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Clinical Practice Guidelines of the Russian Scientific Liver Society, Russian Gastroenterological Association, Russian Association of Endocrinologists, Russian Association of Gerontologists and Geriatricians and National Society for Preventive Cardiology on Diagnosis and Treatment of Non-Alcoholic Liver Disease

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Aim: present clinical guidelines, aimed at general practitioners, gastroenterologists, cardiologists, endocrinologists, comprise up-to-date methods of diagnosis and treatment of non-alcoholic fatty liver disease.
Key points. Nonalcoholic fatty liver disease, the most wide-spread chronic liver disease, is characterized by accumulation of fat by more than 5 % of hepatocytes and presented by two histological forms: steatosis and nonalcoholic steatohepatitis. Clinical guidelines provide current views on pathogenesis of nonalcoholic fatty liver disease as a multisystem disease, methods of invasive and noninvasive diagnosis of steatosis and liver fibrosis, principles of non-drug treatment and pharmacotherapy of nonalcoholic fatty liver disease and associated conditions. Complications of nonalcoholic fatty liver disease include aggravation of cardiometabolic risks, development of hepatocellular cancer, progression of liver fibrosis to cirrhotic stage.
Conclusion. Progression of liver disease can be avoided, cardiometabolic risks can be reduced and patients' prognosis — improved by the timely recognition of diagnosis of nonalcoholic fatty liver disease and associated comorbidities and competent multidisciplinary management of these patients.
Keywords: non-alcoholic fatty liver disease, steatosis, liver fibrosis, steatohepatitis, insulin resistance, cardiovascular diseases, metabolic disorders
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Клинические рекомендации Российского общества по изучению печени, Российской гастроэнтерологической ассоциации, Российской ассоциации эндокринологов, Российской ассоциации геронтологов и гериатров и Национального общества профилактической кардиологии по диагностике и лечению неалкогольной жировой болезни печени

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Цель: в клинических рекомендациях, предназначенных для врачей общей практики, врачей-терапевтов, врачей-гастроэнтерологов, врачей-кардиологов, врачей-эндокринологов, представлены современные методы диагностики и лечения неалкогольной жировой болезни печени.

Основное содержание. Неалкогольная жировая болезнь печени — самое частое хроническое заболевание печени, при котором более 5 % гепатоцитов аккумулирует жир, представлено двумя гистологическими формами: стеатоз и неалкогольный стеатогепатит. В клинических рекомендациях описаны современные представления о патогенезе неалкогольной жировой болезни печени как мультисистемного заболевания, методы инвазивной и неинвазивной диагностики стеатоза и фиброза печени, принципы немедикаментозного лечения и фармакотерапии неалкогольной жировой болезни печени и ассоциированных с ней состояний. Представлены осложнения неалкогольной жировой болезни печени, такие как усугубление кардиометаболических рисков, развитие гепатоцеллюлярного рака, прогрессия фиброза печени до стадии цирроза.

Заключение. При своевременной диагностике неалкогольной жировой болезни печени и ассоциированных коморбидных состояний, грамотном междисциплинарном ведении этих пациентов можно избежать прогрессии заболевания печени и уменьшить кардиометаболические риски, улучшить жизненный прогноз пациентов.

Ключевые слова: неалкогольная жировая болезнь печени, стеатоз печени, фиброз печени, стеатогепатит, инсулинорезистентность, сердечно-сосудистые заболевания, метаболические нарушения

Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов

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1. Brief Information on the Disease or Condition (Group of Diseases or Conditions)

1.1. Definition of the Disease or Condition (Group of Diseases or Conditions)

Non-alcoholic fatty liver disease (NAFLD) is a condition in which more than 5 % of hepatocytes accumulate fat, which occurs in the absence of excessive alcohol consumption.

Several NAFLD types can be distinguished: 1) simple steatosis, as a benign condition with neither inflammation, nor progressive pathological process in the liver; however, according to the recent data, steatosis is an independent risk factor for developing CVD (cardiovascular diseases) and their complications; 2) non-alcoholic steatohepatitis (NASH), which, in addition to steatosis, is characterized by lobular inflammation, ballooning, and fibrosis with the risk of progressing to LC and developing hepatocellular carcinoma (HCC) [1].

1.2. Ethiology and Pathogenesis of the Disease or Condition (Group of Diseases or Conditions)

Previously, pathogenesis of NAFLD was presented as a "two-hit" hypothesis [2]. It was suggested that the "first hit" was characterized by an increase in fat content in the liver and steatosis development. This is followed by mitochondrial dysfunction and oxidative stress, stimulation in production of proinflammatory cytokines leading to the development of NASH and progressive fibrosis. Currently, there is a concept of multifactorial pathogenesis, which includes various parallel processes, such as insulin resistance (IR), lipotoxicity, inflammation, imbalance of cytokines and adipokines, activation of innate immunity and microbiome, and exposure to environmental and genetic factors [3–5]. One of the key moments of NAFLD is an imbalance of the systemic energy, characterized by an excess of substrates, mainly carbohydrates and fatty acids. The main sources of Free (unesterified) fatty acids (FFA) to the liver are adipocytes (approx. 60 %, i.e., there is an increased release of FFA), *de novo* lipogenesis (approx. 26 %, i.e., conversion of carbohydrates into fats in the liver), and excess dietary intake of fats (approx. 14 %) [6, 7].

Insulin Resistance

IR and NAFLD are closely related [8, 9]. IR is characterized by a decreased sensitivity of peripheral tissues (muscles, adipose tissue, liver) to insulin. At the adipocyte level, metabolic dysregulation due to impaired insulin signaling results in excess triglyceride lipolysis and release of FFA into the blood stream. Albumin-bound FFA are delivered to the liver. FFA uptake by hepatocytes is mediated by fatty acid transport proteins, CD36, caveolins, and, to a lesser degree, by passive diffusion [10]. In addition, *de novo* lipogenesis from glucose and fructose occurs and increases in the hepatocytes in NAFLD [11]. Unlike glucose, involvement of fructose metabolites in the *de novo* lipogenesis is not regulated by glycolysis [12]. This is confirmed by epidemiologic studies showing a correlation between a high-carbohydrate diet and NAFLD. A high content of sucrose and fructose in the diet represents a risk factor of NAFLD. Excessive consumption of carbohydrates and, as a result, an elevated blood glucose level have a detrimental effect on cells. This phenomenon is called glucotoxicity. This concept is inextricably linked with IR in the liver, which is manifested by increased gluconeogenesis and decreased glycogenesis, leading to hyperglycaemia [13–15]; moreover, hepatocytes can secrete dipeptidyl peptidase-4 (DPP-4), which promotes inflammation of the adipose tissue and IR. [16].

Hepatic Steatosis and Lipotoxicity

Conditionally endogenous lipids are divided into toxic and neutral ones. An example of toxic lipids are free fatty acids (FFA); an example of neutral lipids triglycerides (TG). FFA in the liver must either undergo mitochondrial beta-oxidation or be esterified to form TG. TG formation presumably serves as an adaptive mechanism for protecting the liver from toxic lipids. TG excess does not have a damaging effect on the liver, in contrast to an excess of FFA [17]. TG can be exported from the liver as VLDL particles or stored as lipid droplets. However, lipolysis of these droplets releases FFA back into the hepatic pool. Regulation of this metabolic stage is of great importance in the pathogenesis of NASH [6]. Among fatty acids accumulating in the liver, saturated acids (palmitic, stearic) predominate over monounsaturated and polyunsaturated ones, which is associated with progression of liver disease. Other lipotoxic lipid types are diacylglycerols, ceramides, lysophosphatidylcholine, and free cholesterol [18, 19].

A recent study showed that a diet rich in saturated fats is more harmful with regard to increased intrahepatic TG levels than a diet rich in free sugars in overweight men. This fact confirms the predominant role of lipotoxicity in the pathogenesis of NAFLD [20]. At the molecular level, lipotoxicity leads to endoplasmic reticulum stress, lysosomal dysfunction, activation of inflammation, cell death, and activation of

inflammatory reactions due to lethal and sublethal damage to hepatic cells.

Oxidative Stress and Lipid Peroxidation

An increased entry of FFA to the liver promotes to rising VLDL secretion, a growing role of β-peroxisomal and ω-microsomal oxidation, which occurs with the participation of cytochrome P-450 (CYP2E1, CYP4A), resulting in a decrease of mitochondrial oxidation and onset of ATP deficiency [21]. Mitochondrial dysfunction leads to oxidative stress, production of reactive oxygen intermediates and triggers lipid peroxidation (LP) [22]. LP results in formation of new free radicals and lipid hydroperoxides, which form secondary (lipid) free radicals, under the influence of the catalytic activity of iron. LP is the main process leading to inflammation, cytokine activation, hepatocyte damage, stellate cell stimulation, and fibrogenesis [23].

Adipose Tissue as an Endocrine Organ

The vast majority of patients with obesity and NAFLD have various metabolic disorders, such as dyslipidaemia, hypertriglyceridaemia, decreased HDL cholesterol in the blood, disturbed fasting glycemia and/or impaired glucose tolerance, hyperinsulinaemia, T2DM. Generally, these disorders are combined in nature and increase in frequency and intensity as NAFLD progresses [24–29]. Adipose tissue is not the only source of FFA, but also an endocrine organ secreting adipokines with systemic regulatory effects. Leptin and adiponectin, produced by visceral adipocytes, influence NAFLD and other MetS components by regulating food intake, body fat composition, insulin sensitivity, and inflammation. Patients with NAFLD have a decreased production of protective adiponectin and an increased production of leptin. Leptin executes its influence in peripheral tissues by interacting with specific transmembrane receptors. The soluble form of the leptin receptor (sLep-R) is the main leptin-binding protein. Hyperleptinaemia and low levels of sLep-R indicative of leptin resistance in peripheral tissues are found, to a greater extent, in patients with NAFLD than in obese persons without hepatic steatosis [30]. Serum leptin levels are elevated in patients with NASH compared with healthy individuals [31, 32].

Excessive production of proinflammatory cytokines by macrophages of visceral adipose tissue is critical to slow inflammation of adipose tissue associated with obesity. Activated macrophages of the adipose tissue secrete cytokines and chemokines, including TNF-α, IL-1β, IL-6, and CCL2, which not only induce local IR leading to lipid dysregulation, but also contribute to systemic IR. Immune activation in the adipose tissue presumably precedes inflammation in the liver [33–36]. Production of proinflammatory mediators activates key transcriptional factors, such as JNK and NF-kB, leading to the development of steatohepatitis. Simultaneous disorder in anti-inflammatory adipokine production (e.g., adiponectin) reduces insulin sensitivity [37–39]. An increased production of proinflammatory cytokines and other inflammation factors leads to hepatocyte damage and fibrogenesis stimulation [3, 40, 41].

Inflammation and Fibrogenesis Mechanisms

With an excessive flow of FFA and/or other pathogens (such as endotoxins) from the intestinal tract to the liver, Kupffer cells phagocytize them and present them to the immune system via pattern recognition receptors (PRRs) [42]. PRRs include toll-like receptors (TLRs) such as TLR4, TLR9, and nucleotide-binding oligomerization domain-like receptors (NLRs) [43]. Inflammasomes (multiprotein oligomeric complexes responsible for inflammatory response activation) activate a cascade of events via NLR resulting in production of IL-1, IL-8, and IL-1, contributing to activation of the NF-kB transcription factor [44, 45]. Kupffer cells, in turn, differentiate into M1 or M2 phenotypes, depending on the external inducer; M1 produces cytokines such as TNF-α, IL-1, and IL-12, while M2 is able to stimulate the secretion of IL-4, IL-10, and TGF-β [46]. IL-6 and TNF-α are cytokines responsible for progression of NASH [4, 47]. It is expected that TLR suppression may block the immune response, thus reducing the degree of hepatic inflammation.

