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**NON-ALCOHOLIC FATTY LIVER DISEASE, MODERN VIEWS**

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**Abstract***This article presents the literature about the problem of non-alcoholic fatty liver disease, which is a poly-etiological disease. Excessive consumption of foods rich in fats and carbohydrates leads to the release of large amounts of free fatty acids (FFA) from the gastrointestinal tract into the blood and further into the liver, resulting in the development of steastosis. Inflammatory mediators actively released by adipose tissue directly damage hepatocyte membranes, which leads to the accumulation of fibrous tissue in the liver. The main feature of this disease is that it is often asymptomatic and is diagnosed accidentally on the basis of laboratory or instrumental studies performed in patients with metabolic syndrome. Being a very common pathology, non-alcoholic fatty liver disease requires a thorough study of the mechanisms of its pathogenesis and the search for the most optimal non-invasive methods for identifying and assessing its complex forms (steatohepatitis, fibrosis, cirrhosis)*.

**Keywords: Non-alcoholic fatty liver disease, steatosis, steatohepatitis, liver cirrhosis, non-invasive diagnostic methods.**

**Introduction**The liver performs a number of vital functions in the human body, including control of metabolic processes is one of the main functions of the liver. For this reason, we find it appropriate to consider this liver function in more detail. The metabolic role of the liver in the body is to carry out the exchange of proteins, lipids, carbohydrates, pigments, biologically active compounds and trace elements.  
There are a number of mechanisms that cause disruption of the metabolic function of the liver, which are primary (endogenous) factors, that is caused by gene mutations, as well as secondary factors, the action of exo- and endogenous xenobiotics. In turn, they, affecting the function of hepatocytes, lead to disruption of the metabolism of bilirubin, bile acids, proteins and amino acids, carbohydrates and glycoproteins, lipoproteins and lipids, porphyrin, trace elements, mucopolysaccharides. [1,2]. In particular, the liver regulates the distribution of food components, especially fatty acids, throughout the body, which are supplied from the small intestine through the portal vein. In the liver of a healthy person, lipids (mainly triglycerides, cholesterol, phospholipids) make up 0.8-1.5% of the liver weight. Elevated levels of this type of lipid lead to the development of fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease that occurs in people who do not drink more alcohol than usual, that is, ethanol does not exceed 40 g per day for men and 20 g for women, due to the accumulation of lipids in liver cells, causing clinical and morphological changes that are morphologically united and manifest in the form of steatosis, steatohepatitis, fibrosis, cirrhosis [1,2,3,6].  
Today the conceptNAFLD is manifested by the following pathogenetically caused changes in the liver:

\* liver steatosis, excessive accumulation of triglycerides in the cytoplasm of hepatocytes (if they constitute more than 5% of the liver mass); small fat bodies in hepatocytes (if the fat content increases to 2-3%) can be detected under a light microscope and assessed as the onset of the pathological condition - hepatic steatosis.[4,7,9].

\* Non-alcoholic steatohepatitis (NASH), a chronic diffuse liver disease accompanied by necrotic inflammatory processes leading to the formation of fibrosis;

\* liver fibrosis, proliferation of connective tissue without changing the structure of the organ;

