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THERAPY

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MODERN TRENDS IN THE DIAGNOSIS AND TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE IN OVERWEIGHT SUBJECTS (review)

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a scourge of the planet's population, especially the developed countries. NAFLD development is due to the global increase in the number of overweight and obese people. NAFLD in its turn is the main factor of cardiovascular risk development. Early detection of the cardiovascular risk development with underlying NAFLD and overweight remains understudied. This article reviews the literature dealing with the diagnosis and treatment of NAFLD in overweight subjects.

KeyWords: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, hypertension, endothelial lipase, lipid metabolism, overweight.

1.1 Non-alcoholic fatty liver disease: modern understanding and the state of affairs in relation to overweight.

According to one of the leading gastroenterological and hepatological organizations – the World Gastroenterology Organisation (WGO) – non-alcoholic fatty liver disease (NAFLD) usually means a common chronic hepatic disease mainly manifested as accumulation of triglycerides in hepatocytes contributing to the development of subclinical inflammation not associated with alcohol abuse. NAFLD is a complex of pathologies from steatosis to progressive inflammation – non-alcoholic steatohepatitis (NASH) with possible development of hepatic cirrhosis and hepatocellular carcinoma [1]. Morphological criteria of steatosis include macrovesicular lipid storage in more than 5% of hepatocytes [2].

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NAFLD is diagnosed in 20-30% of population in Western European countries and the USA and in 15% of Asian population [7].

The prevalence of NASH as one of NAFLD forms is lower and amounts to 2-3% in general population and 16-37% in overweight groups [8]. NAFLD increases general mortality rates in patients as compared to general population of the same age and sex [9]. The main mortality factor of patients with NAFLD is cardiovascular diseases (25%) [10]. According to G. Marchesini et al. (2001), 67% of patients with NAFLD suffer from overweight; 57% have impaired glucose tolerance, 47% – hypertriglyceridemia, 27% – decreased alpha cholesterol rates, and 17% – hypertension [11].

Manifestations of NAFLD are rather scarce. Common reasons for visiting a doctor include arterial hypertension (AH), diabetes mellitus (DM), coronary artery disease

Steady increase in the incidence of NAFLD correlates with the growing number of overweight patients [3, 4]. For this reason, NAFLD is considered as one of the most common hepatological conditions leading to deteriorated life quality, disability and mortality [5, 6].

(CAD), and cholelithiasis. The majority of patients are females (65-85%) with a mean age of 50 years old. In most cases, BMI is greater than 25 kg/m^2. Clinical symptoms are absent in 50-100% with the most common ones being asthenic syndrome, abdominal discomfort, and heaviness in the right subcostal area [12].

The generalizing NAFLD pathogenesis model was previously believed to be the "theory of two hits", according to which the "first hit" is an increased influx of free fatty acids (FFA) in the liver. The accumulation of fat in hepatocytes is a consequence of FFAs coming from the fatty tissue, their slower oxidation in mitochondria and excessive synthesis of FFAs from acetyl coenzyme A. The increased influx of FFAs and their slower oxidation lead to FFA esterification with excessive formation of triglycerides in hepatocytes and excessive secretion of very-low-density lipoprotein cholesterol (VLDLP CS), which enhances free-radical oxidation of lipids and accumulation of the peroxidation products ("second hit") [13]. Thus, the liver is a target organ in this case; hepatomegaly in patients with overweight or abdominal obesity (AO) is due to the accumulation of fat on account of its expansion from natural sources and to the fact that the hepatocyte apoptosis rate is lower than the proliferation rate [14].

