УДК 616.36-003.836-007.1+616.379-008.64]-07-08
DOI http://doi.org/10.30978/MG-2023-6-59

ISSN 1727-5725 (Print)
ISSN 2521-649X (Online)

T. M. Bentsa
Shupyk National Healthcare University of Ukraine, Kyiv

Non-alcoholic fatty liver disease and type 2 diabetes mellitus: diagnostic and therapeutic aspects. Review

The increase in the prevalence of non-alcoholic fatty liver disease (NAFLD) occurs in parallel with the global epidemic of obesity and type 2 diabetes mellitus (T2DM) in the world. T2DM is an independent risk factor for the development of NAFLD. At the same time, researchers found that patients diagnosed with NAFLD have a two-fold increased risk of developing T2DM. NAFLD is encompasses a spectrum of liver manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, which may ultimately progress to hepatocellular carcinoma. NASH is an aggressive form of NAFLD, associated with an increased risk of liver and non-liver-related mortality. Liver-biopsy remains the gold standard for diagnosis, but the majority of patients liver damage can be diagnosed accurately by noninvasive methods.

The presence of NAFLD in a patient with T2DM makes it difficult to achieve adequate glycemic control, deepens the manifestations of insulin resistance and atherogenic dyslipidemia, increases the risk of serious cardiovascular events and chronic kidney disease. Lifestyle modification and treatment of concomitant T2DM should be undertaken in all patients with NAFLD. To reduce the severity of liver steatosis, weight reduction by 3—5 % is necessary, to reduce the inflammatory-necrotic process, a more significant reduction may be required — up to 10 % within 6—12 months. Physical activity increases the sensitivity of insulin receptors, and in combination with diet leads to a significantly significant improvement in biochemical and histological indicators in patients with NAFLD. Early identification and management of patients with intensive dietary and lifestyle modification are essential to prevent the development of advanced liver disease and its complications. Pharmacological therapy should be administered to patients with NASH purposed on the fibrosis inhibition, especially in case of the established predictors of high risk of disease progression (age > 50 years, metabolic syndrome, T2DM, or increase in the activity of alanine aminotransferase), as well as to the patients with active NASH with high inflammatory activity.

At the congress of the European Association for the Study of the Liver (EASL), which took place in Vienna on June 21—24, 2023, a new classification and nomenclature of NAFLD was adopted. It was proposed to replace the term «non-alcoholic fatty liver disease» to the term «metabolic dysfunction-associated steatotic liver disease» (MASLD). This diagnosis is established in patients with confirmed steatosis of the liver and one of five cardiometabolic risk factors: obesity, T2DM, insulin resistance, hyperlipidemia, atherosclerosis. The concept of «non-alcoholic steatohepatitis» (NASH) has been changed to the concept of «metabolic dysfunction- associated steatohepatitis» (MASH). Coordination of the views of international and domestic experts in the field of studying this pathology will be important for clinical practice and scientific research.

Keywords: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, type 2 diabetes mellitus, diagnostics, treatment.

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, which in recent years has become an epidemic of the 21st century [11, 60]. The study of trends and changes in the prevalence, morbidity and mortality from chronic liver diseases among adolescents

Отримано • *Received* 30/09/2023. Прийнято до друку • *Accepted* 29/10/2023

Контактна інформація • *Corresponding author*
Бенца Тетяна Михайлівна, д. мед. н., проф., проф. кафедри терапії. E-mail: bentsa_t@i.ua. http://orcid.org/0000-0001-9427-2549

and young people in 21 regions made it possible to establish that during the years 2009—2019 there was an increase in indicators due to NAFLD [47]. A systematic review and meta-analysis of 92 epidemiological studies (9 million participants from 22 countries) showed that 30 % of the world's adult population suffers from NAFLD [69]. The increase in the prevalence of this pathology occurs in parallel with the global epidemic of obesity and type 2 diabetes mellitus (T2DM) in the world [60].

It is known that T2DM is an independent risk factor for the development of NAFLD [3]. According to the results of a meta-analysis of 10 studies, the prevalence of NAFLD among patients with T2DM was 55.5 %, and nonalcoholic steatohepatitis (NASH) was 37.3 % [68]. Significant regional differences in the prevalence of NAFLD among T2DM patients deserve special attention: the highest in Europe (62.1—73 %), the lowest in the African continent [68].

At the same time, researchers found that patients diagnosed with NAFLD have a two-fold increased risk of developing T2DM [59], which is closely correlated with the severity of NAFLD, the progression of NASH, the severity of fibrosis, and the development of hepatocellular carcinoma (HCC) [38, 67].

NAFLD is closely associated with conditions characterized by systemic low-grade inflammation and insulin resistance (IR). IR is a driver of NAFLD progression, and the presence of diabetes predicts the possibility of progression of steatosis to advanced liver fibrosis. Hyperinsulinemia induced by peripheral IR can stimulate lipogenesis in the liver. As a result of the development of IR, the absorption of glucose by hepatocytes, adipocytes, and muscle tissue decreases, the synthesis of glycogen and triglycerides in the liver is inhibited, and glycolysis, lipolysis, and neoglycogenesis are activated [5].

It is known that up to 80 % of patients with NAFLD suffer from obesity and have a body mass index (BMI) > 30 kg/m^2. However, adipose tissue distribution plays a more important role in IR than BMI. A greater amount of visceral adipose tissue in morbidly obese individuals contributes to the development of NAFLD [5, 21]. Free fatty acids from visceral adipose tissue, as well as from food and synthesized by *de novo* lipogenesis, enter the portal vein system in large quantities. An excess of free fatty acids (the phenomenon of lipotoxicity) and chronic indolent inflammation are considered important factors in the progression of liver damage, which contribute to the transformation of steatosis into NASH. It was established that free fatty acids due to their active metabolism in the mitochondria of target tissue cells accelerate free radical peroxidation of lipids. Oxidative stress inhibits the replication of hepatocytes, which leads to an increase in the number of progenitor cells that can differentiate into both hepatocytes and cholangiocytes, and their number correlates with the stage of fibrosis [18]. A study of 342 serial biopsy samples and liver gene expression profiles in 118 subjects clinically diagnosed with NAFLD and diabetes suggested that diabetes-induced hypoxia and oxidative stress injure central sinusoidal endothelial cells in zone 3 hepatocytes, which may mediate inflammation and stellate cells activation, leading to liver fibrosis. Elevated glycosylated hemoglobin (HbA1c) in patients with NAFLD and diabetes was significantly associated with progression of liver fibrosis independent of weight gain, which may be a valuable therapeutic target to prevent pathological progression of NASH [53].

