NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract: Extensive research has found an association between the severity of metabolic disease, the stages of nonalcoholic fatty liver disease, and the severity of fibrous processes in the liver in patients with abdominal-type obesity. The proportion of patients with symptoms of hepatic fibrosis in obese patients is 50% and rises to 73% in the presence of early disorders of carbohydrate metabolism.

Keywords: non-alcoholic fatty liver disease, metabolic syndrome, abdominal obesity, insulin resistance, changes in glucose tolerance, liver fibrosis, liver elastometry

Noalcoholic fatty liver disease (NAFLD) is primarily a dramatic result of obesity, and the steady increase in patients with this pathology is associated with an increase in the number of overweight people. Overweight has become as widespread as an epidemic: its prevalence in the world has doubled in the last 20 years. According to the World Health Organization, in 2014, 11 percent of men

and 15 percent of women over the age of 18 were overweight. The ESSE-RF study found that obesity accounts for 29.7% (one-third!) Of the adult population in Russia. Traditionally, the development of diabetes, metabolic syndrome, and cardiovascular disease has been associated with an increase in the number of patients with NAFLD. In Russia, the NASG frequency was 27% in 2007 and 37.1% in 2014 (an increase of more than 10%). [1]

Clinical appearance and diagnosis. NAFLD is an asymptomatic disease that a physician can accidentally diagnose cytolysis syndrome in a biochemical study. The patient, as a rule, does not complain or is unknown - asthenovegetative syndrome (weakness, fatigue) and may feel a slight discomfort under the right rib arch. Itching, dyspeptic syndrome, jaundice, and portal hypertension indicate the next stage of NAFLD [4].

Hepatomegaly (50-75% of cases) and splenomegaly (25%) are of interest in the objective examination of patients with NAFLD. The biochemical manifestations of NAFLD are manifested by moderate cytolytic syndrome - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are much higher (four to five times). In some patients, the activity of cholestasis - alkaline phosphatase (AF) and gamma-glutamyl transpeptidase (GGTP) is increased (usually not more than two or three). In patients with nonalcoholic steatohepatitis (NASG), bilirubin levels are usually normal, protein-synthetic function of the liver is preserved, albumin and prothrombin levels are reduced in cirrhosis and liver failure. Absence of changes in laboratory parameters (ALT, AST, ALP, GGTP) characterizing liver function does not exclude the presence of

inflammatory processes and fibrosis. Homeostasis Model Assessment of Insulin Resistance (assessment of insulin resistance using the Homeostasis model) The HOMA-IR helps determine the presence and weight of the insulin resistance index I: HOMA-IR = I0 x G0 / 22.5, where I0 is the insulin level (mIU) / ml). G0 - fasting glucose level (mmol / l). The presence of insulin resistance (IR) is defined as the HOMA-IR value> 2.7. Based on the histology of the liver, NAFLD course can be assessed. However, when biopsy is not possible, assumptions should be used to assess the high risk of developing NAFLD with the development of hepatitis and fibrosis. These estimates are derived from statistical processing of the results of many observations [2]. These include: over 45 years of age; female gender; body mass index more than 28 kg / m2; Two or more increases in ALT activity; triglycerides above 1.7 mmol / l; arterial hypertension; More than 5 NOMA-IR 2 type diabetes. Detection of more than two criteria indicates a high risk of liver fibrosis. [5]

The most common method of accurate histological evaluation of NAFLD is biopsy [6, 7]. This examination is invasive. The presence of pain during biopsy makes a large proportion (1/3) of patients refuse to perform it. The emotional state of the patient before the procedure plays an important role. Given the above shortcomings, this manipulation is currently being phased out.

Morphological examinations. There are no specific histological signs that allow the differentiation of alcoholic steatosis or steatohepatitis, so the diagnosis is made only in the absence of a significant history of alcohol consumption.

In recent years, specific semi-quantitative methods have been developed that

allow the use of a digital equivalent to determine the activity of the process (Knodell, Ishak, METAVIR) and the stage of fibrosis (Desmet). However, the lack of a clear difference between the criteria for assessing the severity of liver fibrosis and necroalysis leads to ambiguous interpretation of the data. In addition, morphological assessment is largely subjective and depends on the experience and qualifications of the pathomorphologist. It should be noted that the result of such a morphological study is statistical data that does not reflect the balance between the synthesis and destruction of the components of the extracellular matrix, and therefore has no information on the degree of development of fibrosis [8].

Assessment of liver fibrosis. Serum markers of fibrosis. Serum markers of fibrosis include:

a) mediators of fibrogenesis and extracellular macrix components detected in serum (types 1, 2, 4 collagen, hyaluronic acid, laminin and its fractions, metalloproteinases, tissue inhibitors of metalloproteinases, cytokines, etc.). An important disadvantage of these methods today is the low specificity of fibrogenesis processes in the liver, as these indicators may reflect any other localization process (lung, pancreatic fibrosis);

b) indirect indicators. A number of biochemical indicator panels (AST, ALT, alkaline phosphatase, GGTP, bilirubin, etc.) and acute phase proteins (α-2-macroglobulin, haptoglobulin, ferritin, etc.) have been proposed to study fibrogenesis activity in the liver. The discriminant functions obtained on the basis of changes in the level of these indicators reflect the activity of the

inflammatory process in organ tissue and the violation of its synthetic function, which allows an indirect assessment of the stage of liver fibrosis.