Fibrosis is a result of the steatohepatitis transformation through the merging of fat deposits during hepatocyte breaking with the formation of cysts, inflow of a large amount of lipids from hepatocytes to the interstitial region with an inflammatory reaction and fibrotic changes, mechanical and inflammatory damage of hepatic veins and development of perivenular fibrosis. The development of hepatic cirrhosis is due to the obstruction of hepatic veins, ischemic necroses and collapse of hepatic lobes with the development of connective tissue septa. It is known that the liver performs a number of functions to ensure normal activity of the human body – excretory, digestive, energy, exchange, blood-making, synthetic, deintoxicating, protective, homeostatic, endocrine, and metabolic. The metabolic role consists in the exchange of lipids, proteins, carbohydrates, pigments, enzymes, bioactive substances and microelements. Hepatic metabolic impairments can be divided into primary, which are due to endogenous factors and genetic mutations, and secondary, which are caused by exogenous and endogenous xenobiotics. Thus, primary and secondary hepatic metabolic impairments affect hepatocyte functions disrupting the exchange of bilirubin, biliary acids, proteins, amino acids, glyco- and lipoproteins, porphyrin, copper, iron, mucopolysaccharides, carbohydrates and lipids. Therefore, NAFLD can be both an independent disease and combined with obesity, diabetes mellitus and dyslipidaemia [15].

It has been found in the process of studying lipid exchange that some of its types, especially FFA, have independent toxic action on hepatic cells. It initiated the study of "lipotoxicity" and helped substantiate the relation between the excessive influx of FFAs with food, insulin resistance and the order of events leading to hepatocyte damage. Steatosis ceased to be considered as a precondition for hepatocyte damage. Excessive accumulation of triglycerides (TG) in the cells reflects the adaptive reaction of neutralizing the excess of FFAs [16].

Excessive accumulation of FFAs in hepatocytes plays an important role in NAFLD pathogenesis. The reasons for the "overload" with fatty acids may include:

- excessive influx of FFAs with food (as a result of hydrolysis of food triglycerides) and without it (as a result of active lipolysis in the fatty tissue in case of insulin resistance)
- decreased activity of beta oxidation of fatty acids in hepatocytes in case of insulin resistance (IR)
- impaired export of VLDLPs from hepatocytes in case of impaired synthesis of apoproteins C, E and B.

Unsaturated FFAs are quicker to get bound and prevail in the structure of TGs and phospholipids. Mitochondrial dysfunction combined with NAFLD means structural and functional changes accompanied by membrane damage, disrupted functioning of ion channels and transmembrane potential, decreased synthesis of ATP, pore formation in the membrane, causing an outflow of matrix components

to the cytoplasm. Mitochondrial dysfunction may trigger internal apoptosis and develops at the background of oxidation stress. FFA-initiated cell death is called "lipoapoptosis", and oxidation stress contributes to it [17].

Oxidation stress causes lipid peroxidation, mitochondrial damage and increased secretion of cytokines – TNF-α, IL-6 and IL-8, which leads to inflammation, apoptosis and hepatocyte necrosis further causing fibrosis and hepatic cirrhosis [18].

NAFLD affected by overweight or obesity presupposes impaired secretion of adipokine hormones by the fatty tissue leading to the hyposensitivity of tissues to insulin on account of decreased levels of adiponectin, increased levels of visfatin and resistin and increased levels of chemokines that activate macrophages and contribute to their accumulation in the fatty tissue. Activated macrophages produce cytokines which adversely affect insulin sensitivity [19].

According to I.R. Popova, the prevalence of fatty hepatosis and non-alcoholic steatohepatitis (NASH) is growing with the increase in the body mass index (BMI). In obese patients hepatic steatosis occurs 2.7 times more frequently than in patients with normal BMI, and NASH – eight times more frequently [20].

The notion of abdominal obesity (AO) is introduced which, according to NCEP ATP III, was diagnosed in case of a waist measurement (WM) of more than 102 cm in males and more than 88 cm in females. Abdominal obesity contributes to fast progression of cardiovascular diseases, their severity and incidence of complications. According to INTERHEART study, abdominal obesity is an independent risk factor of myocardial infarction [21].

Abdominal overweight type is an independent risk factor of NAFLD. Progressive weight gain contributes to a faster development of NAFLD; thus, the risk of its development increases by 45% if a person gains 2 kg or more a year. Every 2.5 cm of waist measurement increases blood pressure by 10%, total cholesterol by 8% and triglycerides 18%, and decrease high-density lipoproteids (HDLP) by 15% [12].

