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Contemporary Approaches To The Diagnosis Of Metabolically Associated Fatty Liver Disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD), now referred to as metabolically associated fatty liver disease (MAFLD), is one of the most common liver diseases worldwide, closely linked to the growing obesity epidemic. Despite the growing prevalence of this disease, there is a notable lack of pharmacological agents specifically designed to treat MAFLD. This gap in therapeutic options can be explained by the multifaceted nature of MAFLD, characterized by an incomplete understanding of its underlying mechanisms, a lack of accurate and accessible imaging tools, and the inadequacy of non-invasive biomarkers for effective diagnosis and monitoring.

In addition, this review highlights existing methods for diagnosing MAFLD and emphasizes the growing importance of non-coding RNAs as promising diagnostic biomarkers. Today, the urgent need for non-invasive biomarkers combined with accurate and cost-effective diagnostic tools cannot be overstated, as they play a key role in identifying early signs of MAFLD progression.

Keywords: Non-alcoholic fatty liver disease (NAFLD); metabolically associated fatty liver disease (MAFLD); non-alcoholic steatohepatitis (NASH); metabolically associated steatohepatitis (MASH); liver; biomarkers.

Introduction: Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of liver disease worldwide, and its prevalence is steadily increasing [1]. Today, it costs more than €35 billion per year in the four largest European countries and more than $100 billion in the United States alone [2]. Since the term “non-alcoholic fatty liver disease” (NAFLD) was introduced into the medical reference book, there has been discussion about changing the name to better reflect the disease process and expand the terminology beyond the superficial histopathological similarity to alcoholic liver disease [2,3]. In early 2020, an international group of experts conducted a consensus process to develop a more appropriate term for this disease. Using a two-stage Delphi consensus method, the term “metabolic dysfunction-associated fatty liver disease,” or MAFLD, was proposed [4].

MAFLD includes fatty liver disease, characterized by more than 5% of the liver's mass being fat, with the possibility of progression to non-alcoholic steatohepatitis (NASH), characterized by inflammation, cell damage, and increased severity [4]. In addition, its consequences extend beyond the liver and include cardiovascular complications and links to other metabolic disorders such as obesity and type 2 diabetes mellitus (T2DM) [5,6].

The prevalence of MAFLD has grown alongside the obesity epidemic and is estimated to be around 24% of the general population [6]. The prevalence of this disease is particularly high among people with obesity and T2DM: it affects up to 70% of overweight individuals and more than 90% of those classified as obese [7]. It is alarming that MAFLD can also occur in thin people, and ethnic differences further complicate its prevalence and manifestation [9,12].

Children and adolescents have not been spared from this epidemic, as evidenced by the increase in MAFLD incidence in this demographic group [13]. Despite its growing prevalence, MAFLD still lacks specific pharmacological therapy. This therapeutic gap can be explained by the multifaceted nature of MAFLD, characterized by limited understanding of its pathogenetic mechanisms and the lack of accurate non-invasive biomarkers for diagnosis and monitoring.

The purpose of this review is to clarify the complex mechanisms underlying the pathogenesis of MAFLD.

Pathogenesis of MAFLD

Mechanisms of MAFLD pathogenesis

The prevailing model explaining the development of inflammation and progression of MAFLD is the "multiple hit" model, which involves various stress factors [4,5]. Despite advances in understanding the development of hepatic steatosis, the pathogenesis of non-alcoholic steatohepatitis (NASH) remains incomplete. The progression of NASH is influenced by lipotoxicity, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, oxidative stress, endotoxins from the gut, and changes in the composition of the gut microbiota [12,15]. Lipid overload can provoke lipotoxicity, contributing to the development of inflammation, oxidative stress, and fibrosis. A high-calorie diet and sedentary behavior are key factors in the development of MAFLD. The intake of free fatty acids (FFAs) can disrupt the link between respiration and adenosine triphosphate (ATP) production, which leads to worsening MAFLD [8].

Fatty liver disease occurs due to nutrient overload and a sedentary lifestyle. Many factors contribute to the development of inflammation and MAFLD, which ultimately leads to fibrosis.

