Modern view of non-alcoholic fatty liver disease

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Among the metabolic disorders such as diabetes mellitus (DM) type 2, impaired glucose tolerance (IGT), insulin resistance (IR), obesity, and/or changes in lipid profile, leading sometimes to severe inflammatory and destructive processes in the liver, up to cirrhosis, occupies a special place the primary non-alcoholic fatty liver disease (NAFLD).

Morphological picture of the disease is different from detectable in alcoholic liver disease. Therefore J. Ludwig et al., who first described in 1980, inflammatory and necrotic changes of hepatocytes in non-drinking patients with type 2 diabetes and obesity, called this pathology non-alcoholic steatohepatitis (NASH).

Nonalcoholic fatty liver disease is manifested in the form of isolated fatty liver, NASH or a combination of these two pathological conditions. NAFLD is largely associated with obesity and insulin resistance, and is regarded by many as the hepatic component of the metabolic syndrome.

NAFLD liver is the most common disease in the world. This disease is present in 20% of the US population. About one-third of patients with type 2 diabetes suffer from fatty liver. The prevalence of NAFLD is increasing due to the growing number of children and adults who are obese or overweight, have metabolic syndrome or type 2 diabetes [4, 27, 28].

It is now recognized that the majority of patients with cryptogenic cirrhosis is associated with NAFLD [4]. U.S. NAFLD is considered one of the main causes of liver cirrhosis, following hepatitis C and alcoholic liver disease. In 15-25% of patients with NASH develop cirrhosis and its complications in the period from 10 to 20 years. The first biopsy in one third of patients NASH fibrosis was observed, and in 10-15% of patients — liver cirrhosis [12, 23, 30]. The study of mortality in patients with NASH showed significantly higher numbers compared with the general population. NAFLD and associated cirrhosis is an indication for liver transplantation [8.15, 19].

NAFLD is a risk factor for hepatocellular carcinoma (HCC) and is associated with increased mortality from liver disease [7, 34]. According to Japanese authors, the cumulative risk of HCC in 5 years may reach 15% [18]. The combination of NAFLD with hepatitis C, or human immunodeficiency virus worsens the prognosis of these diseases [20]. Furthermore NAFLD is an independent risk factor for cardiovascular disease [4, 36].

Visceral adipose tissue is recognized as a major risk factor for development and progression of NAFLD [3, 10]. As an endocrine organ it secretes a variety of hormones, cytokines and chemokines such as inflammatory and anti [9], some of which may play a role in the progression of NAFLD. IR, being one of the initial processes that contribute to the excessive accumulation of fat in the liver cells and the development of inflammatory reactions, develops as a result of genetic and

exogenous factors, such as lack of exercise, high-calorie diet, excessive increase in the number of bacteria in the gut (endotoxemia) [11].

However, NAFLD is not necessarily associated with obesity, metabolic syndrome or type 2 diabetes. In individuals without these conditions, the disease can also develop. In addition, not all people who are obese or have metabolic syndrome or type 2 diabetes, developing NAFLD.

In addition to the violation of the regulation of lipid metabolism, the immune system of the liver may play a significant role in the development of NAFLD and its progression.

Different susceptibility to NAFLD in distinct ethnic groups can't be associated exclusively with the peculiarities of power or socio-economic differences. There were familial forms of NAFLD [10, 21]. A number of studies conducted over the years, ethnic differences in gene variants PNPLA3 were found [13, 25]. In the US, a high frequency of NAFLD was observed in Hispanic persons and low — in African Americans, despite the higher level of obesity [13]. Another group at high risk for NAFLD includes Indian population in South Asia. NAFLD is also common in other populations of the Asia-Pacific region. [28]

During a recent study of genetic variation in genome-wide association (GWAS) data were collected on five genes (PNPLA3, NCan, LYPLAL1, GCKR and PPP1R3B), responsible for the development of NAFLD, and one gene TRIB1, associated with increased levels of alanine aminotransferase [14].Multivariate analysis conducted by a large team of researchers, has shown a significant association between the four variants of genes (PNPLA3 rs738409, GCKR rs780094, TRIB1 rs2385114 and PPP1R3B rs11777327) and steatosis. PNPLA3, GCKR and TRIB1 genes were also associated with steatohepatitis and fibrosis. At the same time, it was not revealed NAFLD association with genes NCan and LYPLAL1 [1]. The study also found overwhelming importance PNPLA3 locus 22nd chromosomes for all aspects of NAFLD and shown that some genetic variations previously associated with steatosis or soft biochemical abnormalities may in fact have greater pathological significance, affecting the nature of the inflammatory disease and progression of fibrosis in NAFLD. Now there is the search for the so-called chromosomal regions carrying the gene variants influencing the occurrence of NAFLD and its development.

