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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ И ВОЗМОЖНОСТИ ЕЕ ТЕРАПИИ (ОБЗОР)

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Non-Alcoholic Fatty Liver Disease and Possibilities of Its Therapy (Review)

Резюме

НАЖБП является актуальной междисциплинарной проблемой, учитывая ее высокую распространенность во всем мире, а также роль в развитии и прогрессировании кардиометаболических нарушений, онкологических заболеваний. В обзоре проанализированы современные данные, касающиеся эпидемиологии, механизмов развития неалкогольной жировой болезни печени и современных возможностей ее терапии. Проблема НАЖБП хорошо изучена. При этом публикуются новые данные, касающиеся механизмов ее развития, влияния на другие метаболически ассоциированные заболевания. Это доказывает, что необходим дальнейший поиск новых схем лечения таких пациентов, с целью улучшения прогноза и снижения кардиометаболических рисков. Особое внимание в обзоре было уделено возможностям гепатопротективной терапии при стеатозе печени.

Ключевые слова: *неалкогольная жировая болезнь печени, лечение, гепатопротекторы, средиземноморская диета*

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Abstract

NAFLD is an urgent multidisciplinary problem, given its high prevalence worldwide, as well as its role in the development and progression of cardiometabolic disorders and cancer. The review analyzed current data regarding epidemiology, mechanisms of development of non-alcoholic fatty liver disease and current possibilities of its therapy. The problem of NAFLD is well understood. At the same time, new data are published regarding the mechanisms of its development, the impact on other metabolically associated diseases. This proves that a further search for new treatment regimens for such patients is necessary in order to improve the prognosis and reduce cardiometabolic risks. Particular attention in the review was paid to the possibilities of hepatoprotective therapy for hepatic steatosis.

Key words: *non-alcoholic fatty liver disease, treatment, hepatoprotectors, Mediterranean diet*

Conflict of interests

The authors declare no conflict of interests

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NAFLD — non-alcoholic fatty liver disease, MAFLD — metabolic-associated fatty liver disease

Introduction

According to the modern concepts, non-alcoholic fatty liver disease (NAFLD) is an important interdisciplinary problem. Pathogenetically it is often associated with obesity, diabetes mellitus, cardiovascular diseases, and even hepatocellular carcinoma [1, 2].

NAFLD is currently in the lead among all liver diseases [3]. For example, based on the Russian ESSE RF-2 study, fatty liver disorders were detected in 38.5 % males and 26.6 % females [4]. In comparison, it is reported in almost 33 % European citizens, while in Asian countries this parameter does not exceed 18 % [4]. The global prevalence in the general population is somewhat variable, ranging from 6.3 to 33 % [3, 5]. Accounting for the fact that NAFLD verification requires morphological confirmation in the majority of cases, one can propose that these values might be significantly higher.

It is important to underline that fatty liver disease increases the risk of mortality not only from liver diseases (cirrhosis, hepatocellular carcinoma), but also from other associated diseases, i.e. diabetes mellitus, cardiovascular diseases [3].

Despite the prolonged and thorough NAFLD analysis, the current issue of possible drug therapy remains debatable. Studies aimed at searching for optimum treatment protocols of this disease that could lead to the fatty liver regression and cardiometabolic risk decrease are actively ongoing.

Review purpose: analyzing data concerning epidemiology, mechanisms of non-alcoholic fatty liver disease, and its modern treatment options.

Materials and Methods

Russian and foreign publications for the topic analyzed were searched in PubMed, RINC, and eLibrary databases with the use of the following keywords: non-alcoholic fatty liver disease, obesity, cardiovascular risks, treatment, hepatoprotective agents, Mediterranean diet. The information from literature reviews, articles, meta-analyses published within the latest 10 years was analyzed. Information selection criteria: scientific articles in peer-reviewed journals reflecting modern approaches to the NAFLD issue, with specific descriptive statistics. Highly cited articles from leading journals were in priority.

In this review we analyzed the changes in the scientific NAFLD paradigm (etiology, pathogenesis) and also discussed modern approaches to its treatment.