The pool of fatty acids (FAs) in the liver is formed from dietary fat, lipolysis of adipose tissue, or de novo lipogenesis (DNL) from carbohydrates or other dietary precursors. In the liver, FAs undergo esterification into triglycerides (TGs) and are assembled into very low-density lipoproteins (VLDL) for release into circulation, oxidation in mitochondria (β-oxidation), or storage in lipid droplets (LDs) (<5% of liver weight). During fasting, LDs undergo lipid hydrolysis (via lipolysis and lipophagy) to provide FFA for β-oxidation. In MAFLD, chronic nutrient overload and insulin resistance lead to an imbalance where the influx of FFA into the liver exceeds their utilization through VLDL secretion or β-oxidation. This lipotoxicity leads to impaired LP lipolysis and increased lipid accumulation in LCs, which accelerates the development of hepatic steatosis (>5% of liver weight).

Fatty liver disease causes endoplasmic reticulum (ER) stress, oxidative stress, and activation of Kupffer cells (KCs) to produce inflammatory cytokines that exacerbate inflammation. In addition, lipotoxicity causes mitochondrial dysfunction and disrupts the electron transport chain (ETC) function, leading to the formation of reactive oxygen species (ROS), which in turn exacerbates mitochondrial damage, perpetuating MAFLD.

Inflammatory cytokines and ROS activate hepatic stellate cells (HSCs) to produce excessive extracellular matrix, leading to progressive fibrosis.

Liver fibrosis, which is reversible in its early stages, is the most powerful predictor of mortality in people with metabolic-associated steatohepatitis (MAS). Therefore, accurate staging of fibrosis and differentiation of MAFLD from early fibrosis are key to identifying patients at risk of disease progression. A range of diagnostic methods are used to diagnose and classify MAFLD, including both traditional and innovative tools such as imaging and biomarkers, each with its own advantages and limitations.

Blood transaminases: Liver function tests, particularly blood tests for transaminases, are widely used, but their reliability in predicting MAFLD progression remains uncertain. Patients with MAFLD have abnormal and normal levels of liver enzymes, with a decrease in alanine aminotransferase (ALT) levels detected in progressive liver disease. Various biomarker panels are used to assess liver fat, including the hepatic steatosis index (HSI), fatty liver index (FLI), Steatotest, and Liver Fat Score (LFS).

Non-invasive scoring systems: Scoring systems such as Fibrosis-4 (FIB-4), MAFLD Fibrosis Score (NFS), Hepamet Fibrosis Score (HFS), and the automated platelet ratio index (APRI) help determine the risk of MAFLD progression but demonstrate modest sensitivity in diagnosing early stages of NASH and fibrosis. However, there is a noticeable dissonance between these scoring systems when applied to the same patient [15].

Liver biopsy: Despite its invasiveness, cost, sampling errors, and associated risks such as bleeding and, although rare, death, liver biopsy remains the gold standard for diagnosing MAFLD. Histologically, MAFLD manifests as hepatic steatosis, swelling, inflammation, with or without fibrosis [14,15]. Although liver biopsy can distinguish NASH from MAFLD, its drawbacks highlight the need for minimally invasive diagnostic alternatives.

In light of the preventive potential of early detection of MAFLD to prevent the development of fibrosis, efforts are continuing to develop minimally invasive imaging tools and biomarkers to assess MAFLD, the risk of progression, and validate treatment in clinical settings.

Imaging methods:

1. Ultrasound (US): Ultrasound is the primary imaging modality for suspected MAFLD, demonstrating the typical hyperechoic appearance of the liver. However, its effectiveness is limited to the detection of moderate or severe steatosis (>20%) and may be affected by severe fibrosis [14]. New approaches, such as computerized assessment of the liver-to-kidney ratio (H/R) and liver attenuation intensity, offer opportunities for early assessment of steatosis [15].

2. Magnetic resonance spectroscopy (MRS): MRS stands out as the most accurate non-invasive method for quantifying liver fat, based on the separation of the proton signal to differentiate between fat and water fractions. Magnetic resonance imaging that determines the proton density of the fat fraction (MRI-PDFF) is a proven tool for assessing liver fat content, with a relative reduction in liver fat content of 30% associated with an improvement in the histological condition of MAFLD. However, limitations include patient discomfort, cost, and limited availability.