T-helper lymphocytes are also involved in inflammation in the liver, helping B-cells, macrophages and cytotoxic T-cells to eliminate pathogens and damaged cells. After immune activation took place, T-cells differentiate into Th1, Th2, and Th17 effector cells. NASH is characterized by the excess of Th1-derived cytokines, such as IFN-γ, and deficiency of Th2-derived cytokines — IL-4, IL-5, and IL-13 [48]. Th17 cells producing IL-17 accumulate in the liver in NASH and promote inflammation and fibrosis by affecting macrophages and stellate cells (SCs) in the liver [6]. Cytotoxic $CD8^+$ T-cells activated by type I interferons also accumulate in the liver in NAFLD, producing IFN-γ and TNF-α. Their pharmacological or genetic suppression leads to a decrease in steatosis, IR, inflammation, and activation of SCs [49].

Hyperproduction of various inflammatory mediators, hepatocyte damage leads to activation

of hepatic SCs, which are the main pathogenetic link in fibrogenesis. Activated SCs transform into myofibroblasts, actively proliferating, and producing collagen, fibronectin, laminin, hyaluronic acid, matrix metalloproteinases, and their tissue inhibitors [21, 23]. Accumulation of fibril-forming collagens (types I and III) in the Disse's space leads to "capillarization" of sinusoids, liver architectonics disruption, hypoxia, and fibrogenesis progression.

Gut-Liver Axis

Among the commensal organisms inhabiting the human gut, four main types dominate: *Firmicutes, Bacteroidetes, Actinobacteria*, and Proteobacteria. Obese and NASH patients have an increased *Bacteroidetes* and decreased *Firmicutes* levels compared to healthy individuals [50]. An important role in the gut-liver axis dysfunction is played by intestinal dysbiosis, bacterial overgrowth, and changes in mucosal permeability. The gut-liver axis is characterized by bidirectional flow. Nutrients and various compounds from the intestinal lumen reach the liver via portal circulation; bile acids (BAs) produced by hepatocytes enter the small intestine via the biliary tract [51]. The gut barrier and gut microbiota play an important role in liver damage and NAFLD progression [52]. Normally, only a small amount of bacterial metabolic products enter the liver via the portal vein. However, bacterial dysbiosis or changes in the gut barrier permeability increase bacterial influx into the liver, thus stimulating inflammation via TLR and activation of other pattern recognition receptors in Kupffer cells [53].

BAs affect intestinal environment directly by causing membrane damage and indirectly through the activation of special receptors by their metabolites, such as the farnesoid X receptor (FXR). BAs are synthesized and secreted by hepatocytes and are involved in the absorption of dietary lipids. They are transported back to the liver via enterohepatic circulation and bind to FXR, which is also expressed on hepatocytes, affecting glucose and lipid metabolism [54, 55]. BAs, due to their antimicrobial effects, modulate the relationship between the gut microbiota and chronic liver diseases [56] and improve glucose metabolism by activating the G protein-coupled bile acid receptor (GPBAR1) in enterocytes [57]. Therefore, the possible impact on these mechanisms, for example, use of an FXR agonist, is an attractive strategy for treating NAFLD [57].

BAs play an important role in the autophagy process. Autophagy is a process in which the internal components of a cell (mitochondria, peroxisomes, and endoplasmic reticulum) are delivered inside its lysosomes or vacuoles and degrade inside. Autophagy promotes essential liver functions such as lipid, glycogen and protein metabolism. A decreased autophagic function may contribute to reduced insulin sensitivity and liver cell damage, accumulation of cellular lipids, initial development of hepatic steatosis, and its further progression to steatohepatitis. Products that enhance liver autophagy have a therapeutic potential in NASH [58]. In an experiment, ursodeoxycholic acid (UDCA) had a beneficial effect on hepatic steatosis in rats with NAFLD by activating AMP-activated protein kinase. UDCA inhibits apoptosis and induces autophagy influencing the interaction of the Bcl-2/Beclin-1 and Bcl-2/Bax complex, which indicates the possibility of UDCA to be a promising therapeutic target for treating NAFLD [59].

The microbiota plays a vital role in maintaining integrity of the intestinal barrier and intestinal permeability. The intestinal barrier is a unicellular layer including enterocytes, goblet cells, Tufts cells (with chemosensory function), and Paneth cells producing antimicrobial peptides [60–62]. The layer is impermeable to most dissolved substances, which requires a specific carrier to overcome the barrier, a mechanism involving a transcellular pathway. The intercellular spaces are closed by the presence of a certain apical junction complex, i.e. tight junctions and cohesions, which prevent uncontrolled translocation of substances and allows active transcellular transport through enterocytes [63]. The disruption of the microflora composition can damage the intestinal epithelium and destroy tight junction proteins, which is important for keeping harmful substances from the intestine, such as bacteria and ethanol and endotoxins, produced by them from entering the portal circulation [64, 65]. It has been shown that E. Coli, being the predominant microorganism in bacterial overgrowth syndrome, may be associated with the effect of translocation in patients with NAFLD [66].

NAFLD Genetics

The impact of polymorphism of various genes encoding microsomal triglyceride transfer protein, CD14 endotoxin receptor, angiotensin II type 1, TNF-α, TGF-β, superoxide dismutase 2, phosphatidylethanolaminotransferase, apolipoproteins C3 and E, peroxisome proliferator-activated receptors (PPARs) and many others, on NAFLD development is discussed in the literature [67–71]. These mutations may increase the risk of developing steatohepatitis and/or fibrosis.

The most strongly NASH-associated genetic variant is a single nucleotide polymorphism in the gene for the patatin-like phospholipase domain containing protein 3 (PNPLA3), which encodes the lipid droplet protein and is involved in this lipolytic step. The I148M PNPLA variant (PNPLA3/ rs738409 C/G) is resistant to degradation, accumulates on lipid droplets, and is sufficient to induce steatosis [72]. The G rs738409 allele is associated with increased fat accumulation in the liver and inflammation [73]. The homozygous gene in the rs738409 GG variant is common for patients with NASH [74, 75]. The GG genotype is noted more often and correlates with BMI and degree of fibrosis in patients with HCC secondary to NAFLD [76].

In the obesity-associated NAFLD, genetic polymorphisms of adipokine genes are of particular importance. The adiponectin oligonucleotide polymorphisms 45TT and 276GT are more common in NAFLD than in the general population and are associated with the severity of liver disease [77]. Mutations in the genes of leptin and its receptor can lead to hyperleptinaemia and leptin resistance. Mutations in the leptin receptor gene (Gln223Arg) may be risk factors for the development of fatty liver disease, as well as pathology of the coronary arteries [78]. The 223Gln allele in the homozygous state is observed in 48.67 % of patients with NAFLD and only in 21.17 % of healthy individuals [79].

1.3. Epidemiology of the Disease or Condition (Groups of Diseases or Conditions)

Currently non-alcoholic fatty liver disease is the most common chronic liver disease in the developed countires affecting 25 % to 30 % of adults in such countries as the USA and Russia.

The overall prevalence of NAFLD in the world is 25.24 % [80]. According to the DIREG2 multicenter study, the prevalence of NAFLD in outpatients in Russia is 37.3 % [81]. In 2019, data on the NAFLD incidence in the outpatient department of a medical center were obtained and published, encounting 24.9 % [82]. For residents of Moscow as a whole (population study), this figure amounts to 7.4 % [83].

The prevalence of NASH is difficult to estimate precisely, since a liver biopsy is required for a correct diagnosis, being an expensive and invasive procedure. According to the literature data [84], NASH affects 3 to 5 % of the world's population, most of whom suffer from several comorbidities. Development of fibrosis in NASH determines its clinical outcomes: about 20 % of patients develop cirrhosis and/or HCC, which is the principal cause of death in these patients. The use of the Markov mathematical model, taking into account the prevalence of T2DM and obesity, showed that the prevalence of NASH will increase to 15–56 % by 2030 [85]. Accordingly, the efforts of healthcare professionals around the world and in the Russian Federation can and should influence this negative scenario in a positive way.

NAFLD is closely associated with obesity, especially with an abdominal type, and MetS, significantly increasing cardiometabolic risk and affecting the incidence, prognosis, and life expectancy of patients. The prevalence of various clinical forms of NAFLD in obese patients is significantly higher than in the general population, being 75 to 93 %, according to studies, with NASH diagnosed in 18.5 to 26 %, fibrosis in 20 to 37 %, and liver cirrhosis in 9 to 10 % of patients. With morbid obesity, the frequency of NAFLD increases to 95 — 100 %. Among patients with T2DM, NAFLD is detected in 50 to 75 % of patients [86–89]. Therefore, high-risk groups for developing NAFLD may be identified as follows: patients with obesity, T2DM, dyslipidaemia, MetS, polycystic ovarian syndrome. Obesity is a risk factor for development of liver fibrosis in patients with NAFLD [90–92].

The incidence of CKD is estimated at 20 to 55 % in patients with NAFLD compared with 5 to 30 % in patients without NAFLD [93, 94].

Two meta-analyses and data from retrospective follow-up studies indicate a higher incidence of CKD in patients with NAFLD compared with patients without NAFLD, regardless of the DM presence [95–97]. It should be noted that in the majority of studies, the diagnosis was based on ultrasonic data or elevated level of liver enzymes.

In patients with NAFLD and advanced liver fibrosis, CKD is detected more often than in patients without fibrosis. Liver fibrosis, but not steatosis, is significantly associated with the presence of albuminuria (RR 1.52; 95 % CI 1.02–2.28; $P = 0.039$) [98] and increases the risk of CKD by 3.6 times [99]. In a 12-year prospective follow-up study, NAFLD patients with no obesity had a higher risk of developing CKD than patients with NAFLD and obesity [100].

1.4. Considerations for Coding the Disease or Condition (Group of Diseases or Conditions) according to the International Statistical Classification of Diseases and Related Health Problems

K75.8 — other specified inflammatory liver diseases

K76.0 — fatty (change of) liver, not elsewhere classified

1.5. Classification the Disease or Condition (Group of Diseases or Conditions)

Three main clinical and morphological forms of NAFLD are distinguished: a) hepatic steatosis, b) steatosis with lobular or portal inflammation without ballooning degeneration, c) steatosis with ballooning degeneration, but without inflammation [101]. The diagnosis of NASH requires simultaneous presence of steatosis, ballooning degeneration, and lobular inflammation [101–103]. Other histological changes are possible, however, they are not considered necessary for establishing a diagnosis: portal inflammation, polymorphonuclear infiltrates, Mallory-Denk bodies, apoptotic bodies, transparent vacuolated nuclei, microvesicular steatosis, and megamitochondria. Perisinusoid fibrosis is also common, but is not part of the diagnostic criteria; as for the term "borderline" NASH, it is not entirely clear and should not be used. The prospective FLIP algorithm improves the consistency of observations and clearly defines the degree of ballooning degeneration [103]. The concept of "burned-out" NASH describes regression of a severe disease (steatosis, inflammation, or ballooning degeneration) in patients with the metabolic syndrome risk factors.

Liver biopsy is the modern "gold standard" for diagnosing steatosis, inflammation, and fibrosis in NAFLD. This method to a high degree of accuracy allows to confirm the presence of NAFLD, making a differential diagnosis between steatosis and NASH, assessing the fibrosis stage and, based on histological data, making prognosis on further course of the disease [14], as well as excluding other causes of liver damage (Grade A Recommendation, Evidence Level 2). In 2005, based on the expert consensus (CRN) of morphologists, the NAFLD activity score (NAS) for NAFLD assessment was proposed, being a modification of the previously used scales of E. Brunt and Matteoni (1999), and offering assessment of the degree of morphological changes with a score (0 to 8): severity of hepatic steatosis, intralobular (lobular) inflammation, hepatocyte ballooning, and fibrosis stage [104] — Appendix D1.

This score can also be used to assess the efficacy of NAFLD treatment, since it enables determining the reliability of the dynamics of morphological changes in treatment over time in a relatively short period of time [105, 106]. In 2014, another scale, SAF, was proposed for semi-quantitative assessment of NAFLD severity, which includes such characteristics as steatosis intensity (S, steatosis), ballooning degeneration and lobular inflammation (A, activity), and liver fibrosis stage (F, fibrosis) — Appendix D2 (an assessment result is recorded as index S1A2F3, S2A1F1, etc.) [103].