NAFLD Issue and Modern Approach to It

The issue of NAFLD has been analyzed for a long time. In 1849 the Austrian pathologist Carl von Rokitansky detected that the fatty liver dystrophy was directly associated with overweight [6, 7]. Further on, H. Taler (1962) detected hepatic alterations typical for persons abusing alcohol in patients without the toxic component [8]. In 1980 the German scientist Yurgen Ludwig from the Mayo clinic (USA) along with his colleagues formulated the common term "non-alcoholic steatohepatitis" [9]. In 2000 American hepatologists proposed the term "non-alcoholic fatty liver disease". Meanwhile, the Russian physicians started using the latter term only in 2002 [10, 11].

In 2020, a new term "Metabolic-associated fatty liver disease" (MAFLD) was proposed [3, 12]. With the new term scientists underline the association of the fatty liver disease with the metabolic dysfunction; diagnostic criteria were also developed for this diagnosis.

In 2023 the International Expert Group on behalf of the Liver Associations proposed a new nomenclature for the fatty liver disease — Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). This term presumes hepatic steatosis in combination with at least one cardiometabolic risk factor (obesity, diabetes mellitus, hypertension, dyslipidemia). This terminology has been adopted in the Russian Federation, and it is recommended to use new optimized diagnostic criteria. Nevertheless, medical documents still operate designations adopted in ICD-10 [3].

Currently it is considered that non-alcoholic fatty liver disease is a chronic liver disease associated with

metabolic dysfunction, excessive accumulation of lipids (triglycerides) in the hepatic parenchyma, that leads to multiple complications affecting other organs and systems [2, 3].

Pathogenesis of NAFLD and Associated Conditions

Currently two non-alcoholic fatty liver disease forms are reported — steatosis and steatohepatitis. It was considered earlier that NAFLD always started with steatosis. A "two-hit" concept proposed by Day C.P. and James O.F. was a long-term concept supporting this theory. The researchers explained that the first hit was due to the deposition of enhanced triglyceride amounts in the hepatic parenchyma. The second step was associated with cytokine and toxic liver overload, leading to cellular inflammation [13, 14]. Currently steatosis and steatohepatitis are considered independent NAFLD variants according to the "multiple-hit" theory. The latter explains that the disease develops in genetically predisposed patients under the effects of multiple environmental factors. The "multiple-hit" concept defines the whole multifaceted NAFLD pathogenesis. This presumes insulin resistance, imbalance between adipokines and cytokines, dietary issues, enhanced intestinal permeability, etc. [3, 15, 16].

Impaired insulin sensitivity is one of the key mechanisms promoting fatty liver dystrophy and the metabolic syndrome. This promotes metabolic disorders, leading to the increased production of free fatty acids (FFAs). For example, it is well-known that adipocytes produce about 60 % FFAs. Thus, the association of obesity and NAFLD is made clear [3, 15, 16]. β-oxidation of FFAs is impaired due to their excessive amounts entering the liver. Mitochondrial dysfunction provokes oxidative stress. This leads to decreased synthesis and secretion of low-density lipoproteins, which leads to the imbalance between FFA influx and disposal. This leads to the accumulation of triglycerides in the hepatocyte, which lipolysis again forms FFAs that directly injure hepatocytes [3]. Oxidative stress leads to the formation of reactive oxygen species and activation of lipid peroxidation mechanisms, provoking hepatocyte injury [3, 15, 16].

Intestinal flora also plays a huge role in the development of NAFLD. Impaired microbiome leads to the overuse of protective liver mechanisms, which in turn enhances the production of inflammatory markers (i.e. cytokines). This induces inflammation and fibrosis in the liver parenchyma. Intestinal flora also actively participates in the metabolism of bile acids which mediate the sensitivity of tissues to insulin [3, 17].

As a result of all mechanisms described above, chronic inflammation develops, which leads to the activation of Kupffer cells, stellate and fat-storing cells. They start active collagen production. This leads to hepatitis progression and further fibrosis.