For many years, liver biopsy has been the "golden standard" of NAFLD diagnostics. This methods allows assessing pathognomonic morphological symptoms, determine structural organ changes and the degree of connective tissue development [22]. But this method has a number of disadvantages, among which the first is its invasiveness. Biopsy is associated with a risk of complications with the most common being abdominal pain (approximately in 25% of cases). The share of complications requiring hospitalization or extended in-patient care is 1–3%. According to the analysis of the structure and aetiology of biopsy-associated complications, the incidence of complications increases proportionally to the amount of biopsy material and the number of sessions and when biopsy is performed in patients with relative counter-indications [23].

Other limitations include the so called sampling error. It means that, if there is no evidence of pathological processes in the biopsy material, the probability of a hepatic disease cannot be completely ruled out. On the one hand, the possibility of this error is explained by the fact that the morphologist assesses the nature and intensity of hepatic changes based on a fragment of hepatic tissue containing at least 3–4 portal tracts. On the other hand, the sampling error is due to the heterogeneity and different intensity of hepatic changes. In its turn, it results in a low representativeness of biopsy findings [24].

Besides, the interpretation of morphological biopsy findings largely depends on the morphologist's experience so the subjective factor cannot be eliminated, either. Thus, both an underestimation of the existing changes and a hyperdiagnosis of certain liver diseases and fibrosis grades can take place during liver biopsy examinations.

Other limitations include high costs of the procedure, and impossibility to perform frequent repeated biopsies; therefore, this method cannot be used for assessing chronic liver disease progression and therapy efficiency. Furthermore, there is a number of biopsy counter-indications, including coagulopathy, haemangioma or liver echinococcosis [24].

According to 2016 clinical recommendations of EASL-

EASD–EASO for the diagnosis and treatment of NAFLD, the diagnosis of NAFLD is based on the presence of 4 criteria:

1 Liver steatosis according to imaging tests: more clinically applicable ultrasound or MRI, and other techniques such as elastography, MRS, etc.
2 No history of alcohol abuse. According to the past history survey findings of alcohol use and abuse, i.e. more than 21 alcohol units per week for males and more than 14 alcohol units per week for females.
3 No concurrent etiological diseases such as hepatitis C.
4 No other comorbid chronic liver diseases such as virus hepatitis B and C, autoimmune hepatitis, α1-antitrypsin deficiency, Wilson's disease, malignant liver lesions, biliary tract pathology, and drug-induced injury [29].

The most accessible non-invasive diagnostic technique of liver steatosis is abdominal ultrasound scanning. Ultrasound is the preferable technique for the first-line NAFLD diagnosis because it provides additional diagnostic data. It has A1 strength of recommendation [26]. The main diagnostic criteria include increased liver size, increased echogenicity, flattening of the vascular pattern [27]. According to the literature, sensitivity and specificity of this technique is 60–94 and 88–95%, respectively [28].

According to the authors of EASL–EASD–EASO 2016 recommendations for the diagnosis and treatment of NAFLD, the most reliable scales for assessing steatosis are fatty liver index (FLI), SteatoTest and NAFLD liver fat score. Their external validity was confirmed among the general population and among obese patients; they also predict outcomes and mortality rates associated with metabolic, hepatic, and cardiovascular conditions with different degrees of accuracy. These rates are closely linked with IR and reliably predict steatosis [29].

According to S. McPherson et al., the predictive value of the negative AST/ALT test result is 93%, which leads to a conclusion that this index can rule our severe fibrosis in patients with NAFLD with a high degree of confidence [30].

Besides, several authors have offered several other quantitative indices for the estimation of NAFLD and fibrosis risks:

1. HAIR index taking into account hypertension, ALAT > 40 IU/L and IR. It has 80% sensitivity and 89% specificity [31].
2. BAAT index taking into account BMI >28 kg/m^2, age >50 years, ALT and TG increase level [32].
3. Forns index taking into account age, platelet count, GGTP, and cholesterol [33].
4. Bonacini index – platelet count, ALT/AST ratio, INR [34].
5. FIB4 index (ALT, AST, platelet count, age) [35].
6. APRI index (AST to platelet count ratio) [36].