Ultrasound elastography is currently used to assess liver fibrosis, which allows to determine the stage of liver fibrosis.

In recent years, computed tomography (CT) and magnetic resonance imaging (MRI) elastography have been used to diagnose liver fibrosis, but these methods do not have widespread clinical application due to the high cost of research. [9].

Treatment. Currently, there is no standard evidence-based treatment for NAFLD in both the steatosis stage and the steategepatitis stage. Therefore, the main goal of therapy is to improve the biochemical parameters that characterize inflammation and cytolysis, slowing and blocking fibrogenesis.

Drugs used in the treatment of patients with NAFLD should be as safe as possible in terms of hepatotoxicity. It is desirable to have a positive effect on clinical and laboratory parameters and morphological changes in the liver. Therapeutic approaches to NASG include exposure to etiological, pathogenetic factors, and background disease. Avoid alcohol and other hepatotoxins.

Taking into account the pathogenesis of the disease, the main directions of therapy can be distinguished:

1. correction of metabolic diseases;
2. body weight loss (diet and exercise);
3. increase insulin sensitivity of cell receptors (metformin, thiazolidinedion);
4. decrease in triglyceride levels (fibrates, statins);
5. Decreased ONF-alpha concentration of tumor necrosis factor

(pentoxifylline);

6. antihypertensive therapy (angiotensin II receptor antagonists);
7. treatment of oxidative stress (antioxidants and hepatoprotectors (vitamin E, silibinin, betaine, N-acetylcysteine, ursodeoxycholic acid (UDXKA), alpha fatty acid);
8. restoration of intestinal microbiocenosis (eubiotics, probiotics, prebiotics).

With the development of NASG against the background of obesity and diabetes, the treatment program includes gradual weight loss, metabolic control, and exercise. Daily calories are selected individually depending on body weight, age, gender, level of physical activity using special formulas. A gradual decrease in body weight reduces the severity of the steatosis. This is helped by lifestyle changes - changes in diet, increased daily physical activity.

If these methods are ineffective, pharmacological drugs (orlistat, sibutramine) that reduce body weight can be used.

A prerequisite for the treatment of patients with NAFLD is exercise. This helps to reduce body weight and insulin sensitivity (consuming a lot of free fatty acids in muscle tissue, they are oxidized, thereby reducing IR). As a rule, the rate of decrease in IR is related to the intensity of exercise. It is recommended to hold them at least 3-4 times a week, duration - 30-40 minutes. Laboratory and histological changes, as well as liver volume, may gradually decrease with weight loss. But it can also be improved in terms of the duration of obesity. Rapid weight loss was observed with the development of NASG. In addition, it is difficult to assess the long-term positive effects of weight loss because body

weight loss is necessary and this is rarely possible for patients with NASG and obesity.

Among insulin sensitizing drugs, the drug in the metformin group of biguanides causes the fewest side effects. With its use, regression of steatosis and, in some cases, liver fibrosis are noted [10].

New drugs are being developed that increase insulin sensitivity and have anti-inflammatory and antifibrotic properties. Gallbladder acids play a crucial role in regulating liver function and maintaining metabolic homeostasis with hormone receptors, particularly farnezoid X-receptors (FXR) and G-protein-bound cell membrane receptors (TGR5). Activation of FXR improves glucose metabolism and peripheral insulin sensitivity, reduces lipogenesis, and increases beta-oxidation of fatty acids, which protect the liver from fibrosis and inflammation [3]. Such drugs include obetichol acid (OXK) (synthetic bile acid, FXR picomolar agonist) and GFT505 (innovative drug, insulin sensitivity enhancer, bilateral agonist PPAR-alpha / delta).

Improvement in all indicators of statohepatitis, including fibrosis, is observed when using OXK. Thus, according to the data obtained, the severity of fibrosis was reduced (at one stage) in 35% of patients receiving OXK (19% of patients in the placebo group). These data need to be confirmed in large studies. Itching from adverse events and an increase in low-density lipoprotein cholesterol were observed. Clinical studies in patients with abdominal obesity and insulin resistance (with or without diabetes) have shown that GFT505 increases liver and peripheral sensitivity to insulin, reduces dyslipidemia, markers of

inflammation, and improves liver function parameters [3]. . The new drugs also include incretinomimetic - glucagon-like peptide 1 receptor agonists (GLP-1R). Experimental studies have shown that the addition of GLP-1R agonists increases the use of fatty acids in hepatocytes as a result of beta-oxidation and lipid export, as well as increasing the insulin sensitivity of the liver.

In small experiments, the effectiveness of pentoxifylline, which suppresses the release of ONF-alpha, was studied [11]. After several months of treatment with pentoxifylline at a dose of 400 mg three times a day, ALT activity decreased. However, since no histological examination has been performed, repeated tests are required to confirm the initial results.

Hypolipidemic agents (statins, fibrates) are used in patients with severe disorders of lipid metabolism in NAFLD complex therapy. These drugs prevent the development of cardiovascular complications, but in most cases they do not have a positive effect on the biochemical and histological appearance of NASG. In general, the data from the studies performed are contradictory and indicate the need for further study of the use of these drugs in NAFLD.

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