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Hepatocardial relationships in non-alcoholic fatty liver disease: issues of epidemiology, diagnosis, prognosis

Renata R. Savzikhanova[1], Dinara O. Subkhangulova[1], Elena V. Khazova[1,2]

[1]Kazan State Medical University, Kazan, Russia;
[2]Kazan (Volga Region) Federal University, Kazan, Russia

ABSTRACT

World statistics indicate a steady increase in the prevalence of non-alcoholic fatty liver disease, which correlates with the pandemics of obesity and diabetes, which are quite common in Russia. The commonality of cardiometabolic risk factors, the high global prevalence of non-alcoholic fatty liver disease and atherosclerotic cardiovascular diseases generates the interest of researchers in studying hepatocardial relationships. Currently, non-alcoholic fatty liver disease is positioned as a hepatic manifestation of a multisystem disorder, heterogeneous in underlying causes, manifestations, course and outcomes. The purpose of this review was to analyze hepatocardial relationships based on publications. 76 sources on the epidemiology of non-alcoholic fatty liver disease, published from 2011–2023 in journals indexed in Pubmed and eLibrary, were analyzed. Age and gender aspects of the development of non-alcoholic fatty liver disease were considered. The pathogenetic mechanisms of hepatocardial relationships, which were closely related to systemic inflammation, insulin resistance, metabolic syndrome and its components, were highlighted. The criteria and methods for diagnosing non-alcoholic fatty liver disease and metabolic-associated liver disease were outlined. Recent studies demonstrated the presence of hepatocardial connections, characterized by an increased risk of developing atherosclerosis, cardiomyopathy and rhythm disturbances, changes in the structural and functional parameters and geometry of the heart, as well as diastolic dysfunction, which may precede and/or contribute to the development of chronic heart failure in patients with non-alcoholic fatty liver disease. The article presents data on non-alcoholic fatty liver disease as a new factor associated with the development of adverse cardiovascular events to a greater extent than the outcome of liver diseases themselves, which confirms the need for primary and secondary prevention of cardiovascular diseases in this cohort of patients.

Keywords: non-alcoholic fatty liver disease; cardiovascular diseases; diagnostics; epidemiology; forecast.

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Гепатокардиальные взаимоотношения при неалкогольной жировой болезни печени: вопросы эпидемиологии, диагностики, прогноза

Р.Р. Савзиханова[1], Д.О. Субхангулова[1], Е.В. Хазова[1,2]

[1] Казанский государственный медицинский университет, г. Казань, Россия;
[2] Казанский (Приволжский) федеральный университет, г. Казань, Россия

АННОТАЦИЯ

Мировая статистика свидетельствует о неуклонном росте распространённости неалкогольной жировой болезни печени, коррелирующей с пандемиями ожирения и сахарного диабета, достаточно распространёнными в России. Общность факторов кардиометаболического риска, высокая глобальная распространённость неалкогольной жировой болезни печени и атеросклеротических сердечно-сосудистых заболеваний формирует интерес исследователей к изучению гепатокардиальных взаимоотношений. В настоящее время неалкогольную жировую болезнь печени позиционируют как печёночное проявление мультисистемного расстройства, неоднородного по основным причинам, проявлениям, течению и исходам. Целью настоящего обзора был анализ гепатокардиальных взаимоотношений на основе публикаций. Проанализировано 76 источников, посвящённых эпидемиологии неалкогольной жировой болезни печени, опубликованных в 2011–2023 гг. в журналах, индексируемых в Pubmed и eLibrary. Рассмотрены возрастные и половые аспекты развития неалкогольной жировой болезни печени. Освещены патогенетические механизмы гепатокардиальных взаимоотношений, находящихся в тесной связи с системным воспалением, инсулинорезистентностью, метаболическим синдромом и его компонентами. Изложены критерии и методы диагностики неалкогольной жировой болезни печени и метаболически-ассоциированной болезни печени. Исследования последних лет демонстрируют наличие гепатокардиальных связей, характеризующихся повышением риска развития атеросклероза, кардиомиопатии и нарушением ритма, изменением структурно-функциональных параметров и геометрии сердца, а также диастолической дисфункцией, которые могут предшествовать и/или способствовать развитию хронической сердечной недостаточности у пациентов с неалкогольной жировой болезнью печени. В статье приведены данные о неалкогольной жировой болезни печени как новом факторе, ассоциированном с развитием неблагоприятных кардиоваскулярных событий в большей степени, чем исход самих заболеваний печени, что подтверждает необходимость первичной и вторичной профилактики сердечно-сосудистых заболеваний у данной когорты пациентов.