According to Shimada M. et al. (2007), almost all patients with NAFLD and overweight had symptoms of IR assessed through the insulin resistance index HOMA-IR [38]. As a non-invasive marker during the measurement of IR quantitative characteristics at the background of the activity level of the synthesis of adiponectin, HOMA-IR and collagen 4, sensitivity and specificity were 94% and 74% [38].

In an attempt to build an optimum predictive model using clinical and laboratory values for the differentiation of fatty hepatosis from NASH, the complex NashTest system was proposed that encompasses 13 variables such as age, sex, height, weight, TG level, cholesterol, α2-macroglobuline, apolipoprotein A1, haptoglobin, GGT, ALT, AST, and bilirubin. This model demonstrated 33% sensitivity and 66% specificity [39].

Another study used hypertension, DM, AST, ALT, obstructive sleep apnea syndrome, and belonging to a non-black racial group as components of the diagnostic model for determining the NAFLD stage in patients with obesity [40].

Miele et al. proposed a mathematical model based on the analysis of age and the concentration of hyaluronic acid and metalloproteinkinase 1 tissue inhibitor. The sensitivity and specificity of this method during the NASH diagnostics was 86% and 90% respectively; however, these findings need to be confirmed in larger independent studies [41].

The issue of the presence and grade of fibrosis was relevant for diagnosing NAFLD severity and progression. FibroTest was created with the aim to diagnose liver fibrosis in patients with chronic viral hepatitis C. It includes the

following biochemical parameters: α2-globulin, apolipoprotein A1, haptoglobin, total bilirubin and GGT. While testing this method in patients with NAFLD, it was established that the mean FibroTest result grows steadily as the fibrosis stage goes up. Thus, at 0.3 points, FibroTest demonstrated 77% sensitivity and 90% general predictive value for diagnosing fibrosis at F1 and F2 stages [42]. However, similar values at 0.7 points were 98% and 76%, respectively [43], which indicates better results for diagnosing F3 and F4 stage fibrosis.

Another relatively new method for diagnosing fibrosis is FibroScan elastography, which is based on determining liver tissue elasticity by measuring the velocity of ultrasound wave propagation through liver parenchyma. Parenchyma elasticity expressed in kPa is significantly correlated with the liver fibrosis grade [44]. However, according to D.Roulot et al., increased BMI without pronounced liver fibrosis is associated with increased liver density, which means low descriptive value of this method for overweight and obese patients [45].

1.2 NAFLD treatment principles

The pandemic of obesity and diabetes mellitus along with improved control of chronic virus hepatitis caused NAFLD to become a major chronic liver disease and a serious health care issue due to a rise in hepatic and extrahepatic mortality. This shift in the epidemiology of the chronic liver disease in the context of a great number of ambiguous recommendations concerning the diagnostics and treatment of this disease make physicians face many questions because these patients need a multidisciplinary approach in order to take into account all possible modifying factors [46].

It should be taken into account that strict clinical recommendations for the strategic approach of NAFLD treatment has not been developed so far. In 2012, the American Association for the Study of Liver Diseases (AASLD), the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) published the practical guideline “Diagnosis and Treatment of Fatty Liver Disease”, which states that body mass reduction achieved by a hypocaloric or combined diet with increased physical activity leads to a decrease in the intensity of liver steatosis. It is also stated a 3-5% body mass reduction is needed to reduce the intensity of steatosis, but a 10% body mass reduction is needed to reduce the intensity of necrosis and inflammation. Increased physical activity as a monotherapy of NAFLD may reduce the intensity of steatosis, but it still unknown of other histological liver indicators also improve [47].

The recommendations of the World Gastroenterology Organisation (WGO) concerning a number of questions do not comply with the AASLD recommendations. 2012 WGO recommendations maintain that NASH therapy objectives include the improvement of the histological picture, IR and oxidation stress reduction, and normalization of the transaminase rate. It is emphasized that there is currently no medicinal therapy for NAFLD/NASH based on the principles of the evidence-based medicine. It is recommended to change the lifestyle (5-10% body mass reduction, increased physical activity) and correct diabetes, hyperlipidaemia, and cardiovascular risks [1].