Hormones adipose tissue and active substances that regulate the sensitivity insulinoretseptorov whose output increases due to an increase in visceral fat mass, enhance lipolysis and activation of Kupffer cells of bacterial toxins portal vein affect the progression of the disease [4, 10].

According to the "theory of the two strikes" pathogenetic mechanisms potentiate each other and form a vicious circle. Destructive changes in tissue that develop as a result of the accumulation of fat in the liver, which are so-called "first strike", increase of liver sensitivity to the supposed "second strike" — oxidative stress associated with the induction of cytochrome R4502E1 (SYR2E1) and cytokines (mainly tumor necrosis factor α — TNF-α), which action causes damage to hepatocytes, fibrosis and inflammation [8, 21].

NAFLD initially rarely has noticeable symptoms and is detected incidentally during ultrasound (US) of the liver. The manifestations of NAFLD is usually inconspicuous and are characterized by a feeling of heaviness in the epigastric region, nausea, unstable chair, discomfort or pain in the right upper quadrant, fatigue, weakness. In children with NAFLD may experience abdominal pain, fatigue sometimes, in some cases, the skin may be dark in color. It is necessary to emphasize the possibility of the return of non-alcoholic fatty disease on the background of weight loss.

Upon cirrhosis liver observed characteristic signs — palmar erythema, spider veins, palpation — thickened edge of the liver, ascites, splenomegaly, jaundice or less appears itching, signs of portal hypertension (ascites, variceal bleeding). Most patients are characterized by obesity (47-90%), diabetes (28-55%), different incidence of hyperlipidemia (4-92%), and hypertension [11].

In the diagnosis of NAFLD important role played by a thorough medical history, combined with liver function tests, ultrasound or computed tomography (CT) scan and liver biopsy [24, 26].

NAFLD is the most common cause of unexplained persistent elevations of liver enzymes after hepatitis and other chronic liver diseases were excluded. In patients with suspected NAFLD or NASH baseline study should include the levels of alanine aminotransferase and aspartate aminotransferase activity (ALT and AST), indicators of total and direct bilirubin, fasting glucose in the blood serum, as well as the lipid profile.

The progression of NAFLD is seen in increase in the serum ALT and AST, alkaline phosphatase and gamma-glutamyl transpeptidase. In the chronic form of NAFLD liver function tests may be normal and fatty liver — minimum [5, 17]. If the disease has not progressed to cirrhosis, the levels of albumin, bilirubin, platelet count is usually normal.

Ultrasound is an informative noninvasive method of instrumental diagnosis of steatosis: marked enlargement of the liver, hyperechogenicity or "brightness" of its tissue due to the diffuse fatty infiltration. The advantages of ultrasound also include the ability to record the dynamics of the signs of steatosis, including during treatment. Unfortunately, the ultrasound can’t exclude steatohepatitis or fibrosis, and the sensitivity drops sharply when <30% of the hepatocytes comprise fat droplets [5, 27]. Ultrasound also has low accuracy in patients with obesity.

In diffuse lesions of the liver CT is less informative than the US, but it is the method of choice for focal diseases. The advantages of modern high field magnetic resonance imaging (MRI), as compared with other methods of imaging are high tissue contrast, the possibility of obtaining a holistic body images in any projection, as well as great resources software used for differential diagnosis [16, 26, 30]. Hepatic elastography is a noninvasive assessment of liver fibrosis by measuring liver stiffness, which increases with fibrosis [28].

However, all the imaging methods of diagnosis, despite the rather high information do not allow to assess signs of steatohepatitis, the degree of activity and stage of fibrosis in the liver.

Due to the low diagnostic accuracy of non-invasive methods, it is currently the only reliable way to diagnose NAFLD, the so-called "gold standard", a hepatic biopsy, which allows on the basis of histological data to predict the further course of the disease and to exclude other causes of liver disease [26, 27 33]. Liver biopsy may be associated with serious risks, including bleeding. Indications for use of the biopsy can be clinical factors and basic laboratory shifts, especially in patients over the age of 45 years and/or obesity, type 2 diabetes, the ratio of AST to ALT is greater than 1. Histological examination of the progression of the disease is manifested lobular inflammation on a background of steatosis liver tissue.

Severe course of NAFLD contributes to age more than 45 years, obesity with a body mass index (BMI) over 28 kg/m²; type 2 diabetes; female; ALT increase (more than 2-fold from the norm), and triglycerides (TG) in serum (over 1.7 mmol/l); liver fibrosis and genetic factors. Revealing more than two criteria indicates a high risk of liver fibrosis [3].