1.6. Clinical Picture of the Disease or Condition (Group of Diseases or Conditions)

The clinical picture of NAFLD is nonspecific. Patients with hepatic steatosis are generally asymptomatic and the diagnosis is made incidentally during abdominal ultrasonography and/or blood chemistry tests that show slight elevations in ALT and/or GGTP. If NASH occurs with a high biochemical activity, patients may experience weakness and/or malaise/pain in the right upper quadrant. The clinical picture of liver cirrhosis is usually determined by its complications, such as ascites, hepatic encephalopathy, etc. [107].

2. Diagnostics of the Disease or Condition (Group of Diseases or Conditions), Medical Indications and Counterindications for Using Diagnostics methods

Diagnosis criteria: NAFLD is diagnosed with 1) confirmed hepatic steatosis with/without inflammation, and 2) exclusion of other causes of hepatic steatosis, such as alcohol intake in hepatotoxic doses, genetic diseases, drug intake, etc. (Table 1) [25].

2.1. Complaints and Past Medical History

Complaints and past medical history should be taken aiming at detection of cardio-metabolic diseases and complications associated with NAFLD (overweight/obesity, dyslipidaemia, arterial hypertension, DM, atherosclerosis).

2.2. Physical Examination

Generally, physical examination reveals signs of obesity. It is necessary to evaluate such clinical sing as body mass index (BMI), waist and hip circumference. Palpation and percussion of the abdomen in patients with NAFLD without signs of advanced fibrosis reveals a moderate enlargement of the liver; its edge is rounded, the consistency is "doughy". In advanced fibrosis, the liver becomes stiff; at the cirrhosis stage "liver signs" splenomegaly, and ascites may be noted [108].

Table 1. Causes of Hepatic Steatosis

Macrovesicular steatosis	Microvesicular steatosis
Alcohol intake in hepatotoxic doses	Reye's syndrome
Hepatitis C virus (genotype 3)	Medications (valproic acid, antiretroviral therapy)
Wilson's disease	Steatosis of pregnancy
Lipodystrophy	HELLP syndrome
Fasting	Congenital diseases (lysosomal acid lipase deficiency)
Parenteral nutrition	
Abetalipoproteinaemia	
Medications (Amiodarone, Methotrexate, Tamoxifen, corticosteroids)	

2.3. Laboratory Diagnostic Testing

For patients with NAFLD, it is recommended to undergo a general (clinical) blood test to assess hemoglobin, platelet and leukocyte levels [81].

Grade C Recommendation (Evidence Level 4)

Comments: At cirrhosis stage, cytopenia is most often noted (to a greater extent, thrombocytopenia with varying severity). Two-lineage cytopenia (leukocytopenia and thrombocytopenia) is possible reflecting hypersplenism syndrome (sequestration and/or immune cytopenia).

A general biochemical blood assay is recommended, including such values as: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gammaglutamine transpeptidase, glucose, total protein, albumin, total bilirubin, direct bilirubin, creatinine, uric acid in patients with NAFLD to assess necroinflammatory activity, cholestasis, liver and kidney function, as well as associated metabolic disorders [109].

Grade B Recommendation (Evidence Level 2)

Comments: The biochemical blood assay may show an increase in the activity of serum transaminases (ALT and AST), GGT (an increase in the activity of this enzyme may be isolated), alkaline phosphatase (AP) and bilirubin levels. A number of large clinical studies suggest that the relationship between the ALT activity increase and severity of inflammatory response and liver fibrosis is not always observed [105]. In NAFLD, transaminase activity in the blood serum generally does not exceed the upper limit of the reference range by more than 4–5 times. ALT activity predominates in most patients. If the AST activity predominates, the AST/ALT ratio, generally, does not exceed 1.3, however, it increases with advanced fibrosis. Taking this ratio into account may be useful in making a differential diagnosis with the alcoholic liver disease (AST/ALT ratio is often higher than 2). Generally, GGT activity in most patients is increased not more than two times, and in some of them, this may be the only abnormality in the biochemical blood tests. ALP activity is increased in one third of patients, generally not exceeding the reference range by more than two times. Approximately 20 % of patients reveal a moderate (1.5 to 2 times) increase in the total bilirubin content due to the direct fraction. With the development of liver cirrhosis and a decrease in the synthetic function of the liver, a decreased level of albumin is noted with a normal/borderline level of total protein. To diagnose hyperuricaemia, all obese patients are recommended to study the uric acid level in the blood serum. It is recommended to consider the uric acid level above 360 umol/l as a marker of hyperuricaemia.

It is recommended to determine carbohydrate metabolism parameters (fasting blood glucose, fasting blood insulin, glucose tolerance test according to indications, insulin resistance index) in patients with NAFLD in order to assess the risk of combined metabolic disorders [110, 111].

Grade A Recommendation (Evidence Level 2)

Comments: It is recommended to screen patients with NAFLD for T2DM and other carbohydrate metabolism disorders by measuring fasting plasma glucose or glycated hemoglobin. An oral glucose tolerance test with 75 g of glucose can also be used for screening. IR testing is performed to confirm that the existing metabolic abnormalities are observed within the framework of the metabolic syndrome. To assess IR, the HOMA-IR index (Homeostasis Model Assessment of Insulin Resistance) is used according to the formula: HOMA-IR = fasting plasma insulin (uIU/ml) x fasting plasma glucose (mmol/l)/ 22.5. A HOMA-IR value >2.5 indicates the presence of IR. It should be noticed that the diagnostic value of this

index in patients with overt diabetes mellitus is reduced [112].

In patients with NAFLD, it is recommended to measure lipid metabolism (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) in order to assess the risk of associated cardiovascular diseases [113, 114].

Grade A Recommendation (Evidence Level 2)

Comments: Diagnostically significant deviations typical for NAFLD as part of the metabolic syndrome are increased triglycerides (1.7 mmol/l or more) and decreased HDL cholesterol level (below 0.9 mmol/l in men and below 1.0 mmol/l in women).

It is recommended to perform a coagulogram (an indicative study of the hemostasis system), including such indicators as INR, fibrinogen, prothrombin, prothrombin (thromboplastin) time for patients with NAFLD with suspected liver cirrhosis to assess coagulation status and liver function [114–120].

Grade C Recommendation (Evidence Level 4)

Comments: NAFLD is a prothrombotic condition triggered by chronic subclinical inflammation [115]. Disorders of the hemostasis system progress with development of the hepatic process and affect all three stages of hemostasis. Disorders of primary hemostasis in NAFLD are associated with aberrations in the formation and function of platelets in the presence of chronic inflammation [116]. NAFLD leads to numerous abnormalities of secondary hemostasis, which include increased activity of coagulation factors VII, VIII, IX, XI, and XII, irrespective of the age, sex, and BMI. Studies with measurement of the endogenous thrombin potential confirm that NAFLD is a prothrombotic state, which is associated with its stage [120, 121]. Fibrinolysis disorders (the third stage of hemostasis) are also present in NAFLD, irrespective of its phenotype (in particular, cirrhosis). PAI-1 plays an important role in this process [118]. PAI-1 levels increase in patients with NAFLD as steatosis severity, activity, and fibrosis increase; in its turn, an increase in PAI-1 reduces tPA activity leading to a chronic hypofibrinolytic and prothrombotic status, which is associated with an increased risk of CVD [118, 119]. Weight loss reduces the PAI-1 level; this effect is similar to some antidiabetic medications. In addition, PAI-1 can accelerate progression of liver damage due to local tissue ischemia owing to the formation of intrahepatic thrombi [115]. As it is known, within the framework of hepatic failure, there is a decrease in the synthesis of all plasma coagulation factors, whether pro- or anticoagulants. To a greater extent, signs of hypocoagulation are identified when using standard tests: increased INR, decreased prothrombin index, fibrinogen level. In some cases, it is indicated to study the D-dimer level (exclusion of active thrombosis and efficacy of anticoagulant therapy), activated partial thromboplastin time (to control efficacy of therapy with low molecular weight heparins), antithrombin III (with the factor deficiency, the effect of low molecular weight heparins may be incomplete or absent).

It is recommended to study Urinalysis in patients with LC in order to rule out urinary infection, as well as in patients with LC with an increased creatinine level — in order to exclude proteinuria, cylindruria as a sign of an independent kidney disease [100].

Grade C Recommendation (Evidence Level 4)

It is recommended to study the markers of viral hepatis (serum hepatitis B virus antigen (HbsAg), total M and G antibodies to the hepatitis C virus in the blood (anti-HCV IgG and anti-HCV IgM); protein electrophoresis, blood immunoglobulins, ferritin, percentage of transferrin saturation with iron, ceruloplasmin, as screening indicators for patients with suspected NAFLD to exclude other etiological factors of liver disease [24].

Grade C Recommendation (Evidence Level 5)

2.4. Instrumental Diagnostic Testing

For patients with NAFLD, it is recommended to perform (complex) ultrasonography (US) of the abdomen to determine the size and ultrasound characteristics of the liver, diagnose portal hypertension (detection of ascites, measurement of the portal and splenic vein diameter, spleen size), and to exclude focal liver lesions [122–124].

Grade A Recommendation (Evidence Level 2)

Comments: The following signs may be considered as ultrasonic signs of NAFLD:

- *diffuse hyperechogenicity of the liver parenchyma and heterogeneity of its structure;*
- *blurred and/or pronounced vascular pattern;*
- *distal echo signal attenuation.*

Ultrasonography has advantages in the diagnosis of NAFLD at the LC stage, especially in patients who do not have clinical symptoms of liver damage.

For patients with NAFLD at the LC stage, it is recommended to perform esophagogastroduodenoscopy (EGD) in order to assess the signs of portal hypertension (varicose veins of the esophagus and stomach, signs of portal gastropathy) [81].

Grade C Recommendation (Evidence Level 4)

Comments: To clarify the presence and severity of portal hypertension signs of the upper

gastrointestinal tract, regular EGD is recommended.

2.5. Other Diagnostic Testing

For patients with suspected NAFLD, it is recommended to perform needle liver biopsy followed by histological examination of the specimen in order to determine the quantitative content of fat, inflammation, and fibrosis in cases where other diagnostic methods do not provide a comprehensive answer [125–127].

Grade A Recommendation (Evidence Level 1)

Comments: In addition to determining such characteristics of NAFLD as steatosis, fibrosis stage, severity of lobular inflammation, a liver biopsy in some cases may identify/exclude other causes of liver damage.

Hepatic Steatosis Diagnosis

Hepatic steatosis can be diagnosed using a liver biopsy, which will describe and express it as a percentage in combination with other characteristics of the histological specimen, such as inflammation and fibrosis. Currently, preference is given to noninvasive techniques for diagnosing liver damage in NAFLD, which is important for the disease screening, correct identification of all its components, prognosis, and evaluation of the treatment efficacy.

For patients with suspected NAFLD, abdominal (complex) ultrasonography is recommended as a first-line tool for detecting steatosis in the clinical practice [124, 128].

Grade A Recommendation (Evidence Level 1)

Comments: Conventional ultrasonography is most commonly used in the diagnosis of hepatic steatosis due to its wide availability, safety, low price, and good reputation. In a large meta-analysis including 34 studies and 2,815 patients with suspected liver disease, the pooled sensitivity and specificity of US in detecting steatosis were 85 % (80–89 %) and 94 % (87–97 %), respectively; comparison was made with the liver biopsy results. The main limitations of ultrasonography are as follows: it can only detect steatosis above 12.5–20 %; it is affected by the operator's experience, and is less accurate in obese patients [124]. Nevertheless, ultrasonography remains the most widely used and acceptable tool [128].

Noninvasive diagnostic techniques based on serum markers/biometrics are not recommended for widespread use in clinical practice for patients with suspected NAFLD to determine steatosis [129].