Ключевые слова: неалкогольная жировая болезнь печени; сердечно-сосудистые заболевания; диагностика; эпидемиология; прогноз.

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Non-alcoholic fatty liver disease (NAFLD) is a significant global issue that is becoming more prevalent as a public health concern [1, 2]. Z.M. Younossi's 2016 meta-analysis reveals that NAFLD and another disease co-occur in 25.24% of the global population [3]. The global prevalence of NAFLD was determined to be 29.8% in a separate meta-analysis conducted by M.N. Le et al. (2022), which included 245 cases (n=5,399,254) [4]. After analyzing the global prevalence of NAFLD, J. Li et al. (2019) reported the disease was present in 42.6% of the population in North Africa, 34.5% in the Middle East, 30.8% in Asia and Latin America, and 22.3% in Japan [5].

In a recent meta-analysis, Z.M. Younossi et al. (2023) determined that the global incidence of NAFLD was 32.16%. The incidence in different geographical zones is as follows: 44.4% in Latin America, 36.5% in the Middle East and North Africa, 33.83% in South Africa, 33.07% in Southeast Asia, 31.2% in North America and Australia, 29.7% in East Asia, and 25.1% in Western Europe [3].

The dynamics of NAFLD prevalence in Russia over the course of eight years are reflected in the epidemiologic studies DIREG 1 (2007) [6] and DIREG 2 (2015) [7]. The prevalence of NAFLD was 26.1% and 37.3% among patients, with the majority exhibiting hepatic steatosis (79.9% and 80.3%), steatohepatitis (17.1% and 16.8%), and cirrhosis (3% and 2.9%) [8]. According to a meta-analysis of five epidemiological studies that was published recently (2022), the prevalence of NAFLD in the Russian adult population is 27.56% [9].

Several authors have noted sex- and age-related disparities in NAFLD prevalence. Accordingly, O.M. Drapkina and V.T. Ivashkin (2014) observed a significant prevalence of NAFLD among individuals aged 50–59 years (31.1%), with a relatively reduced incidence in the 40–49 and 60–69 age groups (23.6% and 18.1%, respectively) [10]. O.O. Sharkhun observed a higher prevalence of NAFLD in males (63.4%) across all age groups than in females (36.6%; $p < 0.001$) [11]. This finding is consistent with the data of E. Hashimoto et al. (2005), who discovered a fivefold higher incidence of hepatic steatosis in males aged 53 years over females [12].

A. Lonardo et al. identified several sex-specific characteristics in a 2019 study. The prevalence of NAFLD was 37% among males and 23% among females. For males, the peak age of diagnosis was 40 years, while for females, it was 50 years. Among females of reproductive age, the lower prevalence of NAFLD may be attributed to the protective properties of estrogen. However, the risk of developing NAFLD and an unfavorable disease course increases after menopause [14].

The current understanding of NAFLD is not limited to the mere progression of hepatic pathologic changes. Rather, it is considered the hepatic component of a multisystem metabolic dysfunction, which contributes to an elevated risk of cardiometabolic conditions [15–17], increases mortality due to cardiovascular complications, oncologic consequences, and the rapid progression of NAFLD to the terminal stage [18–22].

The review aimed to analyze hepatocardial relationships based on publications. The review is intended to raise the awareness and sensitivity of general practitioners and cardiologists to the issue of NAFLD, its prevalence, and the feasibility of defining the disease to identify high-risk groups.

We searched and analyzed sources in the PubMed and eLibrary databases using the keywords “NAFLD and cardiovascular disease,” “NAFLD and heart failure.” The search period spanned 2011–2023. The analysis excluded publications that contained only abstracts, summaries, and duplicate information.

TERMINOLOGY AND DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE

The term “NAFLD” encompasses a spectrum of progressive pathological changes in the liver, including steatosis, which is predominantly benign, and liver conditions with the potential for progression, such as non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma [23–26].

