NON-ALCOHOLIC FATTY LIVER DISEASE: A REVIEW OF EPIDEMIOLOGY, PATHOPHYSIOLOGY, CLINICAL COURSE AND DIAGNOSIS METHODS

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Abstract. *With the increasing prevalence of obesity and diabetes in many countries around the world, non-alcoholic fatty liver disease (NAFLD) is becoming one of the leading causes of liver cirrhosis and hepatocellular cancer. Effective management of NAFLD requires a broad understanding of its development mechanisms, as well as the use of advanced diagnostic and therapeutic methods, making this topic relevant to the scientific and medical community. The use of a variety of radiological techniques, such as MRI with fatty infiltration and elastography, provides a reliable alternative to liver biopsy. An integrated approach to the problem of NAFLD helps to improve the efficiency of diagnosis and develop individual strategies for the treatment and prevention of this disease. The article presents a literature review covering current aspects of multimodal radiodiagnosis of non-alcoholic fatty liver disease.*
Keywords: *non-alcoholic fatty liver disease, steatohepatitis, radiation diagnostics, magnetic resonance imaging, transient elastography.*

Introduction. Liver disease remains a global concern across all age demographics [1]. In the late 1990s and early 2000s, there was a fivefold increase in the incidence of non-alcoholic fatty liver disease (NAFLD) among individuals aged 18–39 years [2, 3]. As individuals reach the age of 50, the incidence of fatty liver disease tends to rise, reaching its peak in the 50–59 age group.

According to the World Gastroenterological Organization, NAFLD and non-alcoholic steatohepatitis (NASH) became the predominant liver diseases in Western countries by the mid-2000s. During this period, the overall prevalence of NAFLD doubled, while the prevalence of other chronic liver diseases either remained stable or declined [4]. The escalating global incidence of NAFLD has spurred increased interest in non-invasive methods for accurately assessing liver fat content in vivo.

Definition of the pathological condition, epidemiological, and etiopathogenetic aspects of NAFLD.

The term "non-alcoholic fatty liver disease (NAFLD)" encompasses various liver pathologies of metabolic origin, confirmed by morphological evidence of steatosis, steatohepatitis, fibrosis, cirrhosis, or adenocarcinoma, in the absence of exogenous toxic factors damaging the liver [5]. Until 2020, debates persisted regarding the clarity of the term "NAFLD."

In 2020, a consortium of experts from 22 countries proposed a new consensus concept, Metabolically Associated Fatty Liver Disease (MAFLD), which encompasses etiological factors

such as overweight, type 2 diabetes, and metabolic syndrome leading to fatty liver disease, primarily not associated with chronic alcohol consumption [6].

MAFLD and NAFLD refer to distinct patient populations: MAFLD applies to patients with designated metabolic risk factors and steatosis, while NAFLD encompasses patients without metabolic risk factors but with steatosis. The revised interpretation of MAFLD facilitates tailored treatment and diagnostic approaches for individual patients with various comorbidities associated with MAFLD [6].

Advocates of the MAFLD criteria contend that they outperform NAFLD criteria in identifying patients at high risk of liver fibrosis, a key determinant of mortality in fatty liver disease [7]. However, it is suggested that WHO-approved ICD-11 disease codes be used in routine practice.

According to Z.M. Younossi et al. (2016), the global prevalence of NAFLD in 2016 was 24% [5]. A more recent study indicated an incidence of NAFLD of up to 32%, suggesting that NAFLD will dominate clinical hepatology in the 21st century [8].

The high prevalence of NAFLD is primarily attributed to the rising rates of obesity and diabetes mellitus. Surprisingly, even among individuals with a normal body mass index (BMI), the incidence of NAFLD in 2022 was 9%. Furthermore, the incidence of NAFLD has risen across all regions, with the most significant increases observed in the Middle East, North America, and East Asia [9].

In the United States, the prevalence of NAFLD in adults was 24.13% in 2016 and is projected to rise to 33.5% by 2030, with an estimated 100.9 million cases of NAFLD by that year [10]. A modeling study predicts a 56% increase in the prevalence of NASH by 2030, accompanied by a twofold rise in associated mortality. The current overall prevalence of NAFLD in Asia stands at 27.37% [5].

