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# ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF MASH: THE ROLE OF TARGETED THERAPIES AND ARTIFICIAL INTELLIGENCE

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***Abstract:*** *Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) currently represents one of the leading causes of chronic liver disease worldwide, with an estimated prevalence of 25% to 30% in the general population, a figure that rises significantly among individuals with obesity, type 2 diabetes or metabolic syndrome. The pathological spectrum ranges from simple hepatic steatosis to more severe forms such Metabolic Dysfunction-Associated Steatohepatitis (MASH), advanced fibrosis, cirrhosis and even hepatocellular carcinoma. Given its asymptomatic progression in early stages, early diagnosis and comprehensive management are essential to avoid serious complications. Currently, there is no approved drug treatment specifically for NASH. However, several therapeutic strategies are under development and investigation. These include drugs that target altered metabolic pathways such as lipogenesis, insulin resistance, inflammation and fibrosis. FXR (Farnesoid X Receptor) agonists, PPAR (Peroxisome Proliferator-Activated Receptors), GLP-1 (Glucagon-Like Peptide-1) and ACC (Acetyl-CoA Carboxylase) inhibitors are among the most promising agents. Artificial intelligence (AI) has begun to play a pivotal role in this context, facilitating early disease detection, risk stratification and progression prediction through advanced analysis of images, biomarkers and clinical data. Integrating personalized predictive models into clinical practice can revolutionize both diagnosis and therapeutic strategies for MASH, bringing us closer to truly effective precision medicine.*

***Key words:*** *Metabolic Dysfunction-Associated Steatohepatitis (MASH), Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), biomarkers, oxidative stress, artificial intelligence*

## 1. Introduction

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Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a common cause of chronic liver disease worldwide [1] with an estimated prevalence ranging from 25% to 30% in the general population and rising in patients with risk factors such as obesity, type 2 diabetes or metabolic syndrome [2]. MASLD is a spectrum of disease characterised by hepatic steatosis when no other causes of secondary hepatic fat accumulation (e.g. excessive alcohol consumption) can be identified [3, 4].

The disease is a major clinical problem as it is associated with cardiovascular comorbidities and has the potential to progress to more advanced stages of liver damage [5]. Histology describes a continuum of liver lesions starting with simple steatosis, progressing to non-alcoholic steatohepatitis characterised by the presence of lesions and hepatocytes with cytolysis. Over time and without intervention, the disease can progress to fibrosis, cirrhosis and hepatocellular carcinoma, resulting in liver morbidity and mortality [6].

Currently, a consensus defines MASLD as an umbrella term for a range of diseases in which steatosis is present in more than 5% of hepatocytes with metabolic risk factors (especially obesity and type 2 diabetes) [7].

In this scenario, artificial intelligence (AI) has begun to play a key role, offering new ways of understanding and tackling this disease. From algorithms that can detect hidden patterns in imaging studies or clinical data, to predictive models that anticipate the response to treatments, AI is emerging as a key ally in advancing towards a more precise, personalized and preventive hepatology. This article reviews the most current therapeutic strategies applied to MASLD, emphasizing the emerging value of artificial intelligence (AI) to transform its diagnosis and clinical management.

## 2. Oxidative Stress and Mitochondrial Dysfunction as Central Mechanisms in the Progression of MASLD

Oxidative stress results from the excessive intracellular accumulation of reactive free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [8]. While ROS and RNS are part of normal cellular function and the host defense system against invading bacteria, excessive amounts contribute to the onset and exacerbation of various pathologies, including neurological diseases and diabetes [9].

The global concept of “oxidative stress” is defined as “an imbalance between oxidants and antioxidants in favour of oxidants, leading to a disruption of redox signaling and control and/or molecular damage” [10]. The basic idea is that, in the open metabolic system, a steady-state redox balance is maintained at a given set point, which provides a basal redox tone, and that a deviation from the steady-state redox balance is considered a stress, initiating a stress response [11]. In the progression of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), oxidative stress and mitochondrial dysfunction act as central pathogenic mechanisms [12]. The accumulation of lipids in the liver (steatosis) causes overload in the mitochondria, which are responsible for energy metabolism and fatty acid oxidation. This lipid excess alters mitochondrial function, producing excessive reactive oxygen species (ROS) [13]. If not adequately removed by antioxidant systems, ROS causes oxidative

damage to lipids, proteins, and mitochondrial DNA, perpetuating mitochondrial dysfunction in a vicious cycle [14].