The absence of specific symptoms associated with liver steatosis complicates the diagnosis of NAFLD in its early phases. However, the recognition of NAFLD as an early predictor of elevated cardiovascular risk and type 2 diabetes mellitus (DM) emphasizes the importance of its timely detection. The diagnosis of NAFLD is considered an exclusionary diagnosis, in accordance with contemporary concepts, and is based on three criteria:

1) The presence of hepatic steatosis (detected by serum biomarkers or scales, imaging techniques, or liver histology).

2) Lack of alcohol abuse (< 20 g/d for women and < 30 g/d for men).

3) Absence of other secondary causes of hepatic steatosis (such as viral diseases, hemochromatosis, autoimmune hepatitis, α_1-antitrypsin deficiency, Wilson disease, or use of potentially hepatotoxic drugs).

A puncture biopsy is the gold standard for diagnosing NAFLD, and enables the differentiation between NAFLD and non-alcoholic steatohepatitis and the quantification of liver fibrosis. Non-alcoholic steatohepatitis is diagnosed based on histopathological features, including the presence of ⩾ 5% steatotic hepatocytes with associated inflammation and increased size, irrespective of the presence of liver fibrosis. The histological confirmation of progressive fibrosis is provided by the presence of "bridging fibrosis" (stage F3 of the Kleiner classification) or cirrhosis (stage F4).

Unlike liver cirrhosis caused by other etiologies, cardiac cirrhosis is characterized by a distinct histological appearance. The hepatic and portal veins exhibit identical degrees of fibrosis, and the centrilobular zone exhibits more pronounced alterations than the periportal zone [29].

In chronic heart failure (CHF) patients, the liver parenchyma exhibits a “nutmeg” pattern, with alternating areas

of venous stasis (reddish) and fibrosis (yellow brown) [30]. The limitations of routine liver biopsy as a screening or diagnostic procedure are well-established, including its invasiveness and potential risk to the patient [29, 31, 32].

The diagnostic validity of non-invasive methods for NAFLD remains a subject of ongoing debate within the scientific community. In accordance with international clinical recommendations, V.T. Ivashkin et al. assert that ultrasound is the primary method for verifying liver steatosis [8]. Zh.A. Aldasheva emphasizes the significance of precisely defining the inferior margin of the liver, which remained unaltered in 78.3% of patients with steatosis and 47.7% of those with steatohepatitis. In contrast, the inferior margin of the liver exhibited a more rounded appearance in all cirrhosis patients [33].

Laboratory markers of NAFLD from routine blood biochemical analysis are employed as a preliminary strategy for assessing liver damage, as they are both cost-effective and widely available [34]. Alternatively, scales that incorporate clinical parameters and blood markers of fibrosis are employed.

Consistent with the prevailing federal clinical guidelines, the following calculation indices and scales are universally recognized as the most informative:

– FIB-4 (Fibrosis-4), FLI (Fatty Liver Index), NASH test;

– Scales NFS (NAFLD Fibrosis Score), HAIR (Hypertension, ALT, and Insulin Resistance), and BARD (BMI, AST/ALT Ratio, and Diabetes Score).

The Hepatic Steatosis Index (HSI) is also of relevance, as it is a non-invasive method of diagnosing NAFLD, exhibits high sensitivity and specificity, and is the least expensive. The Fibrotest panel is the primary tool employed in Russia [35, 36].

Recently, a strong association has been demonstrated between NAFLD and the metabolic syndrome and its components. Patients with NAFLD exhibit progressive disorders of lipid and carbohydrate metabolism, and an increased risk of atherosclerosis and arterial hypertension [37–39]. In 2020, a new term, "metabolic-associated fatty liver disease," was proposed by an international group of experts from 22 countries. This term emphasizes the pathogenetic role of metabolic dysfunction in the development and progression of this liver disease [15, 40]. In patients with hepatic steatosis, the presence of one of the criteria (presence of overweight/obesity, type 2 DM, or evidence of metabolic dysregulation) is recognized as a diagnostic standard [15].