Grade A Recommendation (Evidence Level 2)

Comments: The following non-commercial and commercial noninvasive tests are offered for the diagnosis of hepatic steatosis. Non-commercial tests: FLI (Fatty Liver Index, calculated based on waist circumference, BMI, triglyceride levels, GGTP); HSI (Hepatic Steatosis Index, formula: 8 x(ALT/AST) + BMI (+2 if females; +2, if T2DM)); LAP (Lipid accumulation product, detection threshold (cut-off point) 34.2 cm.mmol/l); NAFLD-LFS (NAFLD — liver fat score — NAFLD — steatosis index; its calculation takes into account the presence of metabolic syndrome, T2DM, ALT and AST levels). Commercial noninvasive tests include SteatoTestTM used as a quantitative biomarker of steatosis [124, 128].

Magnetic resonance imaging (MRI) is not recommended as a first-line tool for diagnosing hepatic steatosis in patients with suspected NAFLD [130].

Grade A Recommendation (Evidence Level 2)

Comments: The quantitative MRI method enables calculation of fat amount (FF — fat fraction) in the liver. The most accurate result is obtained with the value of proton density fat fraction — PDFF. It is the PDFF value that corresponds with high accuracy to the mass and volume content of fat in the liver. In a recent meta-analysis (6 studies involving 635 patients with histologically confirmed NAFLD) for MRI-PDFF, the pooled AUROC values for steatosis in >5 %, >33 %, >66 % were 0.98, 0.91, and 0.90, respectively. The overall sensitivity and specificity were 93 % and 94 %, 74 % and 90 %, 74 % and 87 %, respectively [130]. Despite the high accuracy of MRI-PDFF in steatosis quantitation, a high cost and limited availability of the method restrict its use in wide clinical practice.

Evaluation of the controlled ultrasound attenuation parameter is not recommended as a first-line tool for diagnosing hepatic steatosis in patients with suspected NAFLD [131].

Grade A Recommendation (Evidence Level 2)

Comments: The ability to quantify steatosis by measuring the attenuation of the ultrasonic echo wave was implemented with the FibroScan device and is called CAP (Controlled Attenuation Parameter). The last meta-analysis of 16 studies with individual data from 2,346 patients was published in March 2021 comparing CAP quantification of steatosis with histological data. The M or XL probe was selected according to the developed rules. The XL probe was recommended to 1,050 patients, 930 (89 %) of whom had NAFLD; the result was good for defining any grade of steatosis vs. no steatosis (AUROC 0.819; 95 % CI 0.769–0.869), but suboptimal for distinguishing between

mild and more severe steatosis (S0–S1 to S2–S3; AUROC 0.754; 95 % CI 0.720–0.787). According to this meta-analysis, the optimal threshold value (Youden's index) for detecting steatosis per se in patients with NAFLD is 294 dB/m (sensitivity 0.790; specificity 0.740) [131]. CAP is a promising method for rapid and standardized detection of steatosis using the XL probe. However, it is inferior to MRI-PDF for steatosis quantification.

Inflammation Diagnosis (Non-Alcoholic Steatohepatitis)

The NASH diagnosis is of fundamental clinical importance due to the association of this NAFLD form with the formation and progression of liver fibrosis.

For patients with NAFLD, it is recommended to perform a needle liver biopsy followed by histological examination of the specimen in order to determine inflammation [132].

Grade A Recommendation (Evidence Level 1)

Comments: Liver biopsy remains the main tool for diagnosing NASH and represents a reference standard. Histological criteria for NASH: steatosis, balloon degeneration, predominantly lobular inflammation. All other methods, such as CK-18 (cytokeratin 18), combinations of clinical variables, combination of clinical variables with the PNPLA3 I148M variant, etc., as well as imaging methods offered for noninvasive diagnosis of NASH, are not recommended for use in clinical practice, since they have either contradicting results, or lack of validation studies, or inaccessibility of some variables for wide and easy reproduction [132]. Therefore, liver biopsy currently remains the reference standard for diagnosing NASH in patients with NAFLD.

Hepatic Fibrosis Diagnosis

Hepatic fibrosis is the main predictive factor of the NAFLD course, while severe fibrosis is an independent risk factor for development of both hepatic and extrahepatic complications of this disease and, accordingly, overall mortality and liver-associated mortality. That is exactly why severe fibrosis has been used as the main evaluation criterion in developing and validating noninvasive diagnostic tests for its determination.

Noninvasive diagnostic tests for determining fibrosis and its severity are built according to the principle of using serum markers, biometric parameters, and special equipment. Some of them are freely available for use, while others the patented ones have limited access. Non-patented tests include the following: a) The NFS score (NAFLD fibrosis score) is based on a combination of six parameters such as age, BMI, AST/ALT ratio, platelet count, presence of hyperglycemia, and albumin); b) The FIB-4 scale (index for liver fibrosis) includes four parameters, such as age, AST, ALT and platelet count); c) BARD includes three parameters: AST/ALT ≥0.8 – 2 points; BMI ≥28 – 1 point; presence of diabetes – 1 point; d) APRI (AST to Platelet Ratio Index); e) AAR (AST to ALT ratio); f) eLIFT (Easy Liver Fibrosis Test) includes such parameters as age, gender, GGTP, AST, platelet count and prothrombin time.

The use of non-patented noninvasive tests such as NFS and FIB-4 in patients with NAFLD is recommended in order to rule out severe fibrosis in general clinical practice [133].

Grade A Recommendation (Evidence Level 1)

Comments: The most tested and reliable among non-patented tests (freely available) are NFS and FIB-4. In clinical practice, the following threshold values (cut-off points) are used to decide whether the patient with NAFLD has a severe fibrosis or not: 1.3 for FIB-4 and -1.455 for NFS (high sensitivity), 3.25 for FIB-4 and 0.676 for NFS (high specificity).

NFS and FIB-4 have the following advantages: 1) both tests are based on simple variables widely available in clinical practice; 2) their results can be easily obtained at the patient's bedside using free online calculators; 3) they have good overall diagnostic accuracy for severe fibrosis, as evidenced by a recent meta-analysis (36 studies involving 9,074 patients) – AUROC 0.80 for FIB-4 and 0.78 for NFS, respectively, NPV > 90 % [133].

The disadvantages of NFS and FIB-4 include: 1) risk of obtaining false-positive results for severe fibrosis – PPV <70 %; 2) in one third of cases – an inconclusive result (between the upper and lower threshold values); 3) presumably – an old age affects the diagnostic accuracy. This problem was solved by adoption of a higher threshold for persons over 65 years: 2.0 for FIB-4 and 0.12 for NFS; 4) influence of obesity and DM on the NFS result; this problem is solved by performing FIB-4 rather than NFS in such patients [128].

For ruling out severe fibrosis, the use of noninvasive patented tests such as FibroMeter™, FibroTest® and ELF™ is recommended in patients with NAFLD [134].

Grade A Recommendation (Evidence Level 1)

Comments: Among the patented serum fibrosis markers, the most common are FibroMeter™, FibroTest® and ELF™. FibroMeter™ is applied as FibroMeter^{V2G} (using for calculation platelets, prothrombin index, AST,

alpha-2-macroglobulin, hyaluronic acid, urea, age and sex) and FibroMeter^{V3G} using GGTP instead of hyaluronic acid. FibroTest® includes alpha-2-macroglobulin, haptoglobin, GGTP, patient age and sex, as well as bilirubin and apolipoprotein A1 levels [134]. ELF™ (enhanced liver fibrosis test) consists of three components: procollagen type III peptide (PIIINP), hyaluronic acid and tissue inhibitor of metalloproteinase-1 (TIMP1).

In general, diagnostic accuracy of patented noninvasive serum tests (FibroMeter™, FibroTest® and ELF™) for diagnosing fibrosis is satisfactory; however, their extensive use in clinical practice is limited by high cost and limited availability.

Transient liver elastography is recommended for patients with NAFLD in order to rule out severe fibrosis [133].

Grade A Recommendation (Evidence Level 1)

Comments: Transient elastography is the most widely used method for measuring liver stiffness with the largest data volume in patients with NAFLD. A recent large meta-analysis (17 studies using the M probe and including 2,642 patients; 3 studies using the XL probe and including 318 patients) reported good diagnostic accuracy of this method for detecting severe fibrosis, i.e. stage 3 fibrosis (AUC 0.87 for the M probe and 0.86 for XL probe) and cirrhosis (AUC 0.92 for M probe and 0.94 for XL probe) [133]. In clinical practice, there is no complete concordance on threshold values of liver tissue stiffness for diagnosing severe fibrosis in NAFLD; according to the latest data, a value of >8 kPa and sensitivity of 93 % are suggested [135]. The result of transient elastography is influenced by such factors as ALT level, BMI, distance from the skin to the capsule, and steatosis severity.

For patients with NAFLD, it is recommended to use shear-wave ultrasound elastography as an alternative to transient elastography to assess liver tissue stiffness [136].

Grade B Recommendation (Evidence Level 2)

Comments: Measurement of liver tissue stiffness with shear wave techniques used in modern ultrasound devices, is comparable in accuracy to transient elastography, however, data on patients with NAFLD are limited.

The most accurate tissue stiffness measurements are obtained by magnetic resonance elastography, but this method has a high cost, limited availability, and is used primarily in clinical studies.

For patients with NAFLD, it is recommended to use the following values of various noninvasive diagnostic techniques in order to rule out severe fibrosis: liver tissue stiffness by transient elastography <8 kPa; ELFTM <9.8; FibroMeterTM <0.45; FibroTest® <0.48; FIB-4 <1.3; NFS <-1.455 [128].

Grade A Recommendation (Evidence Level 1)

If a patient with NAFLD has a FIB-4 score more than 1.3, it is recommended to confirm/rule out severe fibrosis using one of the above-mentioned proprietary methods, for example, transient elastography or FibroTest®, etc.

Grade A Recommendation (Evidence Level 1)

In general clinical practice, it is not recommended to use liver biopsy in patients with NAFLD as a first-line study for the diagnosis of hepatic fibrosis [128].

Grade B Recommendation (Evidence Level 2)

Comments: Histological examination of hepatic fibrosis suggests a liver biopsy, which is an invasive and expensive procedure. Currently, the international medical community is trying to replace liver biopsy with non-invasive diagnostics as much as possible.

3. Treatment, Including Drug and Non-Drug Therapies, Diet Therapy, Pain Relief, Medical Indications and Contraindications to the Use of Treatment Modes

The treatment of NAFLD should include two goals:

1. Preventing progression of liver disease; regression of steatosis, steatohepatitis and fibrosis.
2. Decrease in cardiometabolic risk factors.

Essentially, the treatment of NAFLD is divided into non-drug measures (diet and physical exercise) and pharmacotherapy.

3.1. Non-Drug Therapy of NAFLD

One of the effective strategies for the treatment of NAFLD, which is closely associated with such cardiometabolic risk factors as obesity and IR, is weight loss. Weight loss, no matter how it is achieved, is associated with a decrease in ALT, AST, GGTP, degree of inflammation, hepatic steatosis and fibrosis [137, 138].

Among weight loss measures, lifestyle changes (such as physical exercise and diet) are key measures for all patients with NAFLD. According to indications, these measures may be supplemented by pharmacotherapy and bariatric surgery.

3.1.1. Physical Exercise

Any aerobic exercises performed several times a week over a long period of time with an intensity of 45–85 % of the maximum oxygen consumption are recommended for patients with NAFLD for reducing liver fat [139].

Grade A Recommendation (Evidence Level 1)

Comments: Nordic walking may be recommended for patients with NAFLD 2–3 times a week for 30–60 minutes during 6 months and more, which leads to a decrease in the liver fat by 24.4 % [140]. The effect of high-intensity interval trainings on a bicycle ergometer 3 times a week for 12 weeks has also been shown: the liver fat is reduced by 27 % [141]. Systematic reviews and meta-analyses have found that physical exercises reduce liver fat even in the absence of a significant weight loss [92, 95–98]. The mechanisms underlying this effect are underinvestigated. In an experimental study in an obese rodent model, the reduction in hepatic steatosis with regular physical activity was mediated by an increase in hepatic fatty acid oxidation and a decrease in key intermediate proteins associated with the de novo hepatic fatty acid synthesis [146].