In addition, secretion of adipokines from visceral adipose tissue, as well as lipid accumulation in the liver, further contribute to inflammation through nuclear factor kappa B signaling pathways, which are also activated by free fatty acids and contribute to IR. In patients with NAFLD and obesity, the level of adiponectin is significantly lower than in individuals without NAFLD, and it is negatively correlated with the content of fat in the liver. Hypoadiponectinemia is considered as one of the predictors of the development of T2DM and cardiovascular diseases [5].

The level of ferritin as a reagent of the acute phase, induced in conditions of chronic systemic inflammation, increases in patients with T2DM. However, it has been established that elevated ferritin levels are associated with NASH and are an independent predictor of the severity of fibrosis in biopsy-verified NAFLD patients [29].

At the stage of steatosis, NAFLD is characterized by a relatively benign and slowly progressive course. But NASH often remains unrecognized for a long time, in the absence of adequate treatment in 50 % of cases it progresses and can lead to the development of fibrosis and cirrhosis of the liver [6]. Approximately 5 % of patients with NAFLD may develop liver cirrhosis and/or HCC complications during long-term follow-up [50, 52]. However, it should be noted that most patients with non-advanced NAFLD (i.e. fibrosis stage F 0—2) have extrahepatic events, and the main cause of death in these patients is cardiovascular disease rather than liver-related events [49].

Coexistence of NAFLD and T2DM is common in everyday outpatient practice. Not only T2DM, but also prediabetes have been found to be independently associated with portal inflammation, NASH,

fibrosis, and more severe histological manifestations in patients with NAFLD. It is obvious that T2DM is a significant risk factor for the development and progression of liver fibrosis and cirrhosis [14, 36].

A study of 713 patients from the Duke NAFLD Clinical Database with biopsy-proven NAFLD (48 % with T2DM) established a link between liver injury and glycemic control. A higher mean level of HbA1c was associated with a higher grade of steatosis and ballooned hepatocytes. Every 1 % increase in mean HbA1c per year was independently associated with 15 % increased likelihood of developing more severe stages of liver fibrosis, highlighting the impact of glycemia on fibrosis progression [2].

In a recent real-world study examined the healthcare records of 18 million adult patients from European primary care databases. Patients with a recorded diagnosis of NAFLD or NASH were followed up for incident of liver cirrhosis and diagnoses of HCC. The strongest independent predictor of a diagnosis of HCC or cirrhosis was baseline diagnosis of diabetes [1]. Another study found that the presence of T2DM in patients with cirrhosis due to NASH was associated with a fourfold increase in the risk of HCC [67].

The presence of NAFLD in a patient with T2DM makes it difficult to achieve adequate glycemic control, deepens the manifestations of IR and atherogenic dyslipidemia [36]. The diagnosis of NAFLD is associated with a low risk of complications, but the coexistence of NAFLD and T2DM significantly worsens the prognosis and increases the risk of serious cardiovascular events and chronic kidney disease [32]. These patients have dyslipidemia, as well as higher hepatic steatosis and inflammation. Moreover, they demonstrate elevated blood pressure, increased levels of low-density lipoprotein (LDL) and triglycerides (TG), while their high-density lipoprotein (HDL) levels are reduced. Thus, T2DM patients with NAFLD have more severe dyslipidemia, hyperinsulinemia and hepatic IR than those without fatty livers [70].

In addition to the importance of establishing the diagnosis of NAFLD or NASH in a patient with T2DM and the degree of disease activity, the presence and stage of fibrosis must be determined in each patient, as it has been shown that the degree of fibrosis, rather than the presence/absence of NASH, affects the prognosis mostly. Marked fibrosis (F 3—4) is recognized as the strongest predictor of long-term death in NAFLD. Patients with mild steatosis may have significant fibrosis or, on the contrary, with marked steatosis, no fibrosis or a slight degree of fibrous changes [36]. Quantitative indicators of severity and rate of progression of fibrosis are the most important clinical parameters, the determination of which is of crucial importance for its diagnosis, treatment selection and monitoring of therapy effectiveness [4].

Indicators of biochemical blood analysis in patients with steatosis are more often within normal values. In patients with NASH, there is an increase in the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gammaglutamyl transpeptidase (GGTP), alkaline phosphatase (AL). At the same time, the activity of ALT and AST exceeds the upper limit of normal by no more than 4—5 times, the AST/ALT index is no more than 1, and the level of ALT dominates the level of AST. An increase in the activity of AL and GGTP is noted no more than 2 times compared to the norm. In the transformation of fibrosis into cirrhosis of the liver, the predominance of AST over ALT, a decrease in the levels of total protein, albumin, prothrombin index, an increase in the level of bilirubin, and thrombocytopenia are determined. The degree of hypertransaminasemia does not correlate with the severity of steatosis and liver fibrosis [28, 63].

The gold standard for diagnosing and determining the stage of development of NAFLD remains a puncture biopsy of the liver with histological examination. The diagnosis of NAFLD is defined as presence of hepatic steatosis, ballooning and lobular inflammation with or without fibrosis. The main tests of functional liver activity used in clinical practice are nonspecific and do not always correlate with histological changes (damage, inflammation, fibrosis) [51]. The diagnosis of NASH is currently not possible without liver histology, but liver biopsy is usually performed only in patients with a high probability of liver fibrosis and cirrhosis [45].

Calculation algorithms are used for non-invasive diagnosis of NAFLD, which allow obtaining an accurate quantitative and qualitative assessment of fibrosis, steatosis and necroinflammatory changes in the liver at all stages regardless of localization [4]. Among the instrumental methods of diagnosis, ultrasound examination of the liver is the most common. The high sensitivity and specificity of this method in the diagnosis of NAFLD is noted when the fat content in the liver exceeds 30 % [4, 13]. Fibroscan, or transient elastography, is a non-invasive method of assessing liver stiffness using echo-ultrasound. The main disadvantage of the fibroscan is the inability to distinguish the change in liver stiffness (which is measured by determining the wave speed) in fibrosis from the presence of fatty infiltration in liver steatosis. Transient elastography with vibration control, computer and magnetic resonance imaging (MRI) are also used in the diagnosis of NAFLD [51].

To determine the various stages of NAFLD, modern non-invasive research methods are actively used: for the diagnosis of steatosis — Fatty liver index (FLI), ultrasound examination of the liver, FibroScan CAP, proton density of the liver fat fraction, measured by MRI (MR-PDFF); for the diagnosis of steatohepatitis — Cytokeratin-18, NIS4, FAST-Score, magnetic resonance liver MultiScan (MR LiverMultiScan); for diagnosis of fibrosis/cirrhosis — simple indicators (FIB-4, NFS), direct collagen biomarkers (ELF-Test, PRO-C3, NIS4), Fibroscan VCTE; Ultrasound: ARFI, SSI; MR LiverMultiScan; Magnetic resonance elastography [42]. European guidelines emphasize the importance of the widespread use of the NFS and FIB-4 scales, as well as transient elastography as non-invasive methods to identify patients at low risk of developing progressive fibrosis or liver cirrhosis, which will help to reduce the number of diagnostic biopsies in this patient cohort in the future. The use of transient elastography and serum markers makes it possible to diagnose the clinical progression of NAFLD, which requires pharmacological treatment, with a high prognostic significance of a positive result [4].