The development of NAFLD results for the interaction of numerous genetic and environmental factors, which is referred to as the so-called "multiple parallel shocks" concept [24, 41–43]. Dietary characteristics, including hypodynamia, dysbiosis of the intestinal microbiota, and excessive saturated fat consumption, are adaptive factors [24, 44–46].

In patients with visceral obesity and insulin resistance, along with increased fat degradation, the free fatty acid levels in the blood and serum increase due to enhanced fatty acid synthesis and decreased oxidative processes in mitochondria. This leads to triglyceride accumulation and decreased lipid excretion by hepatocytes, leading to fatty liver dystrophic changes such as steatosis. However, decreased insulin clearance in hepatic steatosis can cause hyperinsulinemia. Additionally, the direct lipotoxic effects on pancreatic β-cells and hepatocytes are augmented by the increased accumulation of free fatty acids, which stimulates hepatic glycogenolysis, thereby increasing insulin resistance and hyperinsulinemia.

Prolonged hypertriglyceridemia in insulin resistance impairs endothelium-dependent vasodilation and causes oxidative stress. This results in the formation of lipid peroxidation products, reactive oxygen species, and cytokines, all of which are significant risk factors for early atherosclerosis. Activation of stellate cells upon exposure to aldehyde, a byproduct of lipid peroxidation, triggers the chemotaxis of neutrophils and fibrogenesis. Reduction of protective properties of hepatocyte membrane causes mitochondrial injury, dissociation of tissue respiration processes, apoptosis and necrosis of hepatocytes, activation of collagen synthesis [47–50].

The exact mechanisms of the hepatocardial relationship remain unclear; however, the pathophysiological continuum between NAFLD and CHF with preserved left ventricular ejection fraction is partially attributable to the secretion of adipokines and proinflammatory cytokines [19, 51].

Central perivisceral adipose tissue exhibits intense endocrine activity with pronounced autocrine and paracrine effects. Adipokines participate in the development of insulin resistance, steatosis, and consequently, non-alcoholic steatohepatitis. Leptin is synthesized by adipose tissue, cardiac tissue, and the digestive system. It exerts profibrotic activity at the hepatic tissue level by activating phosphoinositide 3-kinase (PI3K), which in turn promotes the synthesis of osteopontin.

The worsening of insulin resistance in NAFLD predisposes to the formation of atherogenic dyslipidemia, stimulates the synthesis of proinflammatory, profibrogenic and vasoactive mediators that may contribute to the progression of coronary atherosclerosis and the development of myocardial remodeling and hypertrophy, leading to heart failure [52, 54].

The hemodynamic mechanism that underlies hepatocyte damage in patients with CHF of ischemic etiology is a result of elevated physical pressure in the hepatic sinusoids and bile ducts. This is accompanied by elevated serum levels of γ-glutamyl transpeptidase and alkaline phosphatase in the early stages of CHF, which are correlated with the functional class of CHF [53]. Venous stasis, ischemia due to reduced myocardial contractility, and arterial hypoxemia contribute to the development of hypoxia in liver tissue and ischemic damage [55].

Thus, NAFLD not only impacts the liver but also a diverse array of lipid and carbohydrate disorders that contribute to the development and progression of atherosclerotic cardiovascular disease, the primary cause of mortality in the NAFLD cohort [56–58].

RELATIONSHIP BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Most studies have demonstrated a higher frequency of biochemical markers of atherosclerosis in patients with NAFLD than in those without it [31]. Two meta-analyses have verified the increased prevalence of subclinical atherosclerosis, increased plaque/thickness of the carotid intima-media complex, arterial stiffness, and endothelial dysfunction in NAFLD patients [59, 60].

The following conditions are known to occur concomitantly with NAFLD: hypercholesterolemia (68.8%), dyslipidemia (75.9%), and arterial hypertension (69.9%) ($p < 0.001$) [11]. According to A.M. Minhas et al. (2022), NAFLD patients exhibit a higher frequency of cardiovascular comorbidities, including arterial hypertension (81.7% vs. 53.5%), DM (65.1% vs. 17.1%), stroke (7.3% vs. 4.1%), coronary heart disease (14.9% vs. 8.4%), and CHF (10.5% vs. 3.5%) than those without NAFLD [61].