3.1.2. Diet

Dietary changes remain the most effective physiological measure of weight loss.

For reducing liver fat, patients with NAFLD are recommended to follow the Mediterranean diet, which is rich in olive oil, vegetables, fruit and nuts, legumes, whole grains, fish and seafood, and has a low content of red meat, processed foods, sugar and refined carbohydrates [24].

Grade B Recommendation (Evidence Level 1)

Comments: The Mediterranean diet reduces hepatic steatosis in obese individuals even without weight loss [147]. Adherence to this diet in patients with NAFLD reduces the severity of liver damage mediated by increased tissue sensitivity to insulin [148]. These results have been confirmed in systematic reviews [103, 104].

Patients with NAFLD are recommended to follow a hypocaloric diet for losing weight and reducing hepatic steatosis [24, 137, 151].

Grade A Recommendation (Evidence Level 2)

Comments: Hypocaloric diets are those with the daily caloric intake reduced by ≥500 kcal/day, as compared to the physiological requirement [24]. A hypocaloric diet followed for a year improves liver functional tests, NASH histologic pattern, and reduces fibrosis. In obese patients the effect of weight loss on the improvement of biochemical and histological parameters of the liver depends on the degree of weight loss. Weight loss of >5 % is required for reducing liver fat, 7–10 % – for reducing inflammation, and >10 % – for influencing fibrosis, although even less significant weight loss is associated with a beneficial effect [137]. Similar results were obtained in a pilot study in individuals with NAFLD while studying the effects of a ketogenic diet and reduced fructose intake. After six months, improvement in liver functional tests, NASH histologic pattern, and decrease in fibrosis intensity were achieved [151].

Moderate weight loss (3–5 %) is recommended for non-obese NAFLD patients to achieve disease remission [152].

Grade B Recommendation (Evidence Level 2)

Comments: A reduction in calorie intake can be achieved by reducing the content of fats as well as carbohydrates; the effect intensity depends on the percentage of weight loss only. At the same time, it is recommended to reduce the content of alcohol, fructose, saturated fats, sweets, sugary drinks, and ultra-processed foods in any diet [153].

For patients with NAFLD, it is recommended to increase the content of insoluble dietary fiber in the diet in order to reduce hepatic steatosis and the risk of associated metabolic disorders [154, 155].

Grade C Recommendation (Evidence Level 2)

Comments: A high intake of insoluble dietary fiber in the population correlates with a lower prevalence of NAFLD [154], while a high dietary fiber content contributes to the production of short-chain fatty acids by the intestinal microbiota, favorably affecting the course of T2DM [155].

For patients with NAFLD, a combination of a hypocaloric diet (deficit of 500 kcal/day from the physiological requirement) and physical exercise (30–60 min 3–5 times a week) is recommended to maximize the effect of weight loss [156].

Grade B Recommendation (Evidence Level 1)

Comments: Cumulatively, clinical studies evaluating the effect of dietary measures show a positive effect of the Mediterranean diet and caloric restriction on the course of NAFLD. To achieve a positive effect in non-obese patients, it is necessary to reduce weight by 3–5 %, in obese individuals – by 7–10 % [157]. Simultaneously with the reduction in progression/regression of NAFLD, weight loss is associated with a significant reduction of

cardiometabolic risk factors, making non-drug measures the key treatment factor. Maintaining a healthy lifestyle after achieving weight loss target values is essential to prevent NAFLD recurrence and provide a protective cardiometabolic effect.

For increasing compliance to weight loss, patients with NAFLD are recommended to stick to the following factors: quick start of weight loss, personalized feedback, positive reward in a health care institution combined with permanent support from friends and family [158, 159].

Grade B Recommendation (Evidence Level 2)

Comments: This recommendation is based on the fact that about 40 % of patients do not adhere to weight loss measures [158], and weight loss target values for most patients are a major concern.

3.2. Drug Therapy of NAFLD

Currently, despite the progress that has been made in understanding the pathogenesis, clinical course, and prognosis of NAFLD, there are no medication that can cure it. Therefore, the pharmacological studies of NAFLD are extremely active and diverse. They are aimed at different metabolic pathways: insulin resistance and gluconeogenesis, lipid transport and lipogenesis, apoptosis, oxidative stress and inflammation, extracellular matrix and fibrosis. Main targets in treating NAFLD are steatosis, since it serves as an independent factor of cardiometabolic risks [160, 161], inflammation and fibrosis. In NASH, fibrosis is an important histological treatment target, since this factor is also associated with an increased risk of cardiovascular diseases, malignancies, and mortality in NASH [162]. An essential factor in the treatment of NAFLD is its multisystem nature and inextricably related comorbidity. Based on this, two main goals of NAFLD therapy can be formulated: as follows.

1. Removing fat from the hepatocyte and preventing liver damage progression;
2. Reducing the patient's cardiometabolic risks associated with excess liver fat.

Therefore, the optimal medication should have a simultaneous impact on both of these goals, while optimizing economic costs and having a high safety profile.

Currently Used Medications

Several known molecules have been or continue to be investigated in the treatment of NAFLD/NASH. Most of them are actively used for reducing certain cardiometabolic risk factors in patients with NAFLD, such as obesity, dyslipidaemia, or T2DM. For example, orlistat, an inhibitor of gastrointestinal lipases, is used in obesity treatment; statins, 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors, are used in the treatment of hypercholesterolaemia and dyslipidaemia; glucagon-like peptide-1 (GLP-1) receptor agonists, liraglutide, semaglutide, and DPP-4 inhibitors (gliptins), are able to increase incretin levels and are approved for the treatment of obesity and T2DM. An improvement of certain liver function parameters was noted to be associated with these medications: liver function tests, or reduction in hepatic steatosis; no effect on fibrosis has been noted [163].

Ursodeoxycholic acid (UDCA)** in a dose of 10–15 mg/kg/day is recommended for patients with NAFLD at the stage of hepatic steatosis and steatohepatitis in order to normalize liver function tests [164, 165].

Grade A Recommendation (Evidence Level 1)

Comments: UDCA has pleiotropic effects: a cytoprotective, antioxidant and antifibrotic action, modulates the process of apoptosis, has an anticarcinogenic effect, which is complemented by a decrease in the aggressive effect of toxic bile acids on the cells of the liver and organs of the gastrointestinal tract. UDCA has a beneficial effect on hepatic steatosis. It was shown in an experimental model that UDCA clears excess free fatty acids from hepatocytes via regulation of autophagy by acting on AMP-activated protein kinase; inhibits apoptosis by influencing the interaction of the Bcl-2/Beclin-1 and Bcl-2/Bax complex. All that makes it a promising molecule in the treatment of NAFLD [59]. UDCA, as a monotherapy, in a dose of 12-15 mg/kg/day for two years leads to a decreas compared with the placebo. The use of UDCA as part of a combined therapy with vitamin E, phosphatidylcholine, etc. for two years leads to an improvement in liver function, and in some cases to a decrease in signs of inflammation and steatosis according to histological examination [164]. At the same time, according to another systematic review with a meta-analysis, the intake of UDCA, especially for more than one year, leads to a decrease in the level of ALT, AST, GGT, ALP, and bilirubin [165].

Furthermore, UDCA has shown an anticarcinogenic effect in experimental models and clinical studies. It is known that patients with NAFLD have an increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC) [166, 167]. In an experimental model of HCC, it was shown that administration of UDCA for 21 days suppresses its growth through the phenomenon of apoptosis, which makes it a candidate for the use in the

prevention of this tumor [168]. The obesity, as a background for NAFLD development, is also accompanied by the risk of developing tumors of other localizations, including colorectal cancer. Currently, it has been shown that bile acids can activate YAP (Yes Associated Protein), which promotes tumorigenesis. UDCA has the ability to suppress YAP signaling by activating the G-protein-coupled bile acid membrane receptor (TGR5). In a model of colorectal cancer, UDCA inhibits tumor growth in a dose-dependent manner and reduces the expression of YAP and Ki67 [169]. This explains the results of an earlier randomized clinical trial including 1,285 patients who underwent surgery for colorectal adenoma. They were divided into two groups: 661 people received UDCA in a dose of 8–10 mg/kg of the weight; 624 people received a placebo. The treatment was provided for about 3 years, followed by the recurrence rate assessment in two groups. It was shown that the use of UDCA had resulted in a statistically significant (39 %) reduction in the recurrence rate of adenoma with high-grade dysplasia, which has a significant risk of progression to invasive colorectal cancer [170].

The UDCA** monotherapy in a daily dose of 10–15 mg per kg of body weight is recommended for patients with NAFLD at any stage in order to reduce steatosis, prevent the progression of liver damage and reduce the cardiometabolic risks of NAFLD [171, 172].

Grade B Recommendation (Evidence Level 2)

Comments: The simultaneous effect on both goals of NAFLD treatment was evaluated in the international single-arm multicenter study "USPEH", conducted in real clinical practice (Ursodeoxycholic Acid as a Means of Preventing Atherosclerosis, Steatosis and Liver Fibrosis in Patients at Different Stages of Non-Alcoholic Fatty Liver Disease) [173]. Patients received recommendations on lifestyle and dietary changes, and UDCA (Ursosan®) in a dose of 15 mg/kg/day was prescribed as a drug therapy. After 24 weeks, the general group of patients showed a significant decrease in ALT, AST, GGTP, a decrease in steatosis (FLI index), total cholesterol TC, TG, CIMT, and a 10-year risk of cardiovascular complications according to the ASCVD calculator (Atherosclerotic Cardiovascular Disease Risk Calculator) in a subgroup of women. Fibrosis progression according to NAFLD Fibrosis Score was not noted. The study showed that the degree of decrease in liver function tests was most pronounced during the first 12 weeks of treatment, while the intensity of weight loss was equal throughout the first and second half of the study. By the end of the study, only 31 % of patients achieved the target weight loss exceeding 5 %. When comparing subgroups that were successful and unsuccessful in losing more than 5 % of weight, no significant differences were obtained in terms of the effect on the degree of decrease in liver function tests and lipid profile parameters, making it possible to consider the results obtained as an effect of UDCA. It should be noted that patients with >5 % weight loss had a more pronounced decrease in FLI, with originally higher FLI rates in this subgroup [172]. UDCA showed a good safety profile in all studies.

It is recommended to administer vitamin E** in a dose of 800 international units (IU)/day in patients with NAFLD at the stage of steatohepatitis for reducing severity of steatosis and inflammation [174].

Grade B Recommendation (Evidence Level 2)

Comments: Vitamin E, as an antioxidant, has been proposed for the treatment of NAFLD in the American guidelines for patients with histologically confirmed NASH, without T2DM and cirrhosis [25, 175]. They are based on the results of the PIVENS study, in which Vitamin E in a dose of 800 IU/day was used for twenty-two months and outperformed placebo in NASH patients in terms of the effect on steatosis, inflammation, and ballooning degeneration, but had no significant effect on fibrosis [174]. European experts are cautious about recommending the use of vitamin E [24, 153]. A recent study showed that in patients with NASH and T2DM, only combined therapy with vitamin E (800 IU/day) and pioglitazone (45 mg/day) used for eighteen months has an effect on the histological activity of the disease; no effect on fibrosis has been noted [176]. A potential safety problem of using high doses of vitamin E — an increase in overall death rate, was highlighted in the meta-analysis published in 2005. [177]. However, these data were not confirmed in a later meta-analysis in 2011 [178].

It is recommended to administer ursodeoxycholic acid (UDCA)** in combination with vitamin E** in patients with NAFLD at the stage of steatohepatitis for reducing the level of liver enzymes, the severity of liver steatosis and inflammation [164, 179, 180].