It has been established that some non-invasive indicators, in particular the hepatic steatosis index (HSI) and the fatty liver dystrophy index (FLI) can be used not only as predictors of NAFLD, but also to assess carotid atherosclerosis, in particular in T2DM. A cross-sectional study was conducted in patients with T2DM (n = 768). Carotid intima-media thickness (CIMT) was measured using color Doppler. HSI was calculated based on sex, BMI, and transaminase levels. FLI was based on BMI, waist circumference, levels of TG and GGTP. The results showed that increased levels of HSI and FLI were associated with increased levels of CIMT in patients with T2DM. The obtained data indicate that HSI and FLI are independently correlated with carotid atherosclerosis in T2DM. They can be simple and useful markers for assessing the progression of diabetic macrovascular complications [65].

Therapy of liver damage in patients with NAFLD should be aimed at preventing the progression of the disease to the stage of liver cirrhosis and hepatocellular failure, reducing the severity of IR, the activity of serum transaminases, the severity of liver steatosis, and improving the quality of life. Evidence-based clinical practice guidelines published by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), the European Association for the Study of Obesity (EASO) in 2016 [17], the American Association for the Study of Liver Diseases (AASLD) in 2023 (updated) [52].

Lifestyle modification and treatment of concomitant T2DM should be undertaken in all patients with NAFLD. To reduce the severity of liver steatosis, weight reduction by 3—5 % is necessary, to reduce the inflammatory-necrotic process, a more significant reduction may be required — up to 10 % within 6—12 months. A large systematic review and meta-analysis showed that weight reduction (≥ 7 %) is generally safe and improves liver histology and cardiometabolic profile in patients with NAFLD [23]. A study involving 261 patients with NAFLD with paired liver biopsies before and after lifestyle changes aimed at weight loss found that greater weight loss was associated with improved histological features of NASH with the highest rates of reduction in steatosis (100 %), resolution of NASH (90 %) and fibrosis regressions (45 %) observed in those patients with at least ≥ 10 % weight loss [64]. The Diabetes Remission Clinical Trial (DiRECT) demonstrated that weight loss in patients with T2DM for up to 6 years resulted in a reduction in liver fat (from 16.0 % ± 1.3 % to 3.1 % ± 0.5 %, $p < 0.0001$) and pancreas and restoration of β-cell function [35].

Undesirable complete starvation, as well as rapid weight loss (more than 0.5—1 kg per week), as this increases the manifestations of NASH. Reducing caloric intake by at least 500—1000 kcal can reduce hepatic steatosis and IR [23]. A low intake of fiber, vitamins and mineral nutrients supports the progression of NAFLD [27]. At the same time, a diet rich in fruits and vegetables has an antioxidant, anti-inflammatory effect and can improve IR [40].

A protein diet in patients with NAFLD and T2DM promotes the loss of liver fat, which is associated with an improvement in IR and a decrease in the cytolytic profile of the liver [16]. It is advisable to combine a balanced diet therapy with the limitation of fats (up to 25—30 % of the daily caloric intake), carbohydrates, the exclusion of components that contribute to NAFLD (for example, processed food, products with a high fructose content), with a moderate calorie deficit in the daily diet of 500—1000 kcal, adequate physical activity [17]. High fructose intake is associated with an increased risk of steatosis, liver fibrosis, obesity, and IR [12]. Long-term intake of sucrose leads to increased fat accumulation, glucose intolerance and hyperinsulinemia, as well as histological damage, in particular, an increase in the size of hepatocytes [58]. Dietary intake of monounsaturated fatty acids found in foods such as olive oil and avocado improves insulin sensitivity in patients with NAFLD and prediabetes [23].

The Mediterranean diet is high in antioxidants and dietary fiber, polyunsaturated fats, polyphenols,

vitamins, and carotenoids, and has a low glycemic load compared to conventional Western diets. It is rich in minimally processed plant foods, monounsaturated fats from extra virgin olive oil, seafood, but lower in saturated fat, red meat and dairy products. This diet has been shown to be associated with reduced levels of inflammatory biomarkers, effective in preventing cardiovascular disease risk factors [7]. In patients with NAFLD who followed a Mediterranean diet, a decrease in liver transaminase levels, a decrease in BMI, and an improvement in IR were observed [10, 23]. The DIRECT-PLUS 18-month randomized clinical trial in 294 patients with NAFLD studied the efficacy of a green-Mediterranean diet limited in red/processed meat and enriched in green plants and polyphenols. Loss of intrahepatic fat, quantified by proton magnetic resonance spectroscopy, was twice as great compared to other healthy eating strategies [44]. Currently, the current (2016) EASL-EASD-EASO guidelines recommend a Mediterranean diet for all patients with NAFLD [17].

Physical activity increases the sensitivity of insulin receptors, and in combination with diet leads to a significantly significant improvement in biochemical and histological indicators in patients with NAFLD [33]. 150—200 min per week of moderate-intensity aerobic exercise over three to five sessions is recommended [17].

Specific pharmacological treatment is performed mainly in patients with NASH and biopsy-proven fibrosis [52]. According to the current recommendations [17], pharmacotherapy for NASH is prescribed in the presence of significant fibrosis (≥ F2) or in the presence of minimal fibrosis (F 0—1) and a less severe course of the disease, but a high risk of progression (older age, T2DM, metabolic syndrome, persistent elevation of ALT) [17].

PPAR receptors (which are activated by peroxisome proliferator) play a key role in the regulation of lipid and insulin metabolism — the main components of the pathophysiology of NAFLD. Although the PPAR-γ ligand pioglitazone (30 mg/day) did not meet the endpoint in the PIVENS study, the pioglitazone group showed improvement in liver histology in 34 % of patients compared with 19 % in the placebo group, as well as a reduction in TG and an increase in HDL. However, pioglitazone treatment did not affect fibrosis. There was a significant mean weight gain of +4.7 kg at week 96 of treatment in the pioglitazone group [9, 43].