A meta-analysis of 164,494 participants conducted by S. Wu et al. (2016) revealed that NAFLD was linked to an elevated risk of developing cardiovascular disease, coronary heart disease, arterial hypertension, and atherosclerosis. However, the analysis did not uncover a significant association between NAFLD and all-cause or cardiovascular mortality [62].

In a 2021 study, Japanese researchers M. Yoneda et al. analyzed the JMDC database publications from 2013 to 2019 and discovered a higher incidence of cardiovascular disease in the presence of NAFLD (compared with those without NAFLD). The researchers calculated odds ratios (OR) of 2.82 [95% confidence interval (CI) 2.64–3.01] and 0.97 (95% CI 0.94–1.01). In the absence of adjustment, the corresponding ORs for cerebral infarction, coronary heart disease, and cardiovascular disease were 1.3 (95% CI 0.94–1.80), 3.08 (2.85–3.33), and 2.89 (2.68–3.12) in the NAFLD group relative to the non-NAFLD group. The ORs for patients with NAFLD adjusted for gender, age, and smoking status were 1.32 (95% CI 0.95–1.83) for cerebral infarction, 2.70 (2.50–2.92) for coronary heart disease, and 2.56 (2.37–2.77) for cardiovascular disease. Hypertriglyceridemia (63.6% and 13.1%) and DM (20.2% and 4.2%) were more frequently observed in NAFLD patients than in those without NAFLD [63].

Obesity, DM, and NAFLD are all characterized by systemic low-grade inflammation, as determined by H. Tilg et al. (2017). [64]. H.E. Park et al. (2019) reported that hepatic lipid accumulation correlates with coronary plaques, especially uncalcified plaques [65], while hepatic steatosis and fibrosis are significantly associated with cardiac diastolic dysfunction [66]. A study conducted by O.M. Drapkina et al. (2016) demonstrated that patients with CHF exhibited an increase in chamber size, myocardial mass, wall thickness, and epicardial fat in NAFLD [39, 67]. In a study involving 222 patients, A. Mantovani et al. (2015) identified a significant association between NAFLD and left ventricular hypertrophy, and 59% of patients exhibited CHF with preserved left ventricular ejection fraction [68].

In the context of preserved left ventricular ejection fraction, certain authors propose that NAFLD is a novel risk factor for CHF [19]. In multivariate logistic regression models adjusting for age, race/ethnicity, and sex, A.M. Minhas et al. (2022) discovered that participants with NAFLD were 3.5 times more likely to be diagnosed with CHF. The authors determined that older age, male sex, the presence of diabetes, and coronary artery disease were associated with a greater likelihood of CHF in participants with established NAFLD. Participants with NAFLD had a higher risk of all-cause mortality compared to those without NAFLD [61].

G. Targher et al. (2016) examined the OR for combined fatal and non-fatal cardiovascular events (OR=1.63; 95% CI 1.06–2.48) and for non-fatal cardiovascular events (OR=2.52; 95% CI 1.52–4.18) in NAFLD. Patients with more severe NAFLD exhibited a greater risk of fatal cardiovascular events and a higher risk of combined cardiovascular events (fatal and non-fatal) [58].

M. Fudim et al (2021) reported a higher risk of developing CHF during 14.3 months of follow-up in patients with NAFLD compared to patients without NAFLD (6.4% vs. 5.0%; $p < 0.001$) [70]. The risk of developing CHF was more strongly associated with NAFLD when left ventricular ejection fraction was preserved, as opposed to CHF when left ventricular systolic function was reduced [71].

In a review of six cohort studies (n=10,979,967 participants, 55.5% women), the median prevalence of NAFLD was 22.2%. Patients with NAFLD had a higher risk of CHF compared to participants without NAFLD in the unadjusted model and after multivariate adjustment. The absolute risk difference for CHD in patients with NAFLD compared with participants without NAFLD after multivariate adjustment was 11.0 per 10,000 person-years [69].

A meta-analysis by A. Mantovani et al. (2022) revealed that NAFLD (diagnosed by blood biomarkers, imaging, or liver histology) was linked to an increased risk of new-onset CHF, which remained significant after adjustment for age, gender, ethnicity, obesity, arterial hypertension, type 2 DM and other cardiometabolic risk factors [72].

K. Wijarnpreecha et al. (2018) discovered a significant association between NAFLD and diastolic dysfunction of the heart [73].