3. Transient elastography (TE): TE using a Fibroscan device with an M sensor assesses liver fibrosis, while the controlled attenuation parameter (CAP) simultaneously assesses steatosis. The XL probe improves accuracy in obese individuals, but limitations remain, particularly in predicting significant liver fibrosis in severely obese individuals [12,13]. Fibrotouch liver elastography is becoming a cost-effective and simple alternative for assessing fibrosis in all patients, regardless of obesity status.

4. Magnetic resonance elastography (MRE): MRE assesses liver stiffness, offering an accurate assessment that is independent of BMI. However, its implementation is hampered by cost, availability, and time constraints on examination.

Early-stage MAFLD biomarker

An important milestone in the field of internal organ pathophysiology was the discovery of the mechanism of the canonical Wnt signaling pathway. This pathway, which relies on β-catenin, regulates adipogenesis in a complex manner and triggers cell apoptosis in various organs and tissues of the body [10,13]. In addition, its involvement in the genesis of insulin resistance has been emphasized [9,10].

The Wnt pathway is initiated by the Frizzled family of transmembrane proteins, as discovered by Vivian S.W. Lee et al. in 2012. Among these proteins, secreted Frizzled-related protein-4 (SFRP4) has become a key player, demonstrating an affinity for liver tissues and confirming its profound importance in the progression of non-alcoholic fatty liver disease (MAFLD) [11,12].

Despite these successes, the diagnostic potential of serum SFRP4 in MAFLD remains largely unexplored. Thus, a thorough investigation of the sensitivity, specificity, and practical utility of serum SFRP4 expression levels as an early-stage MAFLD biomarker is urgently needed and warrants further study.

This discovery not only sheds light on the complex interactions of molecular pathways in the body, but also opens up prospects for the development of diagnostic and therapeutic strategies for the treatment of MAFLD and related metabolic disorders.

CONCLUSIONS

Significant progress has been made in elucidating the pathophysiology of hepatic steatosis and non-alcoholic steatohepatitis (NASH). However, the transition from NASH to fibrosis, which is the most important factor determining mortality in patients with MAFLD, remains poorly understood. This knowledge gap highlights the need for further research aimed at uncovering the mechanisms that determine MAFLD progression.

Identifying accessible non-imaging tools and accurate biomarkers is crucial for improving MAFLD treatment and validating new therapies in clinical trials. Non-invasive and inexpensive methods for accurately determining the stage of MAFLD progression are urgently needed to improve patient care.

Despite recent advances, there is still an unmet need for reliable biomarkers and cost-effective non-invasive tools to accurately determine the stage of MAFLD progression. Addressing these gaps will facilitate early diagnosis, risk stratification, and treatment monitoring in patients with MAFLD.

The 2018 ASSLD practical guidelines state that weight loss reduces liver steatosis, achieved through a low-calorie diet, increased physical activity, or both. A combination of a low-calorie diet and moderate-intensity exercise is most likely to result in sustained weight loss over time. A 3-5% reduction in body weight improves steatosis, and a 7-10% reduction in body weight is necessary to improve conditions, including fibrosis [13].

Although inflammation plays an important role in disease progression, the strongest predictor of mortality in patients with MAFLD is liver fibrosis. Among patients who lost ~10% of their body weight, 90% showed improvement in MAFLD, and approximately ~45% showed regression of fibrosis. Lifestyle interventions that combine calorie restriction and exercise have a greater effect on reducing liver fat [14]. However, more than 50% of patients included in clinical trials were unable to achieve this level of weight loss. Therefore, despite the fact that lifestyle interventions have a positive effect on the course of MAFLD, it is difficult to achieve sustainable lifestyle changes.

Dietary interventions improve MAFLD progression with or without physical activity; however, the composition of the diet and eating patterns remain controversial [13,14,15]. The picture is somewhat clearer with regard to physical exercise, as most clinical and preclinical studies show that all types and intensities of physical exercise have a positive effect on MAFLD. Physical

exercise has been shown to reduce liver steatosis, liver enzyme levels, blood glucose and insulin levels, and improve the lipid profile, both with and without dietary interventions. Even without weight loss, regular physical exercise reduces liver lipid levels.

In conclusion, despite the progress made in understanding the pathophysiology of MAFLD, significant challenges remain in translating this knowledge into effective treatments. Continued research aimed at elucidating the mechanisms of MAFLD progression and developing new diagnostic strategies is essential to improve patient outcomes in the face of this growing epidemic.

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