In a randomized, double-blind, placebo-controlled trial involving 101 patients with biopsy-proven NASH and prediabetes or T2DM, pioglitazone 45 mg/day for 18 months on a hypocaloric diet (500 kcal/day deficit) reduced histological fibrosis and TG in the liver (from 19 % to 7 %), and the sensitivity of the liver, adipose tissue, and muscles to insulin improved [15]. According to another meta-analysis, treatment with pioglitazone in patients with NAFLD combined with T2DM significantly reduced steatosis, balloonong and inflammation, and a decrease in transaminase levels [37]. In a study by Bril et al. pioglitazone has been shown to be effective in patients with biopsy-proven NASH, both with and without T2DM. However, a significant reduction in the fibrosis index and an increase in the sensitivity of adipose tissue to insulin during treatment with pioglitazone at a dose of 45 mg/day was observed only in patients with T2DM [8].

The EASL-EASD-EASO guidelines [17] state that pioglitazone «can be used» in patients with NASH and significant fibrosis, whereas the AASLD suggests that it «can be used» in patients with biopsy-proven NASH with T2DM [52].

In addition to the PPARγ agonist pioglitazone, which has found its place in international guidelines, several studies have reported the effects of PPAR-δ, -α/δ, -α/γ, and more recently Pan-PPAR agonists in patients with NAFLD.

Elafibranor, which acts as a PPAR-α and PPAR-δ receptor agonist, was developed for the treatment of NAFLD. The obtained data confirm the effect of elafibranor at a dose of 120 mg/day on the histological manifestations of NASH and the improvement of the two main factors of the progression of NASH — IR and dyslipidemia in the blood serum. The safety profile is favorable, although a transient increase in serum creatinine has been observed with this drug, potentially limiting its use in patients with concomitant kidney disease [66].

A randomized controlled clinical trial investigated the efficacy of the PPARα/γ agonist saroglitazar in patients with NAFLD/NASH. Saroglitazar in a dose of 4 mg/day significantly reduced the level of ALT, improved IR and atherogenic dyslipidemia [20].

The Pan-PPAR (peroxisome proliferator-activated receptor) agonist lanifibranor modulates key metabolic, inflammatory, and fibrogenic pathways in the pathogenesis of NASH. In a double-blind, placebo-controlled trial, 247 patients with highly active NASH were randomized, of whom 103 (42 %) had T2DM and 188 (76 %) had moderate or severe fibrosis. Lanifibranor was prescribed at a dose of 800 or 1200 mg once a day for 24 weeks. The best results were observed when taking the drug in a dose of 1200 mg per day. Liver enzyme levels decreased, most lipid, inflammatory and fibrotic biomarkers improved. Most important are resolution of NASH without worsening of fibrosis (49 %

with lanifibranor 1200 mg vs. 39 % with 800 mg vs. 22 % placebo), improvement of at least one stage of fibrosis without worsening of NASH (48 % vs. 34 % vs. 22 %) and resolution of NASH plus improvement stage of fibrosis by at least 1 (35 % vs. 25 % vs. 9 %) — all of which favored the study drug over placebo. Adverse events (diarrhea, nausea, peripheral edema, anemia, and weight gain) were observed in 5 % of patients treated with lanifibranor [19].

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide administered subcutaneously once daily at a dose of 0.1, 0.2, or 0.4 mg showed a significantly higher percentage of patients with resolution of NASH (and no worsening of fibrosis) compared to with placebo in a 72-week, double-blind study in 320 patients with biopsy-proven NASH and stage 1—3 fibrosis [46]. The results of a systematic review and meta-analysis of 11 randomized controlled trials (RCTs) that investigated the efficacy of GLP-1 RAs liraglutide, exenatide, dulaglutide, or semaglutide in 936 patients with NAFLD showed improvement in clinical and histological signs of NASH, reduction in serum liver enzyme levels [41].

A meta-analysis of 8 randomized controlled clinical trials of sodium-glucose co-inhibitors of transporter type 2 (SGLT-2) and GLP-1 RA in NAFLD and T2DM demonstrated a positive effect on glycemic control, a decrease in enzyme activity and an improvement in the histological picture of the liver [22, 61]. The experience of using SGLT-2 in the treatment of patients with NAFLD and T2DM showed that canagliflozin significantly improved liver function indicators, while dapagliflozin had a positive effect on glycemia and insulin sensitivity [37]. Another study found that ipragliflozin and canagliflozin have a beneficial effect not only on HbA1c and body weight, but also significantly reduce the activity of transaminases in patients with NAFLD and T2DM [56].

The FLINT study examined the effect of the steroid farnesoid nuclear X receptor (FXR) ligand obeticholic acid (25 mg/day) for 72 weeks in 283 patients with biopsy-proven noncirrhotic NASH. Significantly more patients in the obeticholic acid group (45 %) compared to placebo (21 %) demonstrated improvement in liver histology. Importantly, however, obeticholic acid reduced fibrosis in 35 % of patients versus only 19 % in the placebo group ($p = 0.004$). Skin itching was the main side effect of obeticholic acid (33 % vs. 6 % placebo). However, the FLINT study also showed an adverse effect on the lipid profile, i.e., a decrease in HDL and an increase in LDL, and these parameters should be closely monitored in patients with NAFLD during FXR ligand treatment [62]. Another study evaluated the effect of obeticholic acid therapy in NASH on lipoprotein subparticles. It was established that the number of small very LDL particles, large and small LDL particles increased and the number of HDL particles decreased after 12 weeks of treatment. However, 24 weeks after discontinuation of the drug, lipoprotein levels returned to baseline [57].

In a double-blind, placebo-controlled study with the participation of 140 patients with NASH, the efficacy and safety of cilofexor, a low molecular weight nonsteroidal farnesoid X receptor agonist, was evaluated. NASH was diagnosed using MRI or liver biopsy. Patients were randomized to receive cilofexor 30 or 100 mg orally once daily or placebo for 24 weeks. A decrease in steatosis, an improvement in the biochemical indicators of the liver and the level of bile acids in blood serum were established. However, significant changes in fibrosis markers and liver stiffness (determined by magnetic resonance elastography) were not observed. Cilofexor was generally well tolerated. Side effect include skin itching [48]. Similar results were obtained when treating patients with NASH with the nonsteroidal farnesoid X-receptor agonist tropifexor at a dose of 140 or 200 mg for 48 weeks. The most common adverse event was dose-dependent skin itching [55]. The ATLAS trial tested combination therapy of a nonsteroidal FXR agonist (cilofexor) with a lipogenesis inhibitor (firsokostat) and found significant improvement in NAFLD subcomponents (steatosis, lobular inflammation, and ballooning); however, there was no effect on fibrosis [39].

Thus, FXR ligands have shown the first promising results in RCTs examining their clinical efficacy. Nevertheless, open questions regarding optimal dosing to minimize potentially harmful side effects (dyslipidemia and skin itching) and the pathophysiological mechanisms of these side effects still remain unanswered and require further research [34].