Ultrastructural mitochondrial lesions, alterations in mitochondrial dynamics, decreased activity of respiratory chain complexes and inability to adequately synthesize adenosine triphosphate (ATP) are observed in liver tissues of patients with alcohol and non-alcohol associated liver disease [15]. These mitochondrial dysfunctions, together with increased lipogenesis and decreased β-oxidation of fatty acids, lead to the accumulation of triglycerides in hepatocytes [16]. This accumulation, combined with elevated levels of reactive oxygen species (ROS), contributes to insulin resistance in patients with steatohepatitis. In addition, mitochondrial ROS mediate signalling of metabolic pathways; alterations in these pathways affect the development and progression of chronic liver disease [17].

### 2.1. Physiological activities of free radicals

Free radicals play essential roles in the body at low to moderate concentrations, such as the synthesis of cellular structures, immune regulation, and intracellular signalling [18]. Its deficiency, as in chronic granulomatous disease, is associated with severe infections, highlighting its protective role [19]. Nitric oxide is a key example, acting as a molecular messenger in vascular, neurological and immunological processes [20]. Reactive oxygen species (ROS) can lead to highly toxic compounds such as hydroxyl radical (-OH) or hypochlorous acid, which are responsible for cell damage [21]. In addition, the interaction between ROS and RNS (reactive nitrogen species), especially the formation of peroxynitrite, reflects the close relationship between redox systems, the dysregulation of which contributes to oxidative stress and the progression of chronic diseases such as MASLD [21].

### 2.2. Redox regulation of enzyme activity in lipid metabolism

In NAFLD, redox imbalance is a central mechanism that alters hepatic lipid metabolism [22]. The activation of de novo lipogenesis is induced by hyperglycemia and hyperinsulinemia, which increases saturated fatty acids, which stimulate ROS production by enzymes such as NOX3 and NOX4. At the same time, uptake and oxidation of fatty acids in the mitochondria generate an excess of reducing equivalents ($NADH/FADH_2$), saturating the respiratory chain and increasing oxidative stress. Peroxisomal and microsomal oxidation reinforces this effect [23]. This altered redox environment inhibits key enzymes of β-oxidation and compromises antioxidant defences, promoting lipid accumulation and cell damage [24]. In addition, lipid export via VLDL is reduced, and cholesterol aggravates oxidative stress through redox-sensitive mechanisms. All this perpetuates a pathological cycle that drives disease progression towards steatohepatitis and liver fibrosis [25].

### 2.3. Biomarkers in the context of redox imbalance

Identifying reliable biomarkers for metabolic dysfunction-associated steatotic liver disease (MASLD) remains a major challenge due to the dynamic and multifactorial nature of oxidative stress (OS) and antioxidant responses [26]. For

instance, the activity levels of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) can vary significantly depending on the disease stage and individual physiological conditions, thereby limiting their reliability for early diagnosis and disease monitoring. Furthermore, the lack of methodological standardization and the influence of external factors contribute to the variability of these biomarkers, reducing their clinical utility [27].

This instability, combined with the often-silent progression of MASLD, poses a significant risk to patient safety. The absence of symptoms and reliable markers may delay diagnosis and the initiation of appropriate treatment, increasing the risk of progression to more severe liver damage [28]. Therefore, developing therapeutic strategies targeting oxidative stress (OS), alongside identifying stable and specific biomarkers, is crucial for improving clinical management.

Several biomarkers have emerged as key indicators of oxidative damage to cellular components. Among them, 8-oxo-2'-deoxyguanosine (8-oxo-dG) reflects oxidative DNA damage, while F2-isoprostanes are considered sensitive and specific markers of lipid peroxidation. Protein carbonyls are widely used to assess protein oxidation, and malondialdehyde (MDA), often measured using the thiobarbituric acid reactive substances (TBARS) assay, provides additional—though less specific—evidence of lipid oxidative stress. In parallel, enzymatic biomarkers such as SOD (superoxide dismutase), CAT (catalase), and glutathione peroxidase (GPx) offer insights into the tissue's antioxidant defense capacity [29].