Modern approaches to the therapy of NAFLD associated with MS are also based on principles that include body mass reduction, hyperglycaemia correction and hyperlipidaemia with obligatory discontinuation of potentially hepatotoxic agents. Primary activities should include those aimed at decreasing body mass: change of lifestyle, reduction of caloric value, and increase in physical activity [48].

Thus, the treatment of patients with obesity and NAFLD is based on non-medicinal techniques: balanced antiatherogenic nutrition with fat content not exceeding 25–30% of daily caloric value: hypocaloric (with moderate caloric deficit of daily ration of 500–600 kcal) diet at the stage of mass reduction and eucaloric at the maintenance stage [49].

One of the central roles in the treatment of patients with early carbohydrate metabolism impairments is played by metformin. Thus, the Diabetes Prevention Program (DPP), 2002 study convincingly demonstrated that the therapy with metformin decreases the risk of DM by 31% in patients

with impaired glucose tolerance, especially in those with BMI >25 kg/m2 [50]. The data collected over many years caused the American Diabetes Association recommends prescribing metformin to all patients with pre-diabetes (impaired glucose tolerance and impaired fasting glucose), especially those with BMI ≥25 kg/m2, aged below 60 years old and females with prior gestation diabetes [51].

Studies of several authors showed that a significant decrease in IR and hepatic transaminases and improvement of metabolic values were reported at the background of metformin therapy combined with hypocaloric diet for 6 months in patients with metabolic syndrome (MS) and NAFLD [3]. However, in a number of studies, metformin therapy in NASH was not accompanied by histological improvement which caused its role in clinical recommendations to be adjusted [52].

Experts of the American Association for the Study of Liver Diseases use statins and vitamin E for the treatment of NAFLD. The efficiency of antioxidants and cytoprotectors for NASH is questioned [53]; however, the findings of the PIVENS study on the efficiency of vitamin E confirm histological shifts towards decreased intensity of inflammation in hepatocytes in patients with NASH [54]. It was shown that in patients without DM with histologically verified NASH, long-term therapy with vitamin E 800 mg/day has a pronounced antioxidant action and leads to both histological and clinical laboratory improvement. Vitamin E is not recommended for the treatment of NASH in patients with DM, confirmed NAFLD biopsy, steatohepatitis with progression to liver cirrhosis and cryptogenic cirrhosis [48].

According to M. Ekstedt (2007), patients with NAFLD who received statins demonstrated more intensive histologically confirmed reduction of liver steatosis as compared to patients with NAFLD who did not receive statins [55]. According to C. Argo (2008), statins influence the level of gene expression responsible for fibrosis progression and the rate of reparation processes [56].

A decrease in the concentration of TNF-α, IL-6, and c-reactive protein (CRP) served as the mechanism of beneficial effect of statins on the development of NASH. It is believed that statins may affect angiogenesis, growth of tumour cells, apoptosis and metastatic activity, which can prevent the development of hepatocellular carcinoma [57].

According to V.T. Ivashkin (2011), for administration of statins is not dependent on the presence of NAFLD and obesity, elevated liver transaminases observed in 0.5-2% of cases, depending on the dose and drug is transient [57], and in patients with initially increased levels of transaminases (AST>40 IU/l, ALT>35 IU/l) the intake of statins did not produse their increase. According to AGC and AGA recommendations, these drugs cannot be used to specifically treat NASH [48].

Medicinal agents from the incretin group have certain potential for inhibiting NAFLD progression to cirrhosis; however, there is no convincing evidence about their efficiency in patients with NAFLD so far although pre-clinical studies point to their ability to decrease the progression of liver steatosis [59].

Anti-cytokine agents (monoclonal TNF-α inhibitors) for NAFLD were studied in a number of small studies showing that their use decreases the intensity of steatosis, inflammation and intensity of oxidation stress in hepatocytes [60].