T.G. Simon et al. (2022) examined the risk of major cardiovascular events, including the risk of CHF, according to the presence and histologic severity of NAFLD. Despite adjusting for prevalent cardiometabolic risk factors, the risk of developing CHF was higher in the group of patients with NAFLD than in those without NAFLD. The incidence of CHF events increased progressively with the worsening severity of NAFLD. The highest incidence rates were observed in patients with non-cirrhotic fibrosis and cirrhosis [74].

CONCLUSIONS

Obesity and diabetes are the primary causes of the non-communicable pandemic of NAFLD that is affecting the population of developed countries. These are quite common in Russia, as evidenced by the literature [22, 75, 76]. Based on available data it is evident that the clinical burden of NAFLD is not limited only to liver-related complications. It also adversely affects many extrahepatic organs and systems, including the heart and vascular system [20–22].

The presence of NAFLD has been observed to induce a variety of alterations in the organism. These include an increase in proinflammatory cytokine synthesis, insulin resistance, oxidative stress, an atherogenic lipid profile, the activation of the renin-angiotensin-aldosterone system, alterations in the intestinal microbiota, and an increase in bioactive microbial metabolite levels. The risk of CHF is increased by the combination of genetic predisposition and these factors, which can lead to microvascular dysfunction, alterations in myocardial function, and hypertrophy [19].

The timely diagnosis and prescription of complex therapy are advisable in view of the high prevalence of NAFLD in the population and the associated risk of potential hepatic complications and adverse cardiometabolic events [24]. Despite the existence of numerous potential pathophysiologic mechanisms through which NAFLD may adversely impact cardiac structure and function and the increased risk of new-onset CHF, the causal relationship has yet to be proven. This creates prerequisites for further study of the complex relationship between NAFLD and CHF.

ADDITIONAL INFORMATION

Authors' contribution. R.R.S. — resources, formal analysis, investigation, writing — original draft; D.O.S. — investigation, formal analysis, methodology; E.V.Kh. — conceptualization, visualization, formal analysis, investigation, writing — review and editing, supervision, validation, data curation, project administration.

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AUTHORS' INFO

Renata R. Savzikhanova, Student, Kazan State Medical University, Kazan, Russia;
ORCID: 0009-0008-5906-7476;
eLibrary SPIN: 1658-9382;
e-mail: renatasavzihanova@mail.ru

Dinara O. Subkhangulova, Student, Kazan State Medical University, Kazan, Russia;
ORCID: 0000-0002-0147-8503;
eLibrary SPIN: 8176-0595;
e-mail: dinara.subkhangulova0404@yandex.ru

***Elena V. Khazova**, MD, Cand. Sci. (Med.), Assoc. Prof., Depart. of Propaedeutics of Internal Diseases Named after Professor SS. Zimnitsky, Kazan State Medical University; Research, UNIL "New Professional Competences in Health Preservation", Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Russia;
ORCID: 0000-0001-8050-2892;
eLibrary SPIN: 7013-4320;
e-mail: hazova_elena@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

Савзиханова Рената Рашидовна, студ., ФГБОУ ВО Казанский ГМУ Минздрава России, г. Казань, Россия;
ORCID: 0009-0008-5906-7476;
eLibrary SPIN: 1658-9382;
e-mail: renatasavzihanova@mail.ru

Субхангулова Динара Олеговна, студ., ФГБОУ ВО Казанский ГМУ Минздрава России, г. Казань, Россия;
ORCID: 0000-0002-0147-8503;
eLibrary SPIN: 8176-0595;
e-mail: dinara.subkhangulova0404@yandex.ru

***Хазова Елена Владимировна**, канд. мед. наук, доц., каф. пропедевтики внутренних болезней имени профессора С.С. Зимницкого, ФГБОУ ВО Казанский ГМУ Минздрава России; науч. сотр., УНИЛ «Новые профессиональные компетенции по здоровьесбережению», Институт фундаментальной медицины и биологии, ФГАОУ ВО Казанский (Приволжский) федеральный университет, г. Казань, Россия;
ORCID: 0000-0001-8050-2892;
eLibrary SPIN: 7013-4320;
e-mail: hazova_elena@mail.ru