Recently published data from studies of the effects of the fibroblast growth factor 19, intestinal hormone (FGF19) mimetic aldafermin in patients with NASH and stage 2—3 fibrosis showed no improvement in fibrosis or resolution of NASH after 6 months of therapy, but an improvement in the proton density of the liver fat fraction was observed, measured by MRI. Aldafermin was generally well tolerated [24].

The analogue of pegylated human fibroblast growth factor 21 (FGF-21) pegbelfermin was administered to obese NASH patients with T2DM subcutaneously at 10 mg once daily. A reduction in liver fat (the proton density of the liver fat fraction measured by MRI) and a decrease in liver transaminase

levels during the 16-week treatment period, as well as an improvement in the lipid profile, were demonstrated, but histological examination was not performed, which prevents the application of the results and requires further studies of the drug [54].

The randomized, placebo-controlled BALANCED trial conducted at 27 US centers in 80 patients with NASH of the FGF-21 mimetic efruxifermin (28, 50, or 70 mg subcutaneously weekly for 16 weeks) showed encouraging results (48 % improvement in fibrosis ≥ stage 1; 28 % disappearance of NASH). Gastrointestinal disorders were observed as side effects [26].

The selective thyroid hormone receptor beta (THR-B) agonist resmetirom (MGL-3196) improves hepatic fat metabolism and reduces lipotoxicity in patients with NASH. In a 36-week, double-blind, placebo-controlled trial, 84 patients were randomized to resmetirom. The drug was prescribed in a dose of 80 mg orally once a day. A reduction in liver fat (assessed by the proton density of the liver fat fraction measured by MRI) and a positive effect on the lipid profile were observed after 12 and 36 weeks of treatment in patients with NASH. Adverse events (nausea, transient diarrhea) were mild to moderate [25]. A phase III clinical trial (MAESTRO) is ongoing to evaluate the effect of resmetirom on the endpoints defined as resolution of NASH without worsening of fibrosis and prevention of progression to cirrhosis [30].

Vitamin E, which can be used in the treatment of selected patients with NASH and at least significant fibrosis (≥ F2) [17], is not recommended for the treatment of NASH in patients with T2DM, NAFLD without liver biopsy, NASH cirrhosis and cryptogenic cirrhosis [52].

It is important that primary care physicians are aware of the extent and long-term consequences of NAFLD in patients with T2DM. NAFLD encompasses a wide range of clinical manifestations, with patients potentially progressing to fibrosis or even cirrhosis and therefore at risk of hepatic decompensation and mortality, as well as a high risk of cardiovascular events. Therefore, one of the urgent tasks of clinical medicine is timely detection of the disease and measures aimed at preventing its progression and reducing the severity of the course. The search for effective methods of treatment of NAFLD will not only improve the quality of life of patients with T2DM, but also significantly reduce mortality from complications.

At the congress of the European Association for the Study of the Liver (EASL), which took place in Vienna on June 21—24, 2023, a new classification and nomenclature of NAFLD was adopted. It was proposed to replace the term «non-alcoholic fatty liver disease» to the term «metabolic dysfunction-associated steatotic liver disease» (MASLD). This diagnosis is established in patients with confirmed steatosis of the liver and one of five cardiometabolic risk factors: obesity, T2DM, insulin resistance, hyperlipidemia, atherosclerosis. The concept of «non-alcoholic steatohepatitis» (NASH) has been changed to the concept of «metabolic dysfunction- associated steatohepatitis» (MASH) [31]. Coordination of the views of international and domestic experts in the field of studying this pathology will be important for clinical practice and scientific research.

Conflicts of interest: none.

References

1. Alexander M, Loomis AK, van der Lei J, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. BMC Med. 2019 May 20;17(1):95. doi: 10.1186/s12916-019-1321-x. PMID: 31104631; PMCID: PMC6526616.
2. Alexopoulos A-S, Crowley MJ, Wang Y, et al. Glycemic control predicts severity of hepatocyte ballooning and hepatic fibrosis in nonalcoholic fatty liver disease. Hepatology. 2021 Sep;74(3):1220-33. doi: 10.1002/hep.31806. Epub 2021 Jun 2. PMID: 33724511; PMCID: PMC8518519.
3. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes — 2020. Diabetes Care. 2020 Jan;43(Suppl 1):S14-S31. doi: 10.2337/dc20-S002. PMID: 31862745.
4. Archer AJ, Belfield KJ, Orr JG, Gordon FH, Abeysekera KW. EASL clinical practice guidelines: non-invasive liver tests for evaluation of liver disease severity and prognosis. Frontline Gastroenterol. 2022 Feb 15;13(5):436-9. doi: 10.1136/flgastro-2021-102064. eCollection 2022. PMID: 36051951; PMCID: PMC9380759.
5. Azzu V, Vacca M, Virtue S, Allison M, Vidal-Puig A. Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in nonalcoholic fatty liver disease. Gastroenterology. 2020 May;158(7):1899-912. doi: 10.1053/j.gastro.2019.12.054. Epub 2020 Feb 13. PMID: 32061598.
6. Benedict M, Zhang X. Non-alcoholic fatty liver disease: An expanded review. World J Hepatol. 2017 Jun 8;9(16):715-32. doi: 10.4254/wjh.v9.i16.715. PMID: 28652891.
7. Bentsa TM. The dietary treatment of obesity. Mižnarodnij endokrinologičnij žurnal. 2023;19(5):376-82. doi: 10.22141/2224-0721.19.5.2023.1302.
8. Bril F, Kalavalapalli S, Clark VC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. Clin Gastroenterol Hepatol. 2018 Apr;16(4):558-66.e2. doi: 10.1016/j.cgh.2017.12.001. Epub 2017 Dec 7. PMID: 29223443.
9. Brunt EM, Kleiner DE, Wilson LA, Sanyal AJ, Neuschwander-Tetri BA. Improvement in fibrosis in nonalcoholic steatohepatitis: results from the Nonalcoholic Steatohepatitis Clinical Research Network Treatment Trials. Hepatology. 2019 Aug;70(2):522-31. doi: 10.1002/hep.30418. Epub 2019 Mar 7.