Ursodeoxycholic acid (UDCA) is a natural hydrophilic biliary acid, and the immunomodulating and antiapoptic properties of UDCA inhibit the development of NAFLD [61]. The most efficient, accessible and pathogenically justified NAFLD treatment technique (especially in cholestatic forms) is the use of UDCA agents. The therapeutic effect of UDCA is primarily accounted for by the membrane-stabilizing, antioxidant, cholestatic, and immunomodulating action; the drug increases the sensitivity of receptors to insulin, activates the farnesoid X receptor playing a key role in the pathogenesis of NAFLD and lipid pathogenesis. UDCA has an anti-inflammatory effect mediated by a decrease in anti-inflammatory cytokines [62]. However, due to the lack of evidence the Association does not recommend prescribing ursodeoxycholic acid agent to patients with NAFLD and NASH [48].

The liver plays an important role in the development of dyslipidemia and is a target for lipid metabolism impairments being one of the pathogenic stages of NAFLD development, which stimulates the search for medicinal hepatocyte "support" methods. Therefore, agents may be recommended that contain essential polyunsaturated fatty acids. The use of essential phospholipid agents as sources of cell membrane structural elements is pathogenically justified and confirmed by multiple studies. The main active substance is 1,2-dilinoleophosphatidylcholine which is not synthesized in the human body. The presence of two essential fatty acids accounts for the advantage of this special phospholipid form over the endogenous ones [63].

The membrane-stabilizing and hepatoprotective effect of essential phospholipids (EPLs) is achieved by the direct incorporation of their molecules into the phospholipid structure of damaged liver cells, recovery of defects and restoration of the barrier function of the lipid layer. Unsaturated fatty acids of phospholipids contribute to increased activity and fluidity of membranes, activation of phospholipid-dependent enzymes and transport proteins, decreased density of phospholipid structures, and normalization of membrane permeability, which in its turn improves the detoxification and excretory liver potential [64]. In terms of their molecular structure, phospholipids are more similar to triglycerides. The only difference is that one of three fatty acids is substituted by a phosphoric acid ester. Phospholipids differ depending on the nature of the substitute bound to the phosphoric group.

The main therapeutic effect of phospholipids depends on the concentration of phosphatidylcholine, whose molecule has a non-polar (two fatty acid groups) and a polar (phosphoryl choline) part. It is this structure that accounts for the active surface features of phosphoryl choline. Besides, being a good emulsifier, phosphoryl choline increases the bioavailability of nutrients, with which it is injected, decreases the depositing of cholesterol in the liver thus promoting the inhibition of cholesterol acyltransferase by phospholipids. EPLs have antioxidant effect and can slow down the synthesis of collagen by increasing the activity of collagenase [65]. The decreased level of blood cholesterol and its increased excretion with bile is associated with the ability of EPLs to concurrently affect the absorption of cholesterol in the intestine, decrease the membrane concentration of cholesterol and, combined with bile acids, improve its solubility in the bile. The efficiency of polyunsaturated phosphoryl choline in patients with fatty liver disease of different genesis is accounted both by its ability to induce the triglyceride-lipase of hepatocytes promoting the release of fatty acids to the bloodstream. The specific nature of essential phospholipids enable them to substitute for the phospholipids of blood lipoproteins – chylomicrons (ranging up to 80%), very low and low-density lipoproteins (up to 15%), but mainly high-density lipoproteins (80%) and thus to be transported with blood and lymph [63].

Dosages and the duration of EPL treatment are individual and depend on the clinical laboratory and instrumental results. Taking into account the increased activity of lipoprotein lipase that enhances the intravascular splitting of chylomicrons and VLDLPs, the improvement of the function of insulin receptors and the increased activity of lecithin-cholesterol acyltransferase involved in the esterification of HDLP cholesterol, the use of EPLs is pathogenically justified for the treatment of NAFLD, especially if accompanied by metabolic impairments [43].

CONCLUSIONS

Non-alcoholic fatty liver disease is a very common disease among the world's population. Most often, NAFLD is associated with visceral obesity, which leads to an increased risk of cardiovascular disease in these patients. Also, it is clear that in the majority of the patients, NAFLD is characterized by a long, stable asymptomatic course. In turn, the timely diagnosis can significantly improve the patient's quality of life and prevent fatal complications.

Conflict of interests

There is no conflict of interests.

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