Moreover, in both clinical and experimental settings, direct quantification of reactive oxygen species (ROS) in immune cells through flow cytometry, as well as assessments of total antioxidant capacity (TAC) in biological fluids, contribute to a more comprehensive understanding of redox status [30]. However, the lack of consensus on measurement protocols still limits translating these markers into routine clinical practice. Thus, combining multiple, well-validated biomarkers is recommended to enhance the precision and clinical relevance of redox status evaluation in liver diseases such as MASLD [31].

## 3. Current Therapeutic Strategies

Currently, there is no approved drug treatment specifically for metabolic dysfunction-associated steatotic liver disease (MASLD) or its progressive form, metabolic dysfunction-associated steatohepatitis (MASH) [32]. Therefore, therapeutic strategies focus mainly on lifestyle modification, with weight loss being the most effective intervention [33]. A 7-10% reduction in body weight has been shown to reverse hepatic steatosis, decrease inflammation and, in some cases, improve fibrosis. In addition, dietary interventions such as the Mediterranean diet and regular physical exercise significantly reduce hepatic fat content [34]. In addition, lifestyle changes allow simultaneous action on other comorbidities such as obesity, metabolic syndrome and type 2 diabetes, which frequently coexist with MASLD [35]. In this sense, treatment is directed at the liver as a target organ and comprehensively impacts the patient's state of health [36]. This ability to influence multiple pathological mechanisms synergistically makes lifestyle modifications a

multidimensional, personalized and sustainable therapeutic strategy, accompanied by health education and appropriate clinical follow-up [37].

### 3.1. Pharmacological treatments

In the absence of approved treatments specifically for metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), the development of targeted pharmacological strategies has become a priority area of research [38]. Therapeutic approaches seek to intervene in the main pathogenic mechanisms driving disease progression: insulin resistance, lipotoxicity, persistent inflammation and liver fibrosis [39].

Among the more advanced agents are farnesoid X receptor (FXR) agonists, such as obeticholic acid, which modulate bile acid metabolism and have been shown to improve liver histology [40]. Furthermore, PPAR receptor agonists (α, γ and δ) offer benefits by stimulating fatty acid oxidation, reducing lipogenesis and improving insulin sensitivity, and are especially useful in patients with metabolic comorbidities [41]. In parallel, GLP-1 receptor agonists, such as liraglutide and semaglutide, promote hepatic fat loss, improve glycemic control, and promote body weight reduction [42].

Another promising line focuses on inhibiting de novo lipogenesis (DNL), a process abnormally activated in MASLD. Acetyl-CoA carboxylase (ACC) inhibitors, such as firsocostat (GS-0976), have shown efficacy in reducing hepatic triglyceride synthesis while promoting mitochondrial fatty acid oxidation [43]. In addition to these agents, therapies targeting the gut-liver axis, antioxidants such as vitamin E, and even anti-diabetic drugs such as sodium-glucose cotransporter type 2 (SGLT2) inhibitors, which have been shown to reduce steatosis and improve metabolic profile, are being investigated [44,45].

### 3.2. Addressing the gut microbiome

The gut microbiome has emerged as a key player in the pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD), due to its influence on energy metabolism, systemic inflammation and intestinal barrier integrity [46]. Alterations in microbial composition (dysbiosis), the production of metabolites such as short-chain fatty acids or endotoxins, and bacterial translocation are mechanisms involved in the progression of steatosis to more severe forms such as MASH and fibrosis [47]. For this reason, therapeutic interventions that modulate the microbiome, such as probiotics, prebiotics, synbiotics, selective antibiotics or even fecal microbiota transplantation (FMT), have been the subject of increasing interest [48]. However, these strategies have significant limitations. First, the clinical evidence is still limited, with small, heterogeneous trials and little standardization in terms of strains used, dosage and duration of treatment [49]. Secondly, therapeutic response is highly variable between individuals, which poses challenges in personalising the approach and selecting "responder" microbiota profiles [50]. Furthermore, there is a lack of validated biomarkers to accurately predict or monitor the clinical efficacy of interventions targeting the gut-liver axis [51]. Finally, long-term follow-up of these treatments is insufficient in terms of the sustainability of the changes in the microbiota and their actual impact on the

histological progression of liver disease [52]. Therefore, although the gut microbiome approach represents a promising and physiologically sound strategy, its clinical application requires further robust evidence, personalized approaches and efficient monitoring tools before it can be systematically incorporated into the therapeutic management of MASLD.