Besides processes in the liver, NAFLD activates the mechanism of development and progression of cardiovascular diseases, chronic kidney disease, with the increased risk of malignancies [18]. Systemic inflammation is key to these conditions. For example, it is well-known that proatherogenic lipoproteins are excessively produced in NAFLD. This leads to enhanced thrombogenesis and vascular injury [3, 18]. Gluconeogenesis and glucose depoing processes are impaired in steatosis, with subsequent decrease in tissue sensitivity to insulin and possible onset of diabetes mellitus. It has also been confirmed that endocrine disorders (gynecomastia, infertility, decreased libido, testicular atrophy) may emerge with the prolonged fatty liver alterations [18].

NAFLD Treatment

The scientists' opinions have changed not only towards NAFLD and mechanisms, but also its treatment. Accounting for the multifaceted etiology and pathogenesis of this disease, the treatment should be complex, safe, and efficient [3].

The whole NAFLD treatment is essentially based on three milestones — physical activity, diet, and drug therapy.

Various groups of drug products and their combinations have been proposed while analyzing the issue of NAFLD. The key fact is that physical activity and diet have always been playing the foremost role in the treatment of liver diseases.

Diet is of utmost importance in NAFLD. Some scientists have considered that quick weight loss is required with the decreased amount of carbohydrates in the diet and consumption of larger fat amounts [19]. Others have proposed the interval diet ("healthy fasting") [19].

In 2016, the European Association of Liver Diseases, Diabetes Mellitus, and Obesity developed the main diet principles in those conditions. Gradual weight loss (5–10 % from baseline) can be achieved by decreasing the amount of calories consumed daily; limiting fatty foods and increasing the amount of complex carbohydrates, plant fibers, and proteins; eliminating toxic alcohol doses and fructose-rich products [20].

Currently the Mediterranean diet takes the lead among all diets used for the treatment of NAFLD [21].

The main principles of this diet are reflected in the so-called correct nutrition pyramid [21]. Products recommended for daily consumption are located at the pyramid base. The closer to the apex, the less should those food products be present in the weekly diet. Physical activity supports the pyramid. It should be selected

individually, accounting for the features of each patient. Moderate-tempo aerobic exercises are the most preferable ones [22, 23].

The Mediterranean diet is beneficial as it can not only decrease the body weight, but also maintain the results achieved within a prolonged time period. This diet type may lead to the recovery of metabolic disorders, which is especially important in liver disorders. Several scientific articles have demonstrated that this diet induces the regression of inflammatory and fibrous alterations in the parenchyma, as well as decreasing cardiometabolic risks [23]. Summing up the aforementioned facts, weight loss is the main goal of non-medication treatment. With that, physical exercises promote not only weight normalization, but also the normalization of metabolic processes. Some articles have also demonstrated that physical exercises decrease the fat contents in hepatocytes [23]. Systematic reviews and meta-analyses have established that adequate physical activity may lead to decreased lipid amounts in hepatocytes even in the absence of significant weight loss [24]. For example, a study conducted in 2017 enrolled 115 patients with NAFLD. All patients undertook aerobic exercises for 30–60 minutes 2–3 times a week for 6 months. The amount of hepatic fat was evaluated afterwards. The results showed that the amount of hepatic lipids decreased by 24.4 % [24].

Currently various groups of drugs are used in the treatment of NAFLD — from herbal drugs to bile acids and succinic acid derivatives. This variety of medications is associated with the multifaceted pathogenesis of hepatic steatosis. However, unfortunately, one can state that no universal drug potentially affecting all NAFLD mechanisms has been developed yet.

Hepatoprotective drugs are the main ones in the treatment of NAFLD [3]. The purpose of their administration is to slow down the progression of pathological processes directly in the hepatic tissue. The following effects are expected from hepatoprotective drugs: anticholestatic, antioxidant, antifibrotic, immune-modulating, etc. [3]. Many of them have multidirected effects and positively affect the cardiovascular system, restore carbohydrate and lipid metabolism disorders [3, 26, 27].