To date, the choice of rational method of treatment of NAFLD remains difficult because there is insufficient data to make informed use of drugs used. The main strategic directions of therapy [26, 33]: weight loss (diet + exercise, bariatric surgery); IR correction; treatment of type 2 diabetes, hyperlipidemia; recovery of liver function and protective properties of hepatocytes by administering anti-oxidant, anti-apoptotic and anticytokine drugs.

NAFLD treatment includes weight reduction through a combination of low-calorie food with increased physical activity [26, 29]. Recommended diet, aimed at getting the deficit 500-1000 kcal per day by reducing dietary carbohydrates, especially fructose. Body weight reduced by 4.3% reduces steatosis and weight loss up to 10% can reduce necrotic inflammation [35]. Numerous studies have seen an inverse relationship between coffee consumption and the severity of fibrosis [6, 36]. Therefore, it may be prudent to recommend to patients with NASH regular consumption of coffee.

Prerequisite is the treatment of patients with NAFLD exercise. It has a positive effect on reducing body weight and insulin sensitivity, this increases the flow of free fatty acids into muscle tissue where they are oxidation, thereby reducing the TS. The degree of decrease in IR tends to be correlated with the intensity of exercise that is recommended at least 3-5 times a week, lasting 30 minutes. [32] In everyday life, patients should be encouraged to self-climbing stairs, walking instead of driving.

The use of herbal medicine in treatment of NAFLD in the hospital and post-hospital step reduces the frequency and severity of adverse reactions accelerates the clinical cure patients, can reduce complications. Various herbal compositions improve fat metabolism, liver function, has anti-inflammatory properties.

Drug therapy includes tools, reducing the sensitivity of the receptors to endogenous insulin (insulin resistance and biguanides drugs), normalize the intestinal microflora (intestinal adsorbents, preservatives, pro- and prebiotics), eliminating the causes of intestinal dysbiosis (treatment of concomitant diseases of the gastrointestinal tract, and the correction hypovitaminous dismetabolic states,

stimulation of your own body's defenses, eliminate pockets of acute and chronic infections, removal of the drug, provoking intestinal dysbiosis).

Correction of IR is an important component in the overall scheme of the treatment of NAFLD. The drug group biguanide metformin stimulates the sensitivity of cell receptors liver and peripheral tissues (skeletal muscle) to endogenous insulin. Antihyperglycemic effect of metformin caused decrease liver glucose production (gluconeogenesis) and free fatty acids (FFA), through the suppression of oxidation of fat, with increasing peripheral glucose uptake [9, 18]. Moxonidine, through activation of imidazoline receptor type 1 in the midbrain and, to a lesser extent, of presynaptic α_2-adrenoreceptor reduces central sympathetic impulses, thereby reducing the hydrolysis of fat, a reduction of FFA, glucose metabolism enhancement and increase insulin sensitivity, reduction in triglycerides and increasing high density lipoproteins (HDL). Both drugs statistically significant increase in insulin sensitivity after glucose load: moxonidine affects blood insulin, metformin regulates glucose levels, accompanied by a decrease of glycated hemoglobin. Both drugs statistically significantly reduced body weight remained metabolically neutral lipid. However, despite the positive effect of metformin on the enzymatic activity of the liver and IR, randomized controlled trials have shown conflicting histological results [21, 36]. In children with NASH use of metformin did not reduce ALT levels showed a stable or improving liver histology.

In 2010, the Italian Association for the Study of the Liver [2, 26], and in 2012, the American Association for the Study of Liver Diseases in collaboration with the American College of Gastroenterology and the American Gastroenterological Association published an evidence-based practice guidelines for the diagnosis and treatment of NAFLD [33], which is not recommended the use of metformin, ursodeoxycholic acid and omega-3 fatty acids.

Selective stimulant gamma receptor, peroxisome proliferator-activated (gamma-PPAR), pioglitazone reduces the IR peripheral tissues and liver reduces glucose levels, insulin and glycolysed hemoglobin in blood. In patients with impaired lipid metabolism reduces triglycerides and increases HDL without changing the low-density lipoprotein (LDL) and total cholesterol (TC) [17]. A randomized, double-blind clinical trial on the use of pioglitazone in the treatment of patients with NASH without DM (PIVENS) showed no difference in the rate of improvement of indicators of aminotransferase and reduce hepatic steatosis compared with placebo [24]. There is a hepatic toxicity of drug. More common side effect is a paradoxical increase in weight. Furthermore, upon using pioglitazone and rosiglitazone, the increased risk of heart failure is described.

For the purpose of correction of lipid exchange number of patients with a body mass index of more than 27 $kg/m^{2,}$ with allowance for the specific situation and the type of dyslipidemia currently recommended five categories of lipid-lowering drugs: fibrates, bile acid sequestrants, nicotinic acid and its derivatives (niacin), orlistat statins.