Grade B Recommendation (Evidence Level 2)

Comments: The benefits of combined use of UDCA and vitamin E were demonstrated in a multicenter, double-blind, placebo-controlled clinical trial: with the intake of UDCA in a

dose of 12–15 mg/kg/day and vitamin E in a dose of 400 IU twice a day for two years, a more pronounced decrease in ALT and AST levels was achieved compared with the placebo group and the UDCA monotherapy group. An improvement in the histological pattern was also noted (signs of liver steatosis and the level of histological activity decreased). The authors also emphasize a good tolerability of the therapy [179]. Another double-blind, placebo-controlled randomized controlled trial of patients with histologically confirmed steatohepatitis with the intake of UDCA in a dose of 12–15 mg/kg/day and vitamin E in a dose of 400 IU daily showed an increase of the adiponectin level and a decrease of the hepatocellular apoptosis. The first one is involved in β-fatty acid oxidation, which leads to a decrease in the content of triglycerides in the liver and severity of its insulin resistance. The combination of UDCA and vitamin E demonstrates both cytoprotective and metabolic effects. [180].

It is recommended to administer Ademetionine** to patients with NAFLD in combination with cholestasis syndrome in order to correct it.

Grade B Recommendation (Evidence Level 3)

Comments: S-adenosylmethionine (ademetionine) acts as the main donor of the methyl group involved in the synthesis of cell membrane components, hormones, and neurotransmitters. Thus, methylation of phospholipids influences the fluidity of cell membranes, transmembrane transport of metabolites, and transmission of signals into the cell. There is an opinion that a decrease in the synthesis of endogenous adenosylmethionine in chronic liver diseases and NAFLD, in particular, contributes to the development of intrahepatic cholestasis by reducing the activity of the BSEP transporter protein (bile salt export pump) and disrupting the integrity of hepatocyte membranes. As a result of cholestasis, potentially toxic bile acids accumulate in the liver and appear in the bloodstream, which in turn leads to oxidative stress, hepatocellular damage, bile duct proliferation, and hepatic fibrosis [181]. A number of publications have confirmed the effectiveness of ademetionine in reducing clinical and biochemical parameters of cholestasis in patients with acute and chronic liver diseases: in a multicentre, double-blind, placebo-controlled study, patients with cholestasis received S-adenosylmethionine in a dose of 800 mg intravenously for two weeks, and further continued to receive the medication per os in a dose of 1600 mg for eight weeks. When compared with the control group, there was a significant decrease in the level of total and conjugated bilirubin, ALT, AST and GGT, as well as a decrease pruritus, up to complete disappearance, in the S-adenosylmethionine group. Continuation of therapy in the form of oral administration of S-adenosylmethionine allowed not only to maintain the previously achieved effect, but also to improve the laboratory and clinical picture in patients who had not responded to intravenous administration of the medication [182]. Another observational multicentre study showed similar results. S-adenosylmethionine intake in patients with NAFLD resulted in a decrease in the level of ALP, ALT and AST, as well as a decrease in clinical manifestations of cholestasis: jaundice, pruritus, weakness and fatigue [183].

3.3. Treatment of NAFLD and Associated Conditions

3.3.1. Treatment of NAFLD in Combination with Carbohydrate Metabolism Disorders

For patients with NAFLD and disorders of carbohydrate metabolism, it is recommended to normalize body weight through diet and increased physical activity for improving tissue sensitivity to insulin and reducing liver fat [137].

Grade A Recommendation (Evidence Level 2)

Comments: The degree of weight loss is associated with the degree of improvement of the histological parameters of NAFLD. A 12-month prospective study conducted by E. Vilar-Gomez et al. [137], showed that all patients who lost more than 10 % of body weight had an improvement in NAFLD Activity Score (NAS), 90 % of patients had resolution of NASH, and 45 % had regression of fibrosis. A greater percentage of body weight loss is associated with a greater degree of improvement of the histological parameters of NASH.

The use of medications is also focused on controlling the main risk factors for this disease, such as obesity, IR, hyperglycaemia, dyslipidaemia, and inflammation. Considering that T2DM and NAFLD have common pathogenetic features, it is not surprising that some of the methods used for treating T2DM are actively used for the treatment of NAFLD.

Currently, numerous studies have been conducted aimed at finding a hypoglycemic medication that could affect pathological changes in NASH. Such a medication should reduce body weight, cardiovascular events, prevent the development of advanced stages of NAFLD, and also have low cost, long-term safety and improve quality of life.

The use of GLP-1# receptor agonists in patients with NAFLD and disorders of carbohydrate

metabolism is recommended in order to reduce body weight, insulin resistance, and normalize serum transaminase levels by reducing the severity of inflammation [184, 185].

Grade B Recommendation (Evidence Level 2)

Comments: Incretin mimetics, including GLP-1 receptor agonists, are used to treat T2DM and obesity. They stimulate glucose-dependent insulin secretion, reduce de novo lipogenesis, and lead to a decrease in body weight, IR, and hepatic transaminase levels. GLP-1 agonists ρργ appear to be a very attractive and promising treatment option for NAFLD, however, it is still unknown whether this medication group has a direct effect on hepatocytes, reducing hepatic steatosis and inflammation, or this effect is achieved through weight loss. In 2016, phase II of the randomized controlled trial LEAN [184] aimed at studying liraglutide safety and efficacy in NASH was completed. This study included 52 patients with NASH: 17 patients with T2DM and 35 patients without T2DM; 26 of them received liraglutide in a dose of 1.8 mg for 48 weeks, the rest received placebo. 39 % of patients in the liraglutide group achieved the primary endpoint (regression of NASH without fibrosis progression), while in the placebo group this parameter was 9 % (p = 0.019). Studies of another medication from the GLP-1 receptor agonist group, semaglutide, have also been initiated. Currently, phase II clinical trial of semaglutide in patients with NASH and fibrosis has been completed [185]. Semaglutide provided a statistically significant regression of NASH (NAS score equal to 0 or 1 for lobular inflammation and 0 for hepatocyte ballooning) without hepatic fibrosis worsening (no progression). However, there is no statistically significant difference between semaglutide and placebo in terms of fibrosis reduction. Phase III clinical trials have been scheduled. Studies of both liraglutide and semaglutide have shown a reduction in cardiovascular events.

Administration of thiazolidinediones (pioglitazone# at a dose of 30–45 mg/day) is recommended to patients with NAFLD and carbohydrate metabolism disorders in order to reduce hepatic steatosis, inflammation, and fibrosis [174, 186–188].

Grade A Recommendation (Evidence Level 1)

Comments: Thiazolidinediones belong to a class of antidiabetic medications that increase tissue sensitivity to insulin and are involved in the regulation of lipid metabolism. A member of this class, pioglitazone in dose of 30–45 mg/day compared to placebo, has demonstrated its efficacy in the treatment of NASH in several studies and meta-analysis with respect to improvement of liver function tests and histologic pattern in NASH patients with and without T2DM [174, 186–188]. However, the negative aspects of such treatment are weight gain, association with urinary bladder cancer in the long term, and risk of developing osteoporosis. This medication is also not recommended in the presence of heart failure signs, in patients receiving high doses of insulin or amlodipine [189]. Thus, both the European and the American associations for the study of the liver recommend the use of pioglitazone for the treatment of NASH in selected patient groups, given the risks of developing the aforementioned conditions.

The use of the sodium-glucose cotransporter type 2 (SGLT-2) inhibitors in patients with NAFLD and T2DM has been recommended for reducing body weight, levels of glycemia and serum transaminases [188].

Grade B Recommendation (Evidence Level 2)

Comments: SGLT-2 inhibit glucose reabsorption in the proximal renal tubules with the insulin-independent mechanism, which leads to a decrease in blood glucose level. Weight reduction is also noted with their use. Currently, five medications from this group are best known on the market: dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, and ertugliflozin. Administration of canagliflozin (100 or 300 mg daily) for 52 weeks is associated with a decrease in serum transaminases, this effect being dose-dependent; however, the impact of this treatment on the liver histologic pattern is not known [188]. Considering that medications of this group lower glucose levels, contribute to weight loss and can improve tissue sensitivity to insulin, they are included in all algorithms for the treatment of T2DM and have become the target of research for the treatment of NAFLD in patients with T2DM.

The addition of UDCA# to hypoglycemic regimens in patients with NAFLD and hyperglycemia is recommended to further influence glucose homeostasis [190].

Grade A Recommendation (Evidence Level 1)

Comments: Pluripotent molecules are of great interest; one of them (UDCA) is used in the treatment of NAFLD. A systematic review and meta-analysis of clinical trials published in 2018 [190] showed the effect of UDCA on glycemic parameters, when administered in different doses for the period from 6 weeks to 2 years. A meta-analysis of seven studies using eight UDCA treatment groups demonstrated a significant decrease in fasting glucose levels

after such therapy (-3.30 mmol/L, 95 % CI: -6.36, -0.24, p = 0.034; I^2 = 28.95 %). A meta-analysis of two treatment groups showed a significant decrease in glycated hemoglobin concentration (-0.41 %, 95 % CI: -0.81, -0.01, p = 0.042; I^2 = 0 %). Moreover, a meta-analysis of four treatment groups also found a significant decrease in plasma insulin levels (WMD: -1.50 mg/dL, 95 % CI: -2.81, -0.19, p = 0.025; I^2 = 67.90 %), but showed no significant effect on HOMA-IR (WMD: -0.20 mg/dL, 95 % CI: -0.42, 0.01, p = 0.057; I^2 = 85.34 %). The results of this meta-analysis showed that UDCA significantly reduces fasting plasma glucose, glycated hemoglobin, and insulin, suggesting a positive effect on glucose homeostasis.

Metformin is not recommended for patients with NAFLD and carbohydrate metabolism disorders for reducing hepatic steatosis [25, 191, 192].

Grade A Recommendation (Evidence Level 1)

Comments: Metformin treatment does not reduce fat content or expression of inflammatory markers in NAFLD. Therefore, metformin is not recommended for the treatment of NAFLD, although its use is associated with a decreased number of detected HCC and extrahepatic malignancies [25, 193].

3.3.2. Treatment of NAFLD in Combination with Obesity

Non-Drug Therapy

For reducing weight and severity of hepatic steatosis, all patients with NAFLD and obesity are recommended to follow a balanced anti-atherogenic diet with fat restriction to 25–30 % of daily caloric intake, hypocaloric diet (with a moderate caloric deficit of a daily ration of 500–1000 kcal) at the stage of weight loss, and eucaloric diet at the stage of weight maintenance [24, 25, 194, 195].

Grade A Recommendation (Evidence Level 2)

Comments: Dietary recommendations should include reducing the caloric content of the diet by limiting easily digestible carbohydrates and saturated fats, avoiding canned foods, and high fructose foods and drinks. Macronutrient composition should be adjusted in accordance with the Mediterranean diet [24]. All dietary recommendations should be performable on a long-term basis. In comparative studies, low-fat and low-carbohydrate diets have shown positive results, suggesting that calorie reduction is more important than specific dietary restrictions. A special factor in improper nutrition leading to the development of hepatic steatosis is excessive consumption of fructose. Its adverse effects are considered to be realized through de novo lipogenesis, increased visceral fat, and negative effect on insulin sensitivity. Therefore, patients are advised to limit the consumption of sugary carbonated drinks, honey, syrups, and excessive consumption of fruit with high amounts of fructose [143]. A large amount of fructose is found in apples, pears, melon, watermelon and dried fruit; berries and citrus fruits contain little fructose.

An obligatory increase of physical activity is recommended for all patients with NAFLD and obesity in order to reduce weight and severity of hepatic steatosis [24, 192, 196–198].

Grade A Recommendation (Evidence Level 1)

Comments: Daily moderate aerobic exercises are recommended, such as walking 30–40 min per day or 150–200 min per week [192,196–198]. Aerobic exercises and strength training are effective in reducing liver fat. Exercises should be selected individually according to the patients' preferences for increasing their adherence [24]. At the same time, severe calorie restriction and rapid weight loss can lead to progression of fibrosis and increased serum transaminase levels. A slow weight loss of 0.5–1 kg per month is recommended.