A large number of drugs with various mechanisms of action currently belong to this group. These include bile acid metabolites, a fixed combination of inosine + meglumine + nicotinamide + succinic acid + methionine (Remaxol), ursodeoxycholic acid, alpha-tocoferol acetate (vitamin E), ademethionine, etc. Every drug has its own evidence base [3].

Being a lipophilic antioxidant, vitamin E can be used in the treatment of NAFLD. The mechanism of its action presumes that due to the inhibition of hydroperoxide production it breaks the chain reaction of lipid peroxidation and promotes the elimination of free radicals [27].

It has been proven that the antioxidant ability of hepatocytes is depleted in chronic liver diseases [3]. It has been shown that the daily use of vitamin E in the dose of 800 international units decreases the severity of steatosis and inflammation [27]. Several articles demonstrated positive effects of using this drug in the form of cytolysis reduction, decreased inflammation activity, although no effects on liver fibrosis were confirmed [3, 27, 28]. In 2005 the meta-analysis showed that the use of large vitamin E doses increased the risks of mortality from other causes [28]. Those data were refuted later by other investigators [27, 28]. Currently the feasibility and safety of this drug still remains debatable, which limits its use.

A fixed combination of inosine + meglumine + nicotinamide + succinic acid + methionine (Remaxol) provides all effects expected from hepatoprotective drugs, including hepatoprotective, anticholestatic, antioxidant effects. Each Remaxol component plays its important role [3, 29].

Succinic acid directly affects the correction of mitochondrial dysfunction, which is the basic step of NAFLD pathogenesis. This is achieved due to antioxidant and antihypoxic effects of this component [29–31].

Nicotinamide (vitamin PP) is a source of nicotinamide-adenine-dinucleotide and nicotinamide-adenine-dinucleotide phosphate, which are coenzymes for many enzymes participating in oxidation-reduction reactions. Nicotinamide also participates in the metabolism of carbohydrates, normalizes the bowel function [30, 31].

Methionine is an essential amino acid required for growth maintenance and nitrogen equilibrium in the body. It is also used for the synthesis of choline required for the production of phospholipids. Methionin also participates in depleting the neutral fat deposits in the liver [30, 31].

Inosine has antihypoxic effects, enhances the energy balance in the whole body, participates in carbohydrate metabolism, enhances the activity of the Krebs cycle enzymes [30, 31].

Due to the unique multicomponent composition, Remaxol affects the main steps in the NAFLD pathogenesis; thus, it can be considered a universal hepatoprotective drug, which may be used as monotherapy.

Its positive effects on cholesterol metabolism have been demonstrated in several investigations [31, 32]. It is important to note that Remaxol can not only decrease the total cholesterol and triglyceride levels, but can also promote the increase in high-density lipoprotein levels. Several studies have demonstrated that the treatment with this drug leads to quick elimination of asthenic and dyspeptic syndromes [32]. In 2021, a multicenter open comparative trial was conducted among 317 patients to compare the effects of ademethionine and Remaxol.

The patients' general condition, laboratory parameters (cytolysis and cholestasis markers), lipid metabolism were evaluated. As a result, both drugs demonstrated positive results. However, in several parameters Remaxol was superior to ademethionine, e.g. concerning the decrease in pruritus severity, along with a quicker drop in bilirubin levels [31].

Ademethionine is a natural substance of the human body synthesized in the liver from L-methionine and adenosine triphosphoric acid. It is required for the synthesis of glutathione, which is considered a very important cellular antioxidant. If glutathione levels in the body decrease (e.g., in chronic liver diseases), the damaging effects of free radicals worsen. In turn this leads to mitochondrial dysfunction, hepatocellular apoptosis, and even possibly to hepatocellular carcinoma [33].

It is well-known that depressive disorders (increased irritability, fatigability, malaise, sleep disorders) are common in chronic liver diseases. The role of ademethionine in the elimination of asthenic syndrome has been demonstrated in several studies [33]. 18 controlled trials showed that the antidepressive effect of this drug had a similar efficacy to chloropiramine, minaprine, and imipranine [33]. Accounting for the latter fact, ademethionine is considered the drug of choice in such clinical situations.