Orlistat, which reduces fat absorption, and sibutramine, a serotonin reuptake inhibitor, reduces the levels of liver enzymes and improved ultrasonic indicators of fatty liver [23]. A meta-analysis of rimonabant, a cannabinoid-1 antagonist,

showed an increase in side effects, and it currently can't be recommended for the treatment of NAFLD.

The statins (simvastatin, atorvastatin, parvastatin, rosuvastatin etc.) — reductase inhibitors of 3-hydroxy-3-methylglutaryl — CoA (HMG-CoA) inhibit the synthesis of cholesterol in the liver and intestine by compensatory expression hepatocytes increased number of LDL and increased clearance receptors LDL from plasma [28, 31]. According to experimental studies and clinical studies revealed several effects of statins 'anti-inflammatory' immunomodulating (reduction in plasma IL-6 and TNF-α), an increase of brain natriuretic hormone, increased secretion of vascular endothelial NO. Using Probucol, a lipophilic lipid-lowering drugs, showed a decrease in the level of not only aminotransferase, but also HDL.

In recent years, it attracted the attention of a new group of drugs — blockers of CB_1-endokannabinoid receptors. The main effects of the activation of these receptors consist in violation of thermoregulation, regulation of smooth muscle tone and blood pressure, inhibition of motor behavior — increased pain and anxiety, stimulate appetite and nicotine dependence (getting pleasure from eating and smoking). Rimonabant was used in obese patients and has demonstrated encouraging results in reducing weight, improving lipid profile and glycemic control in patients with diabetes. Another important factor is that the use of CB_1blockers promotes smoking cessation [27].

PIVENS study also showed that vitamin E (antioxidant) resulted in a decrease in transaminases compared with placebo, but had conflicting results regarding histological improvement [2, 9, 24]. Vitamin E is not recommended for patients with diabetes or cirrhosis of the liver.

Hepatoprotectors (essential phospholipids — EFL, silymarin preparations, agents based on amino acids, ursodeoxycholic acid) have a direct or indirect anti-inflammatory, detoxification, anti-fibrotic, choleregulating action, normalize liver function and eliminate its metabolic abnormalities. Preparations containing EFL, have expressed membrane-strengthening and hepatoprotective effect. In spite of several studies suggesting a role in improving UDCA NASH, a large, randomized, placebo-controlled study failed to demonstrate any advantage of ursodeoxycholic acid against biochemical indicators and liver histology as compared to placebo [2, 8].

Pentoxifylline inhibits a number of proinflammatory cytokines and possibly causes hepatoprotective effect, improving histological picture of NASH compared with placebo. Betaine and N-acetylcysteine showed promising effects, but further larger studies.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can improve insulin sensitivity. Furthermore, studies in a number of ARBs shown histological improvement in inflammation and fibrosis [22].

In a randomized controlled study, L-carnitine improved biochemical and ultrasound parameters of hepatic steatosis [29].

Experimental studies, based on the theory that NAFLD may be associated with bacterial growth in the small intestine, also showed some improvements when using probiotics and prebiotics.

Bariatric surgery is usually only available to individuals with obesity [30]. It accumulated a lot of evidence that this treatment can bring to the regression of NASH, at least in some patients. An important caveat to this therapeutic approach is that rapid weight loss can lead to the progression of NAFLD. Currently, bariatric surgery is suggested for patients with a BMI>40 kg/m^2 or obese, a BMI>35 kg/m^2. However, in patients with cirrhosis of the liver safety of bariatric surgery is still under study.

Patients with decompensated cirrhosis associated NAFLD liver transplant should be considered as an alternative method of treatment [8, 12, 15].Concomitant diseases (e.g., obesity, severe diabetes complications, cardiovascular diseases) and the fear of perioperative liver complications in these patients can prevent transplant. After transplantation of the liver allografts rapid progression of the disease to steatohepatitis and cirrhosis is possible [19].

Thus, prevention of obesity and its complications is currently one of the major health goals. NAFLD early detection is necessary in obese patients with signs of insulin resistance or other components of the metabolic syndrome. Timely diagnosis of possible risk factors for an unfavorable course of the disease is important to select the appropriate treatment, preventing further progression of NAFLD.

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Leading place among metabolic disorders, such as diabetes of the 2nd type, infringement of glucose tolerance, insulin-resistance, adiposity and/or modification of blood lipid spectrum resulting in heavy inflammation and destructive processes quite often up to development of hepatic cirrhosis, is taken by primary non-alcoholic fatty liver disease.

Timely diagnostics and detection of possible risk factors of adverse course of the disease are necessary in veiw of selection of rational methods of treatment preventing further progress of non-alcoholic fatty liver disease.