The escalating prevalence of MAFLD is attributed, in part, to chronic hepatitis B (CHB) being the primary cause of chronic liver diseases in Asia. Although virological outcomes in patients with CHB and MAFLD are favorable, MAFLD has been independently associated with fibrosis progression and poorer prognoses in patients with CHB.

Mortality rates for NAFLD and NASH in 2022 were 0.77 per 1000 and 11.77 per 1000 person-years, and 15.44 per 1000 and 25.56 per 1000 person-years, respectively. Patients with NAFLD have a 34-69% higher likelihood of death within the next 15 years compared to the general population [11]. Several studies have compared the prevalence of MAFLD and NAFLD, generally finding that the prevalence of MAFLD closely mirrors that of NAFLD, albeit slightly higher for obvious reasons [7].

Overall, information on the prevalence of NAFLD/MAFLD and NASH varies widely in terms of definitions, characteristics of study populations, diagnostic methods used, and follow-up periods.

In modern gastroenterology, NAFLD is considered an etiologically heterogeneous disease, characterized by the excessive accumulation of neutral fat - triglycerides and free fatty acids - both inside hepatocytes and extracellularly. This process is accompanied by progressive aseptic inflammation and subsequent fibrosis, triggering a cascade of pathological processes. NAFLD is closely associated with demographic changes (aging population), unhealthy lifestyle (overeating, lack of exercise), and cardiovascular and metabolic diseases (type 2 diabetes, hypertension, dyslipidemia).

Currently, the pathogenesis of NAFLD is considered multifactorial, including processes such as insulin resistance (IR), lipotoxicity, inflammation, imbalance of cytokines and adipokines, activation of innate immunity and microbiota, exposure to environmental and genetic factors.

Clinical course and comorbidity in NAFLD.

In NAFLD, hepatic steatosis occurs without signs of inflammation, whereas in NASH, hepatic steatosis is associated with lobular inflammation and apoptosis, which can lead to liver fibrosis and cirrhosis [12].

NASH can progress and predispose to the development of hepatocellular carcinoma (HCC), which can develop in the absence of cirrhosis. By 2030, the incidence of HCC associated with NAFLD is projected to increase sharply in China, France, and the United States, with increases of 82%, 117%, and 122% compared with 2016, respectively [13].

Age-related characteristics are of great importance in predicting the course and outcome of NAFLD [2]. Several studies have revealed significant gender differences in the clinical manifestations of NAFLD. The prognosis for the development of NAFLD in premenopausal women is more favorable compared to postmenopausal women and men. It has been established that NAFLD more often affects men [14].

Over the past two decades, there has been an increasing trend in the incidence of MAFLD among Asians, who accumulate liver fat at a lower body mass index (BMI) than other races. In such patients, the disease is more severe with more pronounced inflammation and balloon degeneration [15].

NAFLD and MetS are often described as an interrelated process because they share a common pathophysiological mechanism, but each predicts and worsens the outcome of the other, significantly increasing the risk of cardiovascular events and cardiovascular disease (CVD) [16].

Recently, hepatic steatosis has been considered an independent risk factor for cardiovascular disease, but also for kidney disease and cancer [17].

It has been established that NAFLD is associated with the main markers of CVD, namely: endothelial dysfunction, increased impulse wave velocity, and increased calcification of the coronary arteries. At the same time, it should be noted that the issue of the connection between NAFLD/MAFLD and an increase in non-fatal cardiovascular events and death is still a matter of debate [18].

In 2016, the European Association for the Study of the Liver (EASL) published clinical practice guidelines for the management of patients with NAFLD in the setting of obesity, which is a major risk factor for the development and progression of NAFLD and insulin resistance [19].

At the first stage of diagnosis, it is necessary to differentiate NAFLD from alcoholic fatty liver disease (AFLD). When diagnosing NAFLD in non-obese patients, the recommendation of the American Gastroenterological Association (2022) should be taken into account, namely: to determine the presence of other causes of fatty liver, in particular: the presence of metabolic syndrome, HIV, lipodystrophy, lysosomal acid lipase deficiency, familial hypobetalipoproteinemia, and hepatic steatosis, caused by drugs such as methotrexate, amiodarone, tamoxifen, and steroids.