Drug Therapy

Pharmacotherapy is recommended for patients with NAFLD and obesity who have not responded to lifestyle changes in order to reduce weight and severity of hepatic steatosis [24, 25, 184, 199].

Grade A Recommendation (Evidence Level 1)

Comments: In the absence of clinically significant weight loss with drug-free methods, drug therapy may be used to improve the efficacy of obesity treatment: liraglutide (GLP-1 agonist)# 0.6–1.8 mg/day or orlistat (inhibitor of gastrointestinal lipases) 120 mg/day or sibutramine (appetite regulator) 10–15 mg/day. This helps to achieve a more effective weight loss, facilitates implementing nutritional recommendations and developing new eating habits, and also contributes to maintaining reduced body weight in a continuous manner [24, 25, 184, 199].

Surgical Treatment

Surgical bariatric treatment is recommended for reducing body weight and metabolic complications in obese patients with NASH who have not achieved a positive result associated with lifestyle changes and medication-assisted treatment [24, 25, 200, 201].

Grade A Recommendation (Evidence Level 2)

Comments: Bariatric treatment is not contraindicated for patients with obesity and NAFLD or NASH (without confirmed

cirrhosis); it allows to achieve stable long-term results. Prospective data shows a reduction of all adverse histological changes in NASH, including fibrosis, in patients after bariatric surgery [24, 25, 200, 201].

3.3.3. Treatment of NAFLD in Combination with Dyslipidaemia and Atherosclerosis

There is increasing evidence that NAFLD, starting from the stage of steatosis, is a strong independent risk factor for the development of CVD, independent of DM, dyslipidaemia, or obesity.

Statins** have been recommended for lowering LDL levels and preventing cardiovascular risk in patients with NAFLD and clinically significant atherosclerosis [202].

Grade B Recommendation (Evidence Level 1)

Comments: In the context of influencing events associated with atherosclerosis, statins generate principal interest, as they inhibit cholesterol synthesis in the liver, are widely used for primary and secondary prevention of atherosclerotic events, and have proven their safety in NAFLD. Statin doses are calculated based on stratification of the arterial hypertension risk: administration of statins is indicated at the maximum recommended or maximum tolerated dose to achieve target LDL-C levels [203]. Decreased levels of liver enzymes, reduction of steatosis and inflammation may be associated with the use of statins; however, fibrosis reduction in NAFLD does not occur. There is also evidence of a reduced risk of HCC associated with statin intake [204, 205]. The preventive effect of lipophilic statins (atorvastatin and simvastatin) is attributable to some antitumor and antiangiogenic effect.

For patients with NAFLD and clinically significant atherosclerosis, it is recommended to combine statin therapy** with UDCA in order to reduce statin hepatotoxicity and enhance their hypolipidemic effect [206, 207].

Grade B Recommendation (Evidence Level 1)

Comments: This recommendation is primarily based on the results of an observational program studying the UDCA effect on the efficacy and safety of statin therapy in patients with impaired liver function (RACURS). The study evaluated the ability of UDCA to prevent liver dysfunction in patients with CVD and a high risk of cardiovascular complications who are eligible for statin prescription. It was demonstrated that the administration of UDCA in addition to a statin for six months, compared with statin monotherapy, leads to a significant reduction in total cholesterol and LDL cholesterol levels. This effect is expected to increase patients' adherence to statin therapy and potentiate their effect on cardiovascular risks [206].

Ezetimibe# is recommended for those patients with NAFLD and dyslipidemia who have poor tolerance to statins or develop side effects in statin therapy in order to reduce serum transaminase levels and reduce hepatic steatosis [208].

Grade B Recommendation (Evidence Level 1)

Comments: Ezetimibe reduces the uptake of dietary cholesterol by intestinal cells and may result in some improvement in the histological signs of NAFLD. Patients with NAFLD retain favorable cardiovascular effects of statins in monotherapy and in combination with ezetimibe [208]. These data support the suggestion that a moderate elevation of transaminases and a high index of non-alcoholic steatosis may be additional markers for identification of patients with a very high cardiovascular risk who may need more aggressive prevention of atherosclerotic events.

For patients with NAFLD and dyslipidemia, it is recommended to use Omega-3 polyunsaturated fatty acids in order to reduce hepatic steatosis, BMI, and normalize lipid profile parameters [209].

Grade B Recommendation (Evidence Level 1)

Comments: Omega-3 polyunsaturated fatty acids have clearly demonstrated the ability to improve the histologic pattern of NAFLD and NASH, reduce body weight, lower levels of total cholesterol and triglycerides, and increase HDL cholesterol, however, their significance for primary and secondary prevention of cardiovascular events requires further study [209].

3.3.4. Treatment of NAFLD in Combination with Chronic Kidney Disease

A growing number of evidence is accumulating indicating the association between NAFLD and CKD due to the commonality of risk factors for their development, while there is evidence of an independent association between these conditions. Risk factors for CKD in people with NAFLD not related to liver function include older age, DM, hypertension, initially reduced estimated glomerular filtration rate, smoking, thyroid dysfunction (hypothyroidism associated with fat accumulation, hyperthyroidism associated with the formation of active forms of oxygen). In patients with NAFLD, a number of factors are involved in the CKD development, the key of which is systemic low-intensity inflammation,

which is triggered along several inflammatory cascades [210–213].

The use of RAAS inhibitors# is recommended for patients with NAFLD and CKD for reducing steatohepatitis activity [213].

Grade B Recommendation (Evidence Level 2)

Comments: The efficacy of RAAS blockade using ACE inhibitors and ARB was evaluated in small randomized controlled trials in patients with NAFLD. In particular, in the Fatty Liver Protection Trial by Telmisartan (FANTASY Trial), the use of telmisartan, an ARB with activity on PPAR-γ-receptors, was more effective than valsartan in reducing inflammation, activity index, NAFLD fibrosis stage, and microalbuminuria [213]. In another study, a long-term (>1 year) use of ACE inhibitors or ARB in patients with stage 3 CKD, end-stage CKD, and following kidney transplantation was associated with a lower incidence of NAFLD and less liver stiffness compared with patients not taking these medications [213].

3.4. Surgical Treatment

Surgical treatment (bariatric therapy) for reducing body weight and metabolic complications should be considered in patients with obesity and NASH who have not achieved a positive result with lifestyle changes and pharmacotherapy [24, 25, 200, 201] — see Section 3.3.2.

4. Medical Rehabilitation and Sanatorium/Resort Therapy, Medical Indications and Contraindications to the Use of Rehabilitation Methods, Including Those Based on the Use of Natural Therapeutic Factors

There are no specific measures for the rehabilitation of patients with NAFLD. Sanatorium/resort therapy of gastroenterological profile may be recommended with the use of physiotherapy, regular physical activity, fresh air and walking, alcohol abstinence.

5. Prevention and Follow-up Monitoring, Medical Indications and Contraindications to Using Prevention Techniques

Patients with NAFLD should be under the supervision of allied specialists (gastroenterologists, endocrinologists, cardiologists, nutritionists). Medical efforts should be aimed at preventing NAFLD and its consequences (fibrosis progression, development of HCC and other tumors), as well as at preventing cardiometabolic diseases associated with NAFLD.

5.1. Prevention of HCC

HCC accounts for >80 % of primary liver cancers worldwide and most often develops in association with liver cirrhosis [214]. The effective treatment of chronic hepatitis B and C, combined with the current epidemic of sedentary lifestyle diseases, has realized into the leading role of NAFLD in development of liver cirrhosis and HCC in many Western countries. At the same time, the detection rate of HCC in the cohort of patients with NAFLD is 0.44 per 1,000 person years (0.29–0.66) [166]. The pathogenesis of HCC in NAFLD/steatohepatitis is complicated and poorly understood. IR and obesity activate systemic inflammation and pro-carcinogenic cascades, lipotoxicity as a result of fat accumulation, endoplasmic stress and DNA damage induce and stimulate oncogenesis [167]. HCC in the presence of NAFLD can also develop in the absence of cirrhosis; it is more often diagnosed in the advanced stage implying an unfavorable prognosis for such patients [215, 216].

Prevention of HCC in NAFLD does not differ from the general principles of managing these patients, including a healthy lifestyle, general physical activity, and caloric restriction of the consumed food. A potential preventive effect of a number of medications (e.g., UDCA, statins, metformin) has also been shown.

5.2. Prevention of NAFLD-Associated Conditions

Physical activity is recommended for all patients with NAFLD for preventing osteoporosis [217].

Grade A Recommendation (Evidence Level 1)

Comments: Physical activity is now considered the cornerstone of NAFLD and osteoporosis prevention. Physical exercise is believed to strengthen the skeleton bones through gravitational forces and stretching of the muscles causing stretch within the skeleton. There is strong evidence that aerobic exercise and moderate strength training can minimize bone loss and play a critical role in the prevention of osteoporosis. Studies in women with early menopause have shown that strength training resulted in small but significant changes in BMD. A meta-analysis of 16 studies and 699 trial subjects showed a 2 % improvement in BMD in the lumbar spine in the strength exercise group compared to the group without significant physical activity [217].

Patients with NAFLD are also recommended to exercise at least 30 minutes with moderate/

Table 2. Criteria for Medical Care Quality Assessment

No.	Quality Criteria	Performance Evaluation
1	A laboratory and instrumental examination aimed at determining hepatic steatosis, stage of fibrosis has been made	Yes/No
2	Other causes of chronic liver disease have been excluded	Yes/No
3	The combined cardiometabolic pathology has been assessed (obesity, dyslipidemia, atherosclerosis, arterial hypertension, insulin resistance, diabetes mellitus)	Yes/No
4	Lifestyle modification (physical activity, diet) has been recommended	Yes/No
5	Drug therapy has been recommended for failure of lifestyle modification and presence of other indications	Yes/No

high intensity 3–5 times a week for preventing thrombotic complications [218–220].

Grade A Recommendation (Evidence Level 1)

Comments: Physical exercise has a positive effect on the coagulation system at all stages of hemostasis. Parameters of primary hemostasis are improved via endothelium-dependent vasodilation and NO production, which leads to a decrease in excessive activation and aggregation of platelets [221]. Regular exercise with moderate intensity restores the efficiency of fibrinolysis, and aerobic exercise programs lead to a decrease in PAI-1 by 23–37 % within 3–8 months [205, 221–225]. There is also evidence of a beneficial effect of strength training [226].

It is recommended that obese patients use UDCA** to prevent the formation of gallstones during weight loss [227, 228].

Grade A Recommendation (Evidence Level 1)

Comments: It is well known that in obese patients the incidence of gallstone disease is higher than in the general population, while rapid weight loss further increases the risk of stone formation. It was demonstrated that the use of UDCA during a weight loss diet prevents the risk of gallstone formation [227], and treatment with UDCA after bariatric surgery reduces the risk of symptomatic gallstone disease [228].

5.3. Follow-Up Monitoring

Follow-up monitoring of patients with NAFLD is based on the assessment of the dynamics of liver function tests, signs of portal hypertension (ultrasonography of the abdominal organs, EGC). Frequency of examinations will be determined according to the disease stage and general condition/complaints of the patient.

Screening for HCC is not recommended for patients with NAFLD in the absence of severe fibrosis/cirrhosis, due to the low incidence of the tumor in this background (0.01 % in the population) and cost inefficiency [229].

Grade C Recommendation (Evidence Level 4)

For patients with NAFLD at the stage of advanced fibrosis or cirrhosis, abdominal ultrasonography is recommended every 6 months as screening for HCC [230].

Grade A Recommendation (Evidence Level 1)

6. Organization of Medical Care

Most patients with non-alcoholic fatty liver disease need to be observed and treated on an outpatient basis. Indications for planned hospital admission of patients with non-alcoholic fatty liver disease are the following: the need for a differential diagnosis for ruling out other causes of liver damage (for example, the need for a needle liver biopsy), a pronounced clinical picture of the disease, a pronounced activity of serum transaminases, presence of associated cardiometabolic factors that complicating the course of the disease and requiring collegial management of the patient.