10. Bullón-Vela V, Abete I, Tur JA, et al. Influence of lifestyle factors and staple foods from the Mediterranean diet on non-alcoholic fatty liver disease among older individuals with metabolic syndrome features. Nutrition. 2020 Mar:71:110620. doi: 10.1016/j.nut.2019.110620. Epub 2019 Oct 25. PMID: 31838461.
11. Chan W-K, Chuah K-H, Rajaram RB, Lim L-L, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated steatotic liver disease (MASLD): a state-of-the-art review. J Obes Metab Syndr. 2023 Sep 30;32(3):197-213. doi: 10.7570/jomes23052. Epub 2023 Sep 13. PMID: 37700494; PMCID: PMC10583766.
12. Cho Y-E, Kim D-K, Seo W, Gao B, Yoo S-H, Song B-J. Fructose promotes leaky gut, endotoxemia, and liver fibrosis through ethanol-inducible cytochrome P450-2E1-mediated oxidative and nitrative stress. Hepatology. 2021 Jun;73(6):2180-95. doi: 10.1002/hep.30652. Epub 2019 May 31. PMID: 30959577; PMCID: PMC6783321.
13. Choy KW. Non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis. Lancet Gastroenterol Hepatol. 2021 Jan;6(1):9. doi: 10.1016/S2468-1253(20)30314-9. PMID: 33308437.
14. Ciardullo S, Vergani M, Perseghin G. Nonalcoholic fatty liver disease in patients with type 2 diabetes: screening, diagnosis, and treatment. J Clin Med. 2023 Aug 27;12(17):5597. doi: 10.3390/jcm12175597. PMID: 37685664; PMCID: PMC10488336.
15. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med. 2016 Sep 6;165(5):305-15. doi: 70.7326/M15-1774. Epub 2016 Jun 21. PMID: 27322798.
16. Drummen M, Dorenbos E, Vreugdenhil ACE, et al. Long-term effects of increased protein intake after weight loss on intrahepatic lipid content and implications for insulin sensitivity: a PREVIEW study. Am J Physiol Endocrinol Metab. 2018 Nov 1;315(5):E885-E891. doi: 10.1152/ajpendo.00162.2018. Epub 2018 Aug 7. PMID: 30086649.
17. EASL–EASD–EASO Clinical Practice Guidelines for the management of non–alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402. doi: 10.1016/j.jhep.2015.11.004. Epub 2016 Apr 7. PMID: 27062661.
18. Finck BN. Targeting metabolism, insulin resistance, and diabetes to treat nonalcoholic steatohepatitis. diabetes. 2018 Dec;67(12):2485-93. doi: 10.2337/dbi18-0024. PMID: 30459251; PMCID: PMC6245219.
19. Francque SM, Bedossa P, Ratziu V, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N Engl J Med. 2021 Oct 21;385(17):1547-58. doi: 10.1056/NEJMoa2036205. PMID: 34670042.
20. Gawrieh S, Noureddin M, Loo N, et al. Saroglitazar, a PPAR-α/γ agonist, for treatment of NAFLD: a randomized controlled double-blind phase 2 trial. Hepatology. 2021 Oct;74(4):1809-24. doi: 10.1002/hep.31843. Epub 2021 Jul 19. PMID: 33811367.
21. Gerges SH, Wahdan SA, Elsherbiny DA, El-Demerdash E. Non-alcoholic fatty liver disease: An overview of risk factors, pathophysiological mechanisms, diagnostic procedures, and therapeutic interventions. Life Sci. 2021 Apr 15:271:119220. doi: 10.1016/j.lfs.2021.119220. Epub 2021 Feb 13. PMID: 33592199.
22. Ghosal S, Datta D, Sinha B. A meta-analysis of the effects of glucagon-like-peptide 1 receptor agonist (GLP1-RA) in nonalcoholic fatty liver disease (NAFLD) with type 2 diabetes (T2D). Sci Rep. 2021 Nov 11;11(1):22063. doi: 10.1038/s41598-021-01663-y. PMID: 34764398; PMCID: PMC8586228.
23. Hadefi A, Arvanitakis M, Trépo E, Zelber-Sagi S. Dietary strategies in non-alcoholic fatty liver disease patients: From evidence to daily clinical practice, a systematic review. United European Gastroenterol J. 2023 Sep;11(7):663-89. doi: 10.1002/ueg2.12443. Epub 2023 Jul 25. PMID: 37491835; PMCID: PMC10493364.
24. Harrison SA, Abdelmalek MF, Neff G, et al. Aldafermin in patients with non-alcoholic steatohepatitis (ALPINE 2/3): a randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol. 2022 Jul;7(7):603-16. doi: 10.1016/S2468-1253(22)00017-6. Epub 2022 Mar 21. PMID: 35325622.
25. Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2019 Nov 30;394(10213):2012-24. doi: 10.1016/S0140-6736(19)32517-6. Epub 2019 Nov 11. PMID: 31727409.
26. Harrison SA, Ruane PJ, Freilich BI, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. Nat Med. 2021;27(7):1262-71. doi: 10.1038/s41591-021-01425-3. Epub 2021 Jul 8. PMID: 34239138.
27. Hodson L, Rosqvist F, Parry SA. The influence of dietary fatty acids on liver fat content and metabolism. Proc Nutr Soc. 2020 Feb;79(1):30-41. doi: 10.1017/S0029665119000569. Epub 2019 Apr 3. PMID: 30942685.
28. Huang TD, Behary J, Zekry A. Non-alcoholic fatty liver disease: a review of epidemiology, risk factors, diagnosis and management. Intern Med J. 2020 Sep;50(9):1038-47. doi: 10.1111/imj.14709. PMID: 31760676.
29. Italian Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions. Dig Liver Dis. 2017 May;49(5):471-83. doi: 10.1016/j.dld.2017.01.147. Epub 2017 Jan 23. PMID: 28215516.
30. Karim G, Bansal MB. Resmetirom: An orally administered, smallmolecule, liver-directed, β-selective THR agonist for the treatment of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. touchREV Endocrinol. 2023 May;19(1):60-70. doi: 10.17925/EE.2023.19.1.60. Epub 2023 May 1. PMID: 37313239; PMCID: PMC10258622.
31. Kim G-A, Moon JH, Kim W. Critical appraisal of metabolic dysfunction-associated steatotic liver disease: Implication of Janus-faced modernity. Clin Mol Hepatol. 2023 Oct;29(4):831-43. doi: 10.3350/cmh.2023.0277. Epub 2023 Aug 25. PMID: 37634892; PMCID: PMC10577343.
32. Kosmalski M, Ziółkowska S, Czarny P, Szemraj J, Pietras T. The coexistence of nonalcoholic fatty liver disease and type 2 diabetes mellitus. J Clin Med. 2022 Mar 2;11(5):1375. doi: 10.3390/jcm11051375. PMID: 35268466; PMCID: PMC8910939.
33. Koutoukidis DA, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. JAMA Intern Med. 2019 Sep 1;179(9):1262-71. doi: 10.1001/jamainternmed.2019.2248. PMID: 31260026; PMCID: PMC6604126.
34. Kremoser C. FXR agonists for NASH: How are they different and what difference do they make? J Hepatol. 2021. Jul;75(1):12-5. doi: 10.1016/j.jhep.2021.03.020. Epub 2021 May 10. PMID: 33985820.
35. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018 Feb 10;391(10120):541-51. doi: 10.1016/S0140-6736(17)33102-1. Epub 2017 Dec 5. PMID: 29221645.
36. Lee C-H, Lui DT, Lam KSL. Non-alcoholic fatty liver disease and type 2 diabetes: An update. J Diabetes Investig. 2022 Jun;13(6):930-40. doi: 10.1111/jdi.13756. Epub 2022 Feb 14. PMID: 35080136; PMCID: PMC9153839.
37. Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: a meta-analysis. Front Endocrinol (Lausanne). 2022 Feb 16:13:840299. doi: 10.3389/fendo.2022.840299. eCollection 2022. PMID: 35250889; PMCID: PMC8889626.
38. Lonardo A, Lugari S, Ballestri S, Nascimbeni F, Baldelli E, Maurantonio M. A round trip from nonalcoholic fatty liver disease to diabetes: molecular targets to the rescue? Acta Diabetol. 2019 Apr;56(4):385-96. doi: 10.1007/s00592-018-1266-0. Epub 2018 Dec 5. PMID: 30519965.
39. Loomba R, Noureddin M, Kowdley KV, et al. Combination therapies including cilofexor and firsocostat for bridging fibrosis and cirrhosis attributable to NASH. Hepatology 2021 Feb;73(2):625-43. doi: 10.1002/hep.31622. PMID: 33169409.
40. Luukkonen PK, Sädevirta S, Zhou Y, et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. Diabetes Care. 2018 Aug;41(8):1732-9. doi: 10.2337/dc18-0071. Epub 2018 May 29. PMID: 29844096; PMCID: PMC7082640.

41. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. Metabolites. 2021 Jan 27;11(2):73. doi: 10.3390/metabo11020073. PMID: 33513761; PMCID: PMC7911747.
42. Masuzaki R, Kanda T, Sasaki R, et al. Noninvasive assessment of liver fibrosis: current and future clinical and molecular perspectives. Int J Mol Sci. 2020 Jul 11;21(14):4906. doi: 10.3390/ijms21144906. PMID: 32664553; PMCID: PMC7402287.
43. Mazhar IJ, Yasir M, Sarfraz S, et al. Vitamin E and pioglitazone: a comprehensive systematic review of their efficacy in non-alcoholic fatty liver disease. Cureus. 2023 Aug 17;15(8):e43635. doi: 10.7759/cureus.43635. eCollection 2023 Aug. PMID: 37719477; PMCID: PMC10504864.
44. Meir AY, Rinott E, Tsaban G, et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. Gut. 2021 Nov;70(11):2085-95. doi: 10.1136/gutjnl-2020-323106. Epub 2021 Jan 18. PMID: 33461965; PMCID: PMC8515100.
45. Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut. 2020 Aug;69(8):1382-403. doi: 10.1136/gutjnl-2020-321299. Epub 2020 May 28. PMID: 32467090; PMCID: PMC7398479.
46. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021 Mar 25;384(12):1113-24. doi: 10.1056/NEJMoa2028395. Epub 2020 Nov 13. PMID: 33185364.
47. Paik JM, Kabbara K, Eberly KE, Younossi Y, Henry L, Younossi ZM. Global burden of NAFLD and chronic liver disease among adolescents and young adults. Hepatology. 2022 May;75(5):1204-17. doi: 10.1002/hep.32228. Epub 2021 Dec 21. PMID: 34741554.
48. Patel K, Harrison SA, Elkhashab M, et al. Cilofexor, a nonsteroidal FXR agonist, in patients with noncirrhotic NASH: a phase 2 randomized controlled trial. Hepatology. 2020 Jul;72(1):58-71. doi: 10.1002/hep.31205. PMID: 32115759.
49. Pennisi G, Enea M, Romero-Gomez M, et al. Liver-related and extrahepatic events in patients with non-alcoholic fatty liver disease: a retrospective competing risks analysis. Aliment Pharmacol Ther. 2022 Mar;55(5):604-15. doi: 10.1111/apt.16763. Epub 2022 Jan 5. PMID: 34988994.
50. Powell EE, Wong VW-S, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021 Jun 5;397(10290):2212-24. doi: 10.1016/S0140-6736(20)32511-3. Epub 2021 Apr 21. PMID: 33894145.
51. Pouwels S, Sakran N, Graham Y, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022 Mar 14;22(1):63. doi: 10.1186/s12902-022-00980-1. PMID: 35287643; PMCID: PMC8919523.
52. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023 May 1;77(5):1797-835. doi: 10.1097/HEP.0000000000000323. Epub 2023 Mar 17. PMID: 36727674.
53. Sako S, Takeshita Y, Takayama H, et al. Trajectories of liver fibrosis and gene expression profiles in nonalcoholic fatty liver disease associated with diabetes. Diabetes. 2023 Sep 1;72(9):1297-306. doi: 10.2337/db22-0933. PMID: 37343270.
54. Sanyal A, Charles ED, Neuschwander-Tetri BA, et al. Pegbelfermin (BMS–986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. Lancet. 2019 Dec 22;392(10165):2705-17. doi: 10.1016/S0140-6736(18)31785-9. Epub 2018 Dec 13. PMID: 30554783.
55. Sanyal AJ, Lopez P, Lawitz EJ, et al. Tropifexor for nonalcoholic steatohepatitis: an adaptive, randomized, placebo-controlled phase 2a/b trial. Nat Med. 2023 Feb 16;29(2):392-400. doi: 10.1038/s41591-022-02200-8. PMID: 36797481; PMCID: PMC9941046.
56. Seko Y, Sumida Y, Tanaka S, et al. Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. Hepatol Res. 2017 Sep;47(10):1072-8. doi: 10.1111/hepr.12834. Epub 2016 Dec 7. PMID: 27925353.
57. Siddiqui MS, Van Natta ML, Connelly MA, et al. Impact of obeticholic acid on the lipoprotein profile in patients with non-alcoholic steatohepatitis. J Hepatol 2020 Jan;72(1):25-33. doi: 10.1016/j.jhep.2019.10.006. Epub 2019 Oct 18. PMID: 31634532; PMCID: PMC6920569.
58. Souza Cruz EM, Bitencourt de Morais JM, Dalto da Rosa CV, et al. Long-term sucrose solution consumption causes metabolic alterations and affects hepatic oxidative stress in Wistar rats. Biol Open. 2020 Feb 28;9(3):bio047282. doi: 10.1242/bio.047282. PMID: 32086249; PMCID: PMC7055397.
59. Tanase DM, Gosav EM, Costea CF, et al. The intricate relationship between type 2 diabetes mellitus (T2DM), insulin resistance (IR), and nonalcoholic fatty liver disease (NAFLD). J Diabetes Res. 2020 Jul 31:2020:3920196. doi: 10.1155/2020/3920196. eCollection 2020. PMID: 32832560.
60. Tilg H, Byrne CD, Targher G. NASH drug treatment development: challenges and lessons. Lancet Gastroenterol Hepatol. 2023 Oct;8(10):943-54. doi: 10.1016/S2468-1253(23)00159-0. Epub 2023 Aug 16. PMID: 37597527.
61. Tokushige K, Ikejima K, Ono M, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. Hepatol Res. 2021 Oct;51(10):1013-25. doi: 10.1111/hepr.13688. Epub 2021 Sep 17. PMID: 34533266.
62. Venetsanaki V, Karabouta Z, Polyzos SA. Farnesoid X nuclear receptor agonists for the treatment of nonalcoholic steatohepatitis. Eur J Pharmacol. 2019 Nov 15:863:172661. doi: 10.1016/j.ejphar.2019.172661. Epub 2019 Sep 16. PMID: 31536725.
63. Vilar-Gomez E, Chalasani N.. Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers. J Hepatol. 2018 Feb;68(2):305-15. doi: 10.1016/j.jhep.2017.11.013. Epub 2017 Dec 2. PMID: 29154965.
64. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015 Aug;149(2):367-78.e5; quiz e14-5. doi: 10.1053/j.gastro.2015.04.005. Epub 2015 Apr 10. PMID: 25865049.
65. Wang C, Cai Z, Deng X, et al. Association of hepatic steatosis index and fatty liver index with carotid atherosclerosis in type 2 diabetes. Int J Med Sci. 2021 Jul 23;18(14):3280-9. doi: 10.7150/ijms.62010. eCollection 2021. PMID: 34400897; PMCID: PMC8364463.
66. Westerouen Van Meeteren MJ, Drenth JPH, Tjwa ETTL. Elafibranor: a potential drug for the treatment of nonalcoholic steatohepatitis (NASH). Expert Opin Investig Drugs. 2020 Feb;29(2):117-23. doi: 10.1080/13543784.2020.1668375. Epub 2019 Sep 25. PMID: 31523999.
67. Yang JD, Ahmed F, Mara KC, et al. Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease. Hepatology. 2020 Mar;71(3):907-16. doi: 10.1002/hep.30858. Epub 2019 Oct 21. PMID: 31309602; PMCID: PMC6960360.
68. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019 Oct;71(4):793-801. doi: 10.1016/j.jhep.2019.06.021. Epub 2019 Jul 4. PMID: 31279902.
69. Younossi ZM, Golabi P, Paik JM, Henry A, Dongen CV, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023 Apr 1;77(4):1335-47. doi: 10.1097/HEP.0000000000000004. Epub 2023 Jan 3. PMID: 36626630; PMCID: PMC10026948.
70. Ziolkowska S, Binienda A, Jabłkowski M, Szemraj J, Czarny P. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. Int J Mol Sci. 2021 Oct 15;22(20):11128. doi: 10.3390/ijms222011128. PMID: 34681787; PMCID: PMC8537238.