NAFLD/MAFLD and Liver Transplantation

There is no doubt that NAFLD/MAFLD and NASH, and in case of their progression, cirrhosis, and primary liver cancer require expensive treatment, including liver transplantation [9]. The number of patients with terminal or progressive liver disease associated with NAFLD who

require liver transplantation is growing, outpacing the need for transplantation in patients with hepatitis C [20].

Since NAFLD is the second most common pathology requiring liver transplantation and, according to forecasts, will become the leading one over the next decade, an accurate assessment of the possibility of developing steatohepatosis in such patients plays a decisive role in the prognosis of NAFLD and the success of therapy [21].

On the other hand, it is extremely important in this aspect to study potential living donors who donate a liver fragment during related transplantation for NAFLD. Most studies from leading transplant centers around the world have shown that donors with mild steatosis have an increased risk of NAFLD and that liver grafts from these donors may negatively impact liver transplant success [20].

Diagnostic Aspects of NAFLD

Histological examination is still considered the gold standard for diagnosing fatty liver [22]. Various approaches can be used to obtain a liver tissue sample. These include biopsy guided by ultrasonography (ultrasound) or computed tomography (CT).

An endoscopic approach using ultrasound (EUS) has been described [23]. In modern clinical practice, biopsy is a reliable method for differentiating NAFLD from NASH and detecting fibrosis. However, a biopsy is an invasive and painful procedure and requires six or more hours of bed rest.

In addition, its cost and risk of complications should be taken into account, as well as the uneven distribution of fibrosis in the liver, which makes it difficult to create a holistic picture of liver damage [24].

In addition, estimates made from biopsy results are subject to significant intraobserver and interobserver variability. There is also a fairly wide list of conditions when this procedure is contraindicated. Absolute contraindications to liver biopsy include: infectious and inflammatory diseases of the abdominal organs, suspicion of vascular lesions, hemostasis disorders, severe hypofibrinogenemia, sepsis, and ascites. Relative contraindications include cardiac or respiratory failure, respiratory tract infections, and anemia. In clinical practice, to identify NAFLD, track disease processes, and monitor the effectiveness of treatment, preference is often given to effective non-invasive diagnostic methods.

Thus, it has been established that liver fat content, determined using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), closely correlates with histological assessments of liver fat content in populations of patients with NAFLD, as well as with each other [25].

Diagnostic Value of Radioimaging Methods in the Assessment of NAFLD/MAFLD

Ultrasound (US) is the main screening method for the visual diagnosis of moderate to severe NAFL/NASH. Ultrasound diagnostic criteria for identifying NAFL/NASH include several key features such as echo attenuation, liver hyperechogenicity, increased echogenicity, and changes in vascular pattern. However, it should be noted that the presence of fibrosis may complicate the diagnosis as the texture of the liver echo becomes coarser.

The level of fatty infiltration also affects the effectiveness of ultrasound. The sensitivity of this method increases with increasing degree of fatty infiltration, but in obesity its diagnostic accuracy may decrease. With mild steatosis, the sensitivity of ultrasound may be low, and with steatosis less than 20% it may not be detected [26]. It is interesting to note that in the early stages of NAFL/NASH, new approaches are being used for more accurate diagnosis and prognosis,

including the calculated ratio of ultrasound characteristics of the liver and kidneys, as well as the frequency of attenuation of the ultrasound intensity of the liver. In general, ultrasound is an accessible and relatively inexpensive method for diagnosing NAFL/NASH, but its disadvantages include the inability to quantify, dependence on the level of fatty infiltration, and limited ability to distinguish the initial stages of steatosis from NASH, as well as the influence of hemochromatosis and methodological factors on the results of the study.

A review of the literature highlights the importance of elastography, particularly transient elastography (TE) and acoustic radiation force imaging (ARFI). The TRE method, which includes field of study requirements, may be limited in obesity and some other circumstances. Point shear wave elastography (pSWE) has also been used to diagnose liver fibrosis, demonstrating good sensitivity and specificity, especially for cirrhosis.

However, this method has its limitations, including the inability to quantify and the inability to determine tissue composition [27]. An alternative is two-dimensional shear wave elastography (2D-SWE), which has several advantages, including the ability to select the area of interest and create a color map. This method is also used to assess fibrosis stage and predict recurrence of hepatocellular carcinoma.