\* liver cirrhosis (LC) is the irreversible replacement of parenchymal liver tissue with fibrous connective tissue with the formation in its place of a special nodular anatomical structure [9,10,]. In the steatosis stage, NAFLD is relatively safe and characterized by slow progression. However, NASH often does not manifest itself for a long time and, in the absence of adequate treatment, can develop in 50% of cases and lead to the formation of liver fibrosis and cirrhosis. There is evidence that every third patient with NASH in the general population goes to the stage of cirrhosis [1,3,5]. Historically, in 1884, Frerichs described changes in the liver in patients with “sugar disease.” In 1980, Yu. For the first time, the concept of “non-alcoholic steatohepatitis” was formulated by Ludwig and his co-authors when studying the nature of liver changes in patients who did not drink alcohol in hepatotoxic doses, while suffering from obesity and type 2 diabetes mellitus (DM). M. Thaler, on the other hand, discovered the possibility of developing cirrhosis due to fatty liver disease. At the 1st World Congress on Insulin Resistance in Los Angeles in 2003, along with obesity, type 2 diabetes, dyslipidemia, and hypertension, NAFLD was recognized as a manifestation of the metabolic syndrome [3.8,11].  
Today NAFLD is considered the most common form of chronic liver disease, accounting for approximately 70% of all liver diseases [6]. However, the true prevalence of the disease is unknown because most patients do not seek medical attention or seek medical attention for complaints unrelated to diseases of the digestive system.  
NAFLD is a slowly progressive disease, and patients do not always develop cirrhosis. However, a quarter of patients with hepatic steatosis develop liver fibrosis [9.11]. Some authors have concluded that 10% of cases of hepatic steatosis progress to NASH within ten years. In 5-25% of cases, NASH develops into cirrhosis. Approximately 10% of patients with NASH at the stage of cirrhosis developed hepatocellular carcinoma (HTC) within ten years [2,8,11]. Notably, 60–80% of all cryptogenic liver cirrhosis cases are the result of NAFLD [17], and 10% of all liver transplant cases are associated with NASH at the cirrhosis stage. NAFLD is the focus of attention not only by general practitioners and gastroenterologists, but also by cardiologists, endocrinologists, and nephrologists, which is due to the fact that NAFLD increases the risk of developing cardiovascular diseases, type 2 diabetes, and chronic kidney diseases. [5.8.11,].  
In 2020, an international expert consensus statement was published proposing a new adaptive concept, MAFLD: metabolically associated fatty liver disease (MAFLD: metabolically associated fatty liver disease). The proposed interpretation of the disease allows not only to highlight the systemic and multifactorial nature of the pathogenesis of generalized damage to the liver parenchyma, but also to specialize the scope and direction of medical diagnostic care for various clinical variants of other diseases associated with metabolic syndrome (MS). Experts (compilers of these clinical guidelines), expressing full agreement with the concept of MAFLD presented by the authors of the “consensus”, recommend in everyday practice the use of the corresponding codes of WHO-approved nosological forms, designated ICD-10 and ICD-11 [7.8.11].  
NAFLD has specific etiopathogenetic features, which, according to a review of the literature, are primary and secondary factors. Primary factors include a sedentary lifestyle, metabolic syndrome, type 2 diabetes mellitus, obesity, and dyslipidemia. Secondary factors include the use of medications (glucocorticoids, amiodarone, estrogens, non-steroidal anti-inflammatory drugs, antibiotics); poor nutrition (hunger, sharp decrease or increase in caloric intake, excess carbohydrate intake, parenteral nutrition, lack of proteins and important microelements); disturbances of the processes of digestion and absorption (chronic diseases of the gastrointestinal tract, secretory deficiency of digestive enzymes); metabolic disorders (Wilson-Konovalov, gout); hyperfunction of the thyroid gland; pregnancy; oxygen deficiency (anemia, CHF and DN); intestinal dysbiosis and intestinal autointoxication [5, 7,10].  
Excessive consumption of foods rich in animal fats and easily digestible carbohydrates leads to the accumulation of large amounts of free fatty acids (FFA) from the gastrointestinal tract into the blood and then into the tissues. As a result, hypertrophy and hyperplasia of adipocytes occurs. Adipose tissue, which performs the function of an endocrine gland, changes its secretory activity and begins to produce a large number of inflammatory mediators (tumor necrosis factor-alpha (TNF-ɑ), FFA, interleukin-6, etc.), which leads to the development of chronic inflammation with slow progression. [3]. This process, in turn, is accompanied by excessive penetration of FFA into the portal system and liver. An imbalance occurs between the supply of lipids to the liver from the outside, their synthesis and utilization, resulting in the accumulation of fat vacuoles containing triglycerides in hepatocytes, that is, the development of steatosis [3]. Inflammatory mediators, which are actively secreted by adipose tissue, directly damage hepatocyte membranes, which leads to activation of cytochrome P450, increases lipid peroxidation (LPO) and causes the development of oxidative stress, which damages liver cells. The death of hepatocytes by the mechanism of apoptosis and necrosis, as well as the accumulation of fibrous tissue, is observed. Chronic inflammation of the liver gradually leads to the development of NASH [4]. Recently, there has been a lot of thinking about the important role of intestinal microflora in obesity and the formation of NAFLD. In general terms, we can say that the mechanisms of transformation of steatosis into steatohepatitis include: increased production of TNF-a by adipose tissue, increased concentration of FFA, which has a direct damaging effect on hepatocyte membranes, activation of cytochrome P450, increased lipid peroxidation, accumulation of reactive oxygen species (oxidative stress) in excessive quantities with high toxicity, the formation of xenobiotics, as well as intestinal endotoxemia against the background of dysbiosis [1,2,5,6].  
Thus, disruption of the intestinal microbiocenosis in patients with NAFLD leads to increased morphological changes and fibrotic changes in the form of hepatocyte degeneration and histological activity of the process; activation of sinusoidal mononuclear cells; disruption of the synthesis and outflow of bile. Bacterial toxins of pathogenic and conditionally pathogenic intestinal microflora increase the sensitivity of fatty liver tissue to the action of TNF-a, IL-1, IL-6,IL-8, which leads to hepatocyte necrosis and fibrosis [1,6,8].   
Scientific studies of the clinical signs and diagnosis of this disease have shown that the main property of NAFLD is often asymptomatic, and the disease is detected incidentally on the basis of laboratory or instrumental studies performed in patients with metabolic syndrome. NASH manifests itself with nonspecific symptoms. Although these signs indicate liver damage, they do not help determine its severity. Asthenovegetative syndrome is diagnosed in most patients with NASH; sometimes there is a short-term or prolonged feeling of heaviness in the right hypochondrium - dyskinetic syndrome. The appearance of complaints of itching, anorexia, dyspeptic syndrome, and the development of jaundice along with symptoms of portal hypertension indicate that NASH develops into cirrhosis [6].  
During a medical examination, hepatomegaly is diagnosed in 50-75% of patients with NAFLD [5]. Additional diagnostic tests are carried out if the following signs are present:

- asymptomatic increase in the number of aminotransferases;

- presence of unexplained persistent hepatomegaly;

- hepatomegaly on X-ray examination;

- when all other causes leading to hepatomegaly are excluded.

In rare cases, patients with NASH experience symptoms of chronic liver disease, such as telangiectasia and palmar erythema. Symptoms of NAFLD are found in 10-15% of people without clinical manifestations of multiple sclerosis.

The most important thing in diagnosing NAFLD is obtaining a proper history to assess risk factors. First of all, it is necessary to exclude alcoholic liver damage and chronic viral hepatitis B and C, hereditary hemochromatosis, Wilson's disease, and autoimmune liver diseases.   
Numerous observations have revealed predictions indicating a higher risk of developingNAFLD with steatohepatitis and fibrosis:

- Over 45 years old;

- female;

- BMI above 28 kg/m2;

- Increase in ALT activity two or more times;

- TG level more than 1.7 mmol/l;

- presence of arterial hypertension;

- Type 2 diabetes;

-IR index (NOMA-SH) above 5.

Identification of more than two criteria indicates a higher risk of liver fibrosis. Separately, it is worth noting the possibility of reverse development of NAS, NASH against the background of gradual loss of body weight. However, rapid weight loss can help one phase of development and transition to another.  
As for laboratory and instrumental methods for diagnosing NAFLD, the increase in the activity of aminotransferases ALT and AST is no more than 4-5 times, the AST / ALT index is no more than 1 time, often with an increase in ALT activity; , an increase in the activity of alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) occurs in 40-60% of cases (usually no more than 2 times); hypertriglyceridemia, hypercholesterolemia; hyperglycemia (type 2 diabetes mellitus) - increased fasting glucose levels more 6.1 mmol/L, change in glucose tolerance test, increase in C-peptide level; hypoalbuminemia; increased bilirubin levels (within 30-35 mmol/l); thrombocytopenia, increased prothrombin time.  
The main difference between fatty liver (steatosis) and NASH, which is important in clinical practice, depends on the degree of manifestation of the biochemical syndrome of cytolysis. Cytolysis has been described in 50-90% of patients with NASH when analyzing laboratory data obtained in specialized clinics. ALT activity is often higher than AST activity, but sometimes AST activity predominates, especially in patients with cirrhosis. According to some studies, the ALT value, along with other metabolic factors, is an indicator of insulin resistance (IR), which makes it possible to use this indicator as an additional marker in patients with IR determination. Low serum ALT levels combined with high BMI may indicate the presence of NASH and severe fibrosis.  
A marker of NAFLD may be the composition of fragments of the filament protein cytokeratin-18 (CK18-Asp396), formed during cleavage by activated caspases of hepatocytes during apoptosis in the blood serum. High levels of cytokeratin-18 fragments are characteristic of steatohepatitis, which distinguishes it from steatosis. The specificity and sensitivity of this method are 99.9% and 85.7%, respectively [2,3].  
Non-invasive methods for assessing liver steatosis, the activity of inflammatory changes and liver fibrosis have also begun to be used in practice (Fibroscan, Fibromax) [4,6]. The sensitivity and specificity of fibrotests is 70-90%. However, compared with liver biopsy in patients with NAFLD, fiboroscopy is not considered the main method for diagnosing NAFLD due to the lack of reliable test data in comparison with clinical and morphological changes.  
Since the main liver tests used in clinical practice are nonspecific and not always compatible with histological changes (damage, inflammation, fibrosis), liver biopsy is the gold standard for diagnosis.NAFLD, staging and therapeutic efficacy.  
A number of experts use various indices to determine the risk of NASH. For example: indexHAIR (hypertension, ALT > 40 U/L, insulin resistance) has a sensitivity of 80% and a specificity of 89% for NASH [31]. The BAAT index (BMI (>28), age (>50 years), ALT (>2 normal), triglycerides (height)) means the absence of 100% NASH less than 1 [2, 3,10]. J.-H. Lee suggested using the NAFDL index (NAFLD), which is calculated as follows: 8 × ALT/AST + BMI. If the index is less than 31, the diagnosis of NAFLD is unlikely, and if it is greater than 36, the probability of diagnosis exceeds 90%. The specificity of this index is 91.2% [1,3].   
Instrumental diagnosticsNAFLD is varied and includes computed tomography and magnetic resonance imaging (MRI), abdominal ultrasound (US) to detect echogenicity of the liver parenchyma and hepatomegaly. [8]. The sensitivity of ultrasound and MRI for diagnosing NAFLD is 45 and 90.9%, respectively, and the specificity is 90 and 94% [3,5].   
When a patient has no clinical signs, but liver function tests reveal changes, and histological examination of liver tissue is not possible, ultrasound serves as an objective method for diagnosing hepatic steatosis. Ultrasounds are performed when the patient has one or more risk factors for developing NASH, as well as to monitor the dynamics of the disease.   
There are 4 main ultrasound symptoms of liver steatosis:

- distal attenuation of the echo signal;

- diffuse hyperechogenicity of the liver parenchyma (“bright liver”);

- increased echogenicity of the liver compared to the kidneys;

- pale shape of blood vessels.

However, it can sometimes be difficult to diagnose liver fibrosis and even cirrhosis using ultrasound. In some cases, computed tomography and magnetic resonance imaging can detect fatty infiltration in the liver. The main CT sign of fatty infiltration of the liver is a decrease in the densitometric index of the parenchyma. The advantages of modern MRI are high tissue contrast and the ability to obtain a complete image of an organ in any projection.

**Table 1. Algorithm for step-by-step diagnosis of NAFLD.**

|  |  |
| --- | --- |
| Diagnostic parameter | Information sphere |
| Anamnesis | * Alcohol consumption setting amount, non-hepatotoxic dose (less than 20.0 ethanol per day for women, 40.0 for men) * Determination of the presence of other components of the metabolic syndrome: obesity, type 2 diabetes, dyslipidemia, arterial hypertension. * Avoiding the use of hepatotoxic drugs during the last 3 months: * Elimination of risk factors for viral hepatitis: contact with blood, blood transfusion, visit to the dentist, tattoos, piercing. * Exclusion of hereditary diseases: Wilson's disease, hemochromatosis |
| Objective examination | * Assessment of anthropometric parameters (BMI above 30, waist circumference (WC), hip circumference (HC), WC/HC ratio) * Eliminate the presence of alcohol "stigmas" * Rule out symptoms of severe cholestasis syndrome * Rule out the presence of melasma * Check for signs of portal hypertension and hepatic encephalopathy |
| Laboratory research | * Biochemical blood test (cytolysis, cholestasis, immune-inflammatory syndromes, hepatocellular insufficiency), coagulogram, lipidogram * Carbohydrate metabolism study (glucose, insulin, HOMA-IR index) * Viral hepatitis (HBS AG, anti-HBC, anti-HCV) * Autoimmune hepatitis (IgG, IgM, anti-actin antibodies, antinuclear antibodies ANA, antibodies to liver microsomal antigens ASMA, antimitochondrial AMA) * Hemochromatosis (serum transferrin saturation, ferritin, genetic test C282Y, h63d) * Wilson's disease (ceruloplasmin in the blood, daily urinary copper excretion) * Liver cancer (alpha fetoprotein) |
| Ultrasound, CT, MRI | * Ultrasound symptoms of liver steatosis * Exclusion of focal liver damage |
| Liver biopsy | * Large drops of fatty hepatosis symptoms * Symptoms of hepatitis with a predominance of lobular inflammation * Symptoms of fibrosis |

Thus, the diagnosis of NAFLD is made after excluding all other causes of liver damage, primarily viral, alcoholic and drug etiologies. In addition, the risk of developing diffuse liver disease in people of all ages, including the elderly and paediatric, must be considered. It should be remembered that against the background of metabolic syndrome, in addition to NAFLD, comorbidity options are possible. Therefore, the spectrum of testing of patients with suspected NAFLD should include almost all of these indicators. **Recommendations**

As a result NAFLD is a very common pathology that requires studying the mechanisms of its pathogenesis and searching for non-invasive methods for identifying and assessing complex forms of NAFLD (steatohepatitis, fibrosis, cirrhosis). Understanding the multifactorial nature of NAFLD and the associated mechanisms of polymorbidity formation allows us to adequately assess its prognosis and determine priority methods of pharmacological and drug treatment.

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