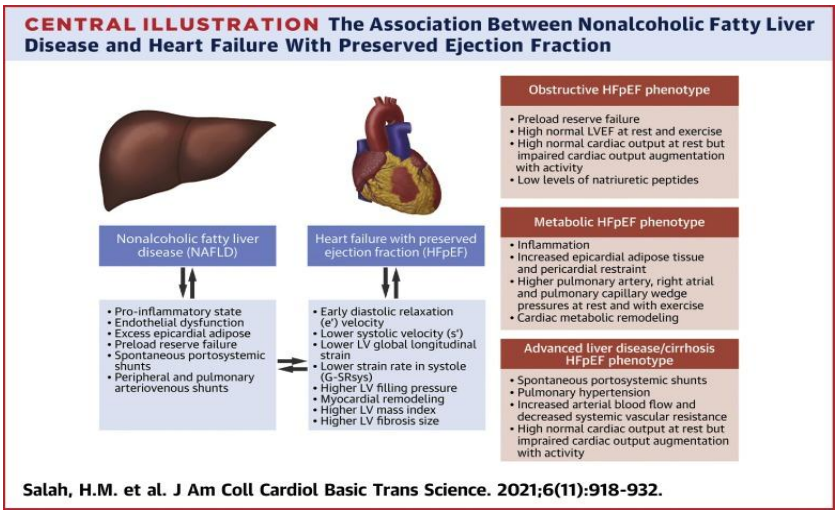
It has been shown that CVD risk in NAFLD patients is associated with increased thickness of carotid intima-media complex, which reflects the manifestation of subclinical atherosclerosis and serves as an important predictor of the risk of myocardial infarction and atherosclerotic plaques in carotid arteries [9-11]. The observed relationship between increased carotid intima-media thickness and the presence of NAFLD has been independently confirmed in several studies showing that the presence of NAFLD is associated with increased intima-media thickness, regardless of the presence of traditional cardiometabolic risk factors [12-14]. It was shown in the work that the degree of histological changes in the liver in NAFLD patients had a strong correlation with the manifestations of atherosclerotic changes in the carotid arteries, regardless of the classical risk factors, indicating that the degree of changes in the liver tissue plays an important role in the progression of atherosclerosis [15].

Currently, it is proved that myocardial steatosis is present in patients with steatohepatosis, which is a predictor of left ventricular dysfunction [16]. Coronary artery calcification determined by computed tomography plays an important role in increasing the risk of CVD [17], and the presence of NAFLD in patients is an independent risk factor of coronary artery calcification [18]. There is evidence that NAFLD correlates independently with impaired diastolic function of the left ventricle, which has been shown in NAFLD patients without obesity, arterial hypertension, type 2 diabetes, in whom impaired left ventricular geometry and signs of diastolic dysfunction were detected [19].

The increased risk of congestive heart failure in patients with NAFLD is considered to be of some importance. In 2 population-based cohort studies including more than 7000 people, it was shown that the presence of NAFLD with elevated transaminase levels was an independent risk factor for heart failure [10, 11]. There are data showing that echocardiographic signs of sclerotic changes of aortic valve had a clear association with the presence of NAFLD, which was an independent risk factor for these changes of the valve [12].

In recent years, it has been shown that in the early stages of NAFLD, patients have an increased content of endothelin precursor cells, the increase in the number of which is directly determined by the severity of NAFLD [13]. It is believed that the increased number of these cells arises as a result of the body's response to endothelial damage to compensate and repair the damaged endothelium, but this compensatory mechanism is unstable and quickly depletes, leading to the progression of systemic endothelial damage. There is a study showing that NAFLD is a serious stimulus for the progression of insulin resistance and dyslipidemia with increased production of triglycerides and low-density lipoproteins, which is a significant risk factor for the formation and progression of systemic atherosclerotic manifestations [14].

Picture 1



Reduced production of adiponectin, which has antifibrotic, antiatherogenic and anti-inflammatory effects, combined with increased production of leptin, which has the opposite effects, promotes the progression of steatohepatosis into steatohepatitis and increased risk of CVD in patients with NAFLD [15].

Genetic mechanisms are of certain importance in the development and progression of CVD in NAFLD patients. In particular, the presence of PNPLA3 GG genotype (patatin-like domain containing phospholipase 3) has been shown to be associated with the severity of atherosclerotic changes in carotid arteries in young NAFLD patients [15]. Variants of the PNPLA3 gene may be associated with increased lipid accumulation in the arterial wall and induce the release of the adhesion molecule, ICAM-1, leading to an increased risk of myocardial infarction and stroke. Thus, the current literature suggests that NAFLD is an independent factor of increased cardiovascular risk, and the risk of death from cardiac pathology may be higher in patients with nonalcoholic steatohepatitis and severe fibrosis compared to those with the initial stage of the disease - steatosis. Given this high risk of CVD, patients with NAFLD should be screened for cardiovascular disease. Conversely, when monitoring a patient with CVD, we should not forget about the possibility of NAFLD, which aggravates the course of cardiovascular disease. It is not for nothing that such "cross screening" (in patients with NAFLD for MS and CVD, and in patients with MS and/or CVD for NAFLD) is included in current international recommendations on the diagnosis and treatment of NAFLD [18]. Therefore, non-drug and drug therapy of NAFLD patients, especially at the stage of steatosis, is extremely important in terms of reducing their risk of formation and progression of cardiovascular pathology.

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