### 3.3. Non-pharmacological treatment strategies. Dietary and lifestyle modifications

In non-pharmacological treatment, dietary interventions have taken centre stage as non-pharmacological strategies aimed at reversing or halting disease progression. Among the most prominent are calorie restriction, nutritional ketosis, reduced free sugars and carbohydrate limitation.

Calorie restriction (CR) is the most widely used intervention in patients with MASLD. Its implementation is associated with significant metabolic improvements, including reduced liver fat, improved insulin sensitivity and total body weight loss [53]. Other strategies, such as ketosis induction, decreased consumption of simple sugars and carbohydrate reduction have shown similar protective effects on liver function [54].

A recent meta-analysis showed that the Western dietary pattern - characterised by high consumption of ultra-processed products, saturated fats and added sugars - increases the risk of developing MASLD by 56%. In contrast, the Mediterranean diet (MD) can reduce this risk by 23%. [55]. This diet is based on a high consumption of plant-based foods, a lipid profile rich in monounsaturated fatty acids (MUFA) and saturated fatty acids (SFA) in smaller proportions, where total fat represents between 30% and 40% of the daily caloric intake. It includes fruits, vegetables, legumes, fish, whole grains and olive oil as the primary source of healthy lipids [56].

#### 3.3.3. Clinical recommendations and metabolic benefits

Clinical guidelines developed by EASL-EASD-EASO recommend DM as a therapeutic strategy for treating MASLD. It has been shown to improve the metabolic profile by reducing insulin resistance (IR), lowering plasma lipids, reversing hepatic steatosis and reducing cardiovascular risk. In this regard, DM is considered to be an effective and safe option for patients with metabolic syndrome and MASLD [57].

In addition to its effects on liver fat, DM contributes to weight loss and a decrease in visceral obesity and may reduce the risk of progression to liver cirrhosis [58]. In adults, it effectively reduces IR and improves the overall clinical condition of patients with MASLD. A meta-analysis by Takumi Kawaguchi confirmed that DM reduces fat accumulation in the liver and improves IR in people with non-alcoholic fatty liver disease [59].

Physical activity is a key strategy in treating metabolic dysfunction-associated steatotic liver disease (MASLD), with benefits that can be seen even without significant weight loss. Moderate to vigorous aerobic exercise and resistance training has been shown to reduce liver fat and improve insulin sensitivity [53, 60]. Combining both types of exercise enhances these effects, and high-intensity interval training (HIIT) offers an effective alternative for people with limited time. At least 150 minutes of physical activity

per week, tailored to the individual patient and, if possible, combined with dietary interventions such as the Mediterranean diet, is recommended [61].

## 4. Patient Safety Considerations in MASLD

In the approach to non-alcoholic fatty liver disease (NAFLD), ensuring patient safety has become a priority, mainly due to the silent and progressive nature of this condition, as well as the absence of specific approved drug treatments [62]. Many patients can progress to more severe stages, such metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis or even cirrhosis, without presenting specific symptoms in the early stages. This silent progression, if not detected in time, represents a serious challenge for patient protection [63].

One of the main obstacles is the lack of consistent and reliable biomarkers, which hinders both early diagnosis and effective treatment evaluation. Without stable clinical tools to monitor the disease, making timely decisions becomes complex and, in some cases, risky [64]. Furthermore, while some treatments in development, such as acetyl-CoA carboxylase (ACC) inhibitors, show promising results, they are not without risks, such as increased blood triglycerides, requiring an individualized therapeutic approach and rigorous monitoring [65].

Late management of metabolic dysfunction-associated steatotic liver disease (MASLD) carries significant clinical risks, especially due to the insidious nature of its progression and the absence of specific symptoms in early stages. Against this background, implementing active monitoring strategies, supported by accessible diagnostic tools and risk-based clinical decision-making, becomes critical [66]. One of the key recommendations is early stratification of patients according to their clinical and metabolic profile, with special attention to high-risk groups such as people with type 2 diabetes, visceral obesity, hypertension, dyslipidemia or metabolic syndrome [67]. These patients are not only more likely to develop aggressive forms of MASLD, but also have a poorer prognosis if the disease is not detected and treated early [68]. Therefore, a proactive approach combining regular surveillance by noninvasive tests (such as elastography or serum scoring) with personalized therapeutic strategies is essential. This can significantly improve clinical outcomes and reduce long-term liver complications [67,68].