Ursodeoxycholic acid is currently widely used in liver diseases, including NAFLD. It has been proven that this drug decreases inflammation, inhibits fibrosis progression, improves the lipid profile parameters [34, 35]. In 2018, a multicenter "Uspekh" trial enrolling 207 patients with NAFLD was arranged. All patients were administered an ursodeoxycholic acid drug for 6 months in a standard dose of 15 mg/kg of body weight. As a result, cytolysis was improved along with cholesterol metabolism parameters, while steatosis and fibrosis severity decreased as well [34, 35]. The role of ursodeoxycholic acid in lipophagy is currently being actively discussed.

Not only hepatoprotective drugs, but also those aimed at correcting comorbidities are currently used in the treatment of NAFLD. For example, glucagon-like peptide 1 analogues (liraglutide, semaglutide) and sodium-glucose co-transporter 2 inhibitors (ipragliflozin, dapagliflozin) are used in type 2 diabetes mellitus [3]. These drugs lead to weight loss, decreased insulin resistance and cytolysis levels, as well as diminish lipogenesis de novo [3, 36]. If NAFLD is combined with dyslipidemia and cardiovascular diseases, HMG-CoA-reductase inhibitors (statins) can be justified to achieve the target low-density lipoprotein levels. Several studies have demonstrated that statins induce the regression of steatosis, inflammation, and liver fibrosis [37, 38]. If HMG-CoA-reductase inhibitors are not tolerated or not efficient, ezetimib is recommended [39]. Fenofibrates are administered to decrease the cardiovascular risks and severity of cytolysis [3, 40].

One should also separately note a group of patients with NAFLD combined with obesity. It is well-known that weight loss promotes the regression of steatosis severity and steatohepatitis activity [41]. Patients not responding to non-medication treatment (diet, dosed physical activity) are administered drug products for the treatment of obesity [3]. For example, liraglutide or orlistat that promote weight loss facilitate the patient compliance with dietary recommendations and help to develop new dietary habits [42]. If lifestyle modifications and pharmacotherapy do not provide positive effects, bariatric surgery is recommended. The results of meta-analysis confirm positive effects of bariatric interventions on the course of non-alcoholic fatty liver disease. 88 % patients demonstrated the regression in steatosis and steatohepatitis severity, with fibrosis regression in 30 % patients [3, 42]. Indications to surgical interventions are defined individually for each patient by the interdisciplinary physician team.

The nuclear transcription factor modulators (e.g., farnesoid X receptor [FXR]) form a prospective direction in the treatment of NAFLD. Obeticholic acid (FXR stimulator) promotes the decreased bile acid levels, also improving other metabolic processes (e.g., gluconeogenesis and lipogenesis) [12, 43].

A new target drug Resmetirom (thyroid hormone receptor agonist) is currently authorized in the USA for the treatment of patients with NAFLD. The MAESTRO-NASH study demonstrated that the latter drug not only decreased the disease activity, but also led to hepatic fibrosis regression [44]. This drug has not been authorized in Russia yet.

Conclusion

Non-alcoholic fatty disease is a chronic multisystemic disease with a multifaceted pathogenesis, characterized by the high global prevalence and associated with the development of other comorbid conditions.

The treatment of this disease should be complex, with the use of medication and non-medication methods. It should lead to the regression of hepatic steatosis, while also decreasing cardiometabolic risks.

The role of Remaxol effects on the course of non-alcoholic fatty liver disease is currently being actively analyzed. The results of recent studies have demonstrated good drug tolerability with its high efficacy concerning the decreased liver enzyme levels, cholesterol metabolism normalization, elimination of dyspeptic signs. This fact enables us to not only include Remaxol into NAFLD treatment protocols in order to decrease the risk of fibrosis progression and the number of complications, but also to consider it for use as monotherapy.

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