7. Additional Information (Including Factors that Affect the Outcome of the Disease or Condition)

No additional information is available.

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Appendix A2.
Clinical Practice Guidelines Development Methodology

The proposed recommendations aim to bring to practitioners modern ideas about the etiology and pathogenesis of NAFLD, to introduce the currently used algorithms for diagnosis, prognosis and treatment.

Target Audience of the Clinical Practice Guidelines:

1. Gastroenterologists.
2. General practitioners (family doctors).
3. Primary care doctors.
4. Cardiologists.
5. Endocrinologists.
6. Oncologists.

Table 1. Evidence Level Rating Scale (EL) for Diagnostic Methods (Diagnostic Interventions)

EL	Interpretation
1	Systematic reviews of trials with reference method control or systematic review of randomized clinical trials using meta-analysis
2	Individual trials with reference method control or individual randomized clinical trials and systematic reviews of trials of any design, excluding randomized clinical trials, using meta-analysis
3	Trials without sequential control with a reference method or trials with a reference method that is not independent of the study method or non-randomized comparative studies, including cohort studies
4	Non-comparative studies, description of a clinical case
5	Only a rationale for the mechanism of action or expert opinion is available

Table 2. Evidence Levels with Indication of the Evidence Level Classification (EL) used

EL	Interpretation
1	Systematic review of randomized clinical trials using meta-analysis
2	Individual randomized clinical trials and systematic reviews of trials of any design, excluding randomized clinical trials, using meta-analysis
3	Non-randomized comparative studies, including cohort studies
4	Non-comparative trials, description of a case or case series, case-control study
5	Only a rationale for the intervention action mechanism (preclinical studies) or expert opinion is available

Table 3. Recommendation Grades (RG) with Indication of the Recommendation Grade Classification Used

EL	Interpretation
A	Strong recommendation (all efficacy endpoints (outcomes) considered are important, all trials are of high or satisfactory methodological quality, their findings are consistent for the outcomes of interest)
B	Conditional recommendation (not all efficacy endpoints (outcomes) considered are important, not all trials are of high or satisfactory methodological quality, and/or their findings are inconsistent for the outcomes of interest)
C	Weak recommendation (absence of proper quality evidence (all efficacy endpoints (outcomes) considered are unimportant, all studies are of low methodological quality and their findings are inconsistent for the outcomes of interest)

Procedure for Updating Clinical Practice Guidelines

The mechanism for updating the Clinical Practice Guidelines provides for their systematic updating at least once every three years, as well as when new evidence-based medicine data appear related to issues of the diagnosis, treatment, prevention and rehabilitation of specific diseases, or when there are reasonable additions/comments to previously approved CPG, but not more than once every 6 months.

Appendix A3. Reference Materials, Including Compliance with Indications and Contraindications for Use, Methods of Administration and Doses of Medications, Instructions for Use of the Medication

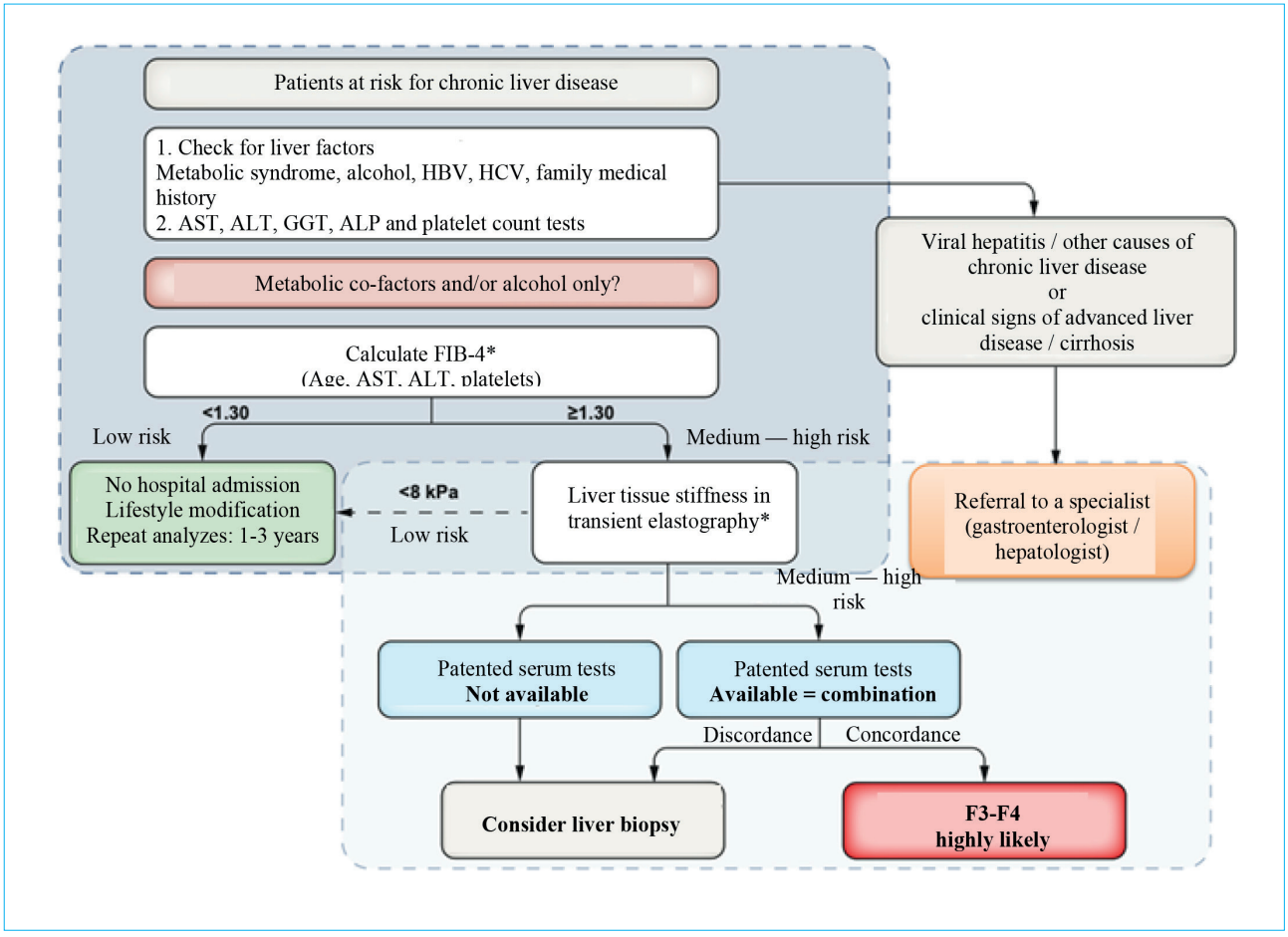
These Clinical Practice Guidelines have been developed in line with the following legal documents:

1. Order of the Ministry of Health and Social Development of the Russian Federation d/d November 12, 2012 No. 906n "On Approval of the Procedure for Providing Medical Care to the Population in the Gastroenterology Profile".

2. Order of the Ministry of Health of the Russian Federation d/d May 10, 2017 No. 203n "On Approval of the Criteria for Medical Care Quality Assessment".

3. Order of the Ministry of Health of the Russian Federation d/d December 27, 2007 No. 811 "On Approval of the Standard of Medical Care for Patients with Other Liver Diseases (in Providing Specialized Care)".

Appendix B. Doctor's Action Algorithms



Appendix C. Patient Information

The main factors leading to non-alcoholic fatty liver disease are a sedentary lifestyle and excess weight. Very often, non-alcoholic fatty liver disease is associated with other diseases, such as diabetes mellitus, impaired cholesterol metabolism, vascular atherosclerosis, and hypertensive disease. In some people, this disease can lead to lever cirrhosis, and in some individuals, it can be complicated by the development of liver cancer. The main treatment for non-alcoholic fatty liver disease is changing lifestyle in order to lose weight: proper diet and physical activity. In your diet, you need to increase the content of olive oil, vegetables, fruit and nuts, legumes, whole grains, fish and seafood. It is necessary to reduce the consumption of red meat, processed foods, alcohol, fructose, saturated fats, sweets, sugary drinks, ultra-processed foods, and refined carbohydrates. Try to do 30–60 minutes of exercise 3–5 times a week, e.g. Nordic walking or high-intensity exercise on a bicycle ergometer. Losing weight by 10 % from the original one will significantly reduce inflammation in the liver and risk of cardiovascular complications (stroke, heart attack). You also need to be under the constant supervision of the doctor, who will determine the list of necessary studies and their frequency, and will prescribe a drug therapy, if necessary.

Appendix D1–D2. Rating Scales, Questionnaires and other Assessment Tools of the Patient's Condition, Given in the Clinical Practice Guidelines

Annex D1. NAS Score (NAFLD Activity Score) [104].

Title in Russian: Шкала оценки активности НАЖБП (NAFLD Activity Score)

Source: Consensus of expert morphologists CRN (Clinical Research Network), 2005

Purpose: for semi-quantitative evaluation of severity and stage of NAFLD

Content (template): The score assesses the degree of morphological changes with a numerical score (0 to 8): severity of hepatic steatosis, intralobular (lobular) inflammation, hepatocyte ballooning, and fibrosis stage.

Steatosis (%)	Lobular inflammation*	Ballooning
<5 (0 points)	none (0 points)	none (0 points)
5–33 (1 point)	<2 foci per field of vision (1 point)	mild (1 point)
34–66 (2 points)	2–4 foci (2 points)	moderate/severe (2 points)
Hepatic fibrosis (stages)	1a, b: zone 3 acini 1c: portal fibrosis 2: zone 3 acini + portal /periacinal fibrosis 3: fibrous septa 4: pseudolobules, impaired architectonics of the liver tissue (cirrhosis)	

Note.* The presence of accumulations of cells of the inflammatory infiltrate with an increase of 20.

Key (interpretation):
- NAS 0–2 – NASH diagnosis is unlikely;
- NAS 3–4 – "grey zone", the patient may have NASH;
- NAS ≥5 – a likely NASH diagnosis.

Appendix D2. SAF Scale [103]

Title in Russian: Шкала для полуколичественной оценки тяжести НАЖБП (Scale for Semi-Quantitative Evaluation of NAFLD Severity)

Source: FLIP pathology consortium, 2014

Purpose: for semi-quantitative evaluation of NAFLD severity

Content (template): The scale includes such histologic characteristics of NAFLD as steatosis intensity (S, steatosis), ballooning and lobular inflammation (A, activity), and liver fibrosis stage (F, fibrosis).

Parameter	Severity of changes	Score
S: steatosis (0–3)	<5	0
	5–33	1
	33–66	2
	>66*	3
A: activity (0–4)	Ballooning	
	None	0
	Accumulations of normal sized hepatocytes with a round shape and pale cytoplasm	1
	Same, but there are also enlarged cells in quantity at least twice as large as normal ones.	2
	Lobular inflammation (≥2 inflammatory cells at 20 × magnification)	
	None	0
	<2 foci per lobule	1
	>2 foci per lobule	2
F: fibrosis (0–4)	None	0
	Perisinusoidal OR portal fibrosis	1
	Perisinusoidal AND portal fibrosis without bridging fibrosis	2
	Same AND bridging fibrosis	3
	Cirrhosis	4
Total points:		0–11

Note. * the presence of (sub)total hepatic steatosis in young patients, especially without evidence of the metabolic syndrome, requires evaluation of lysosomal acid lipase (LAL) activity to rule out cholesterol ester storage disease/Wolman disease or patient's examination for Wilson disease. A more rare cause may be the carriership of recessive POLG, DGUOK, or MPV17 mutations that are characteristic of mitochondrial diseases.

Key (interpretation): the evaluation result is recorded as an index S1A2F3, S2A1F1, etc.

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