Despite their effectiveness, elastography methods are susceptible to false-positive results caused by various factors, such as elevated transaminase levels, extrahepatic cholestasis, and others. In addition, some studies offer criteria to identify unreliable liver stiffness measurements. Overall, elastography remains an important tool for diagnosing and assessing the degree of liver fibrosis, but its use requires consideration of various factors that affect the accuracy of the results.

A study of factors influencing the accuracy of liver stiffness measurements highlights older age, increased body mass index (BMI), and non-hepatitis B liver damage as independent but less powerful predictors of errors. Other researchers have also identified a number of factors that negatively affect the accuracy of such measurements, including a BMI greater than 30 kg/m2, female gender, age over 50 years, and others. However, the effect of steatosis on transient elastography (TRE) results remains controversial.

In cases with equivocal results, single-photon emission computed tomography (CT) of the liver is used, which can detect steatosis by several signs, including changes in liver radiation density and others. Despite this, the specificity of CT in assessing fatty liver disease may be poor and is more often recommended when liver neoplasms are suspected. Some studies also indicate the high ability of CT to detect steatosis without contrast enhancement, but the method has limitations, including radiation exposure and others.

Magnetic resonance imaging (MRI), which has high sensitivity and specificity, is often used to reliably diagnose NAFL/NASH [28]. However, estimates of MRI accuracy may vary depending on the machine model and patient characteristics. MRI has a number of advantages and disadvantages, such as high cost, scanning time, and dependence on the experience of the specialist.

MRI elastography is a promising method for assessing the degree of liver fibrosis, although its use is also limited by certain factors, such as the patient's excess body weight and the presence of metal implants.

It is recommended to detect NASH in patients with type 2 diabetes using MRI, using the assessment of fatty infiltration by calculating the proton density of fat, and determining the degree of liver fibrosis using the MRI elastography method [29]. This method has advantages such as the

ability to evaluate the entire liver and high yield in cirrhosis, although it also has the disadvantages of MRI.

There is inconsistency in comparing the effectiveness of MRI elastography and TrE, which requires further research. Some researchers have stated that acoustic radiofrequency indexing (ARFI) provides better results in liver assessment. A meta-analysis of 13 studies on liver fibrosis by S. Bota et al. (2013) did not reveal significant differences between pSWE/ARFI and TrE [30].

Developments in magnetic resonance imaging techniques include in-phase/out-of-phase (IP/OP) imaging, Dixon technique, and hydrogen MR spectroscopy (H1-MRS) [31]. The main advantage of these methods over ultrasound and computed tomography is the use of a calculated ratio of liver fat proton density to total liver proton density [32]. H1-MRS is capable of detecting even minor lipid accumulation in the liver parenchyma, while its sensitivity and specificity are comparable to biopsy (95-98% and 94-96%, respectively) [33]. These results have been confirmed by several studies [34].

Factors such as age, gender, BMI, and comorbidity do not have a significant impact on the diagnostic accuracy of MRI-PDFF in NAFLD [35]. MRI spectroscopy is a promising method for diagnosing NAFLP, allowing one to study metabolic processes in the liver [8].

Ultrahigh-precision MRS can detect changes in energy metabolism in patients with NASH but requires consideration of various interferences, especially in the early stages of steatosis [36]. Some clinics use bioelectrical impedance analysis for the initial diagnosis of NASH in patients with sarcopenic obesity, although this method is not yet widely used [37].

Despite some limitations, MRI-PDFF is considered the most accurate method for detecting fatty liver disease, while MRE can more accurately assess the extent of liver damage. The combination of MRI-PDFF and MRE allows risk stratification in patients with NAFLD. However, cost and wait times for results remain a challenge for many healthcare institutions [38].

Conclusion.

Timely radiological diagnosis of NAFLD and identification of potential risk factors for poor prognosis play a key role in preventing disease progression. This allows you to detect liver damage in the early stages, choose the appropriate treatment method, and prevent further deterioration of the patient’s condition.

Optimizing the combined use of quantitative imaging modalities, taking into account medical, technical, and social aspects, may provide a reliable and safe alternative to liver biopsy for the diagnosis and monitoring of NAFLD, thereby increasing the effectiveness of treatment.

With an integrated approach to the problem of NAFLD and a deeper understanding of the pathological processes associated with this disease, the collection of information is accelerated, the diagnostic process is improved, and individualized treatment and prevention methods are identified for different age and gender groups of patients with NAFLD.

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