Т. М. Бенца
Національний університет охорони здоров'я України імені П. Л. Шупика, Київ

Неалкогольна жирова хвороба печінки і цукровий діабет 2 типу: діагностичні та терапевтичні аспекти. Огляд

Збільшення поширеності неалкогольної жирової хвороби печінки (НАЖХП) відбувається паралельно із глобальною епідемією ожиріння та цукрового діабету (ЦД) 2 типу в світі. Цукровий діабет 2 типу є незалежним чинником ризику розвитку НАЖХП. Установлено, що пацієнти з діагностованою НАЖХП мають удвічі більший ризик розвитку ЦД 2 типу. Неалкогольна жирова хвороба печінки охоплює спектр виявів з боку печінки від простого стеатозу до неалкогольного стеатогепатиту (НАСГ), фіброзу і цирозу печінки, який може прогресувати в гепатоцелюлярну карциному. Неалкогольний стеатогепатит — це агресивна форма НАЖХП, пов'язана з підвищеним ризиком смертності від захворювань печінки та інших захворювань. Біопсія печінки залишається золотим стандартом для діагностики, але в більшості пацієнтів ураження печінки може бути точно діагностоване неінвазивними методами. Наявність НАЖХП у хворого на ЦД 2 типу ускладнює досягнення адекватного глікемічного контролю, поглиблює вияви інсулінорезистентності й атерогенної дисліпідемії, підвищує ризик серйозних серцево-судинних подій і хронічної хвороби нирок.

Модифікацію способу життя та лікування супутнього ЦД 2 типу слід проводити в усіх пацієнтів із НАЖХП. Для зменшення виразності стеатозу печінки необхідне зниження маси тіла на 3—5%, для зменшення запально-некротичного процесу може знадобитися більше зниження — до 10% протягом 6—12 міс. Фізичні навантаження сприяють підвищенню чутливості рецепторів до інсуліну, а в поєднанні з дієтою — статистично значущому поліпшенню біохімічних і гістологічних показників у хворих на НАЖХП. Фармакологічну терапію слід призначати пацієнтам із НАСГ для гальмування процесів фіброзоутворення, особливо за наявності предикторів високого ризику прогресування захворювання (вік > 50 років, метаболічний синдром, ЦД 2 типу, збільшення активності аланінамінотрансферази), а також хворим з активним НАСГ із високою запальною активністю.

На конгресі Європейської асоціації з вивчення печінки (EASL), який відбувся у Відні 21—24 червня 2023 р., прийнято нову класифікацію та номенклатуру НАЖХП. Запропоновано замінити термін «неалкогольна жирова хвороба печінки» на термін «стеатотична хвороба печінки, пов'язана з метаболічною дисфункцією» (СХПМД). Такий діагноз установлюють у пацієнтів, що мають підтверджений стеатоз печінки та один із п'яти кардіометаболічних чинників ризику (ожиріння, ЦД 2 типу, інсулінорезистентність, гіперліпідемія, атеросклероз). Поняття «неалкогольний стеатогепатит» (НАСГ) змінено на поняття «стеатогепатит, пов'язаний з метаболічною дисфункцією» (СГМД). Узгодження поглядів міжнародних і вітчизняних експертів у галузі вивчення зазначеної патології матиме важливе значення для клінічної практики та наукових досліджень.

Ключові слова: неалкогольна жирова хвороба печінки, неалкогольний стеатогепатит, цукровий діабет 2 типу, діагностика, лікування.

ДЛЯ ЦИТУВАННЯ

Bentsa TM. Non-alcoholic fatty liver disease and type 2 diabetes mellitus: diagnostic and therapeutic aspects. Review. Modern Gastroenterology (Ukraine). 2023;6:59-68. http://doi.org/10.30978/MG-2023-6-59. Urkainian.