## 5. Artificial Intelligence and MASLD: State of the Art

### 5.1. Integrating AI in Therapeutic Strategies: Enhancing Patient Safety

The incorporation of artificial intelligence (AI)-based tools is significantly transforming the approach to chronic diseases such as non-alcoholic fatty liver disease (NAFLD). ]69]. Beyond diagnosis, AI allows accurate prediction of individual response to pharmacological treatments or lifestyle changes, and facilitates ongoing clinical follow-up [70]. These advances are achieved through machine learning models trained on large clinical databases, capable of identifying complex patterns that traditional methods would not detect [71]. This predictive capacity makes it possible to avoid ineffective therapies, reduce adverse effects and personalise therapeutic decisions based on each patient's metabolic, clinical and

genetic characteristics [72].

A concrete example of this application is found in the work of Gawrieh et al. who developed an algorithm capable of digitally analysing liver biopsies to identify signs of steatohepatitis, fibrosis and cell damage with high accuracy, thus overcoming the subjectivity of conventional histological assessment [73]. Similarly, other AI models have shown utility in predicting which patients will respond best to treatments such as obeticholic acid, optimising their indication and reducing unnecessary exposure to side effects [74].

On the other hand, wearable devices connected to AI algorithms offer a new dimension in clinical monitoring [75]. These devices allow continuous collection of key physiological data, such as glucose levels, heart rate or body weight, and enable real-time therapeutic adjustments [76]. An illustrative case is the study by Zeevi et al. (2015), which demonstrated how continuous glucose sensors can detect individualised metabolic responses, facilitating the personalisation of nutritional recommendations [77].

Finally, AI-driven automated clinical support systems can provide immediate alerts to worrisome changes in clinical parameters, such as increased liver enzymes or inflammatory markers, encouraging early medical intervention and decreasing the risk of complications [78].

### 5.2. Challenges and ethical considerations

Despite AI's transformative potential, its application in hepatology faces significant challenges. One of the main problems is the inherent bias in the data used to train the models. These sets often do not adequately represent the diversity of the population, which can lead to inaccurate or unfair decisions. Another challenge is the lack of external validation across multiple clinical centers, which limits the overall reliability and applicability of the models [79].

On the other hand, using sensitive health data raises significant concerns about privacy and patient safety. If algorithms are not adequately regulated or if data protection failures occur, there is a risk of serious ethical violations. To avoid this, responsible implementation is required, including algorithmic traceability, digital informed consent, and robust regulatory frameworks that ensure transparency, fairness, and accountability [80].

### 5.3. Future projections: AI and precision liver medicine

Looking to the future, artificial intelligence has the potential to establish itself as a pillar of precision hepatology. This involves using dynamic predictive models that combine multi-omics data (genomics, metabolomics, transcriptomics), clinical and imaging information, and real-time patient behaviors [81]. To conclude, it is crucial to promote rigorous clinical research that validates the efficacy of AI in medical practice, not only from a technical perspective but also in terms of real clinical outcomes and patient quality of life.

The physician's role in this new environment does not disappear but is transformed: healthcare professionals will need to interpret algorithmic findings, contextualize them clinically, and communicate them to the patient in an understandable and ethical way. This interdisciplinary collaboration between clinicians, data experts, and researchers will be essential to building a more efficient, equitable, and person-centred

healthcare system [82].

## 6. Conclusions

The management of MASLD remains a major clinical challenge due to the absence of specifically approved drug therapies. Current therapeutic strategies focus on multifactorial interventions, with lifestyle changes being the mainstay to reduce disease progression. In parallel, pharmacological research has advanced the development of agents that act on multiple pathogenic pathways, such as insulin resistance, lipotoxicity, chronic inflammation and fibrosis. In addition, the incorporation of artificial intelligence (AI) represents a promising innovation for both early diagnosis and personalization of treatments, improving accuracy and efficiency in clinical decision-making. However, ethical, technical, and regulatory challenges remain that require attention to ensure the safe and equitable implementation of these technologies. Overall, there is a need for a comprehensive, personalized and evidence-based approach to the effective treatment of this chronic and silent disease.

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