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REVIEW

Review and expert opinion on MAFLD, oxidative stress and multifunctional management

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Abstract

Metabolic-associated fatty-liver disease (MAFLD), previously known as non-alcoholic fatty liver disease, is the most widespread and emerging chronic liver disease worldwide, with increasing prevalence rates also in the Asia-Pacific region. The disease has a high socio-economic burden as it negatively impacts the finances and quality of life of individuals affected and has a major burden on healthcare systems. The most important pathological event in MAFLD aetiopathogenesis is oxidative stress, which leads to functional and structural abnormalities in the liver as well as being involved in the development of other concomitant cardiometabolic diseases. MAFLD is a rather complex multisystemic clinical condition involving liver damage and a wide spectrum of extrahepatic manifestations such as obesity, type 2 diabetes, metabolic syndrome and cardiovascular diseases. This complexity requires the cooperation of multiple experts to identify MAFLD at an early stage, treat associated comorbidities, and promptly refer the patient to the hepatologist when needed. This review summarizes the current knowledge about MAFLD and reports the opinion of a group of experts on the increasing prevalence and burden of the disease in the southeast Asia region, the current journey of patients with MAFLD in developing countries, the role of oxidative stress and antioxidant treatment, and the importance of a multidisciplinary approach for early diagnosis and disease management.

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Introduction

This review summarizes the most recent updates in the epidemiology, pathogenesis, diagnosis and treatment of metabolic-associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (NAFLD). Specifically, it focuses on the role of oxidative stress in the pathogenesis and management of MAFLD and summarizes the opinion of key specialists in fatty liver disease, including internists, hepatologists, gastroenterologists, endocrinologists, cardiologists and diabetologists, who participated in an advisory board meeting to discuss the new concept of MAFLD, the current journey of patients with MAFLD in developing

countries, and the role of oxidative stress and antioxidants in the multidisciplinary management of NAFLD and MAFLD.

Review

Fatty-liver disease

Epidemiology of MAFLD in the Southeast Asia region

Fatty-liver disease is a metabolic disorder characterized by different levels of hepatocyte steatosis and liver fat accumulation; when the condition is independent of alcohol consumption or other known causes of fat accumulation, it is called MAFLD.[1]

MAFLD is the most widespread and emerging chronic liver disease worldwide, with approximately 38% of the global population affected and prevalence increasing at an alarming rate in all regions, paralleled by an increase in obesity and type 2 diabetes (T2D).[2] Different meta-analyses have registered a progressive increase in MAFLD prevalence in European regions, with estimates ranging from 23.7% in 2016 (ref.[3]) up to 30.9% in 2019;[4] similarly, a steady increase in NAFLD prevalence has been detected over the last three decades in the USA, reaching up to 54% in 2005–2016.[5]

This review focuses specifically on the Asia-Pacific region, where, over the past three decades, economic growth, improvement in living standards, and changes in lifestyle and dietary habits have led to an exponential growth in MAFLD prevalence, now making it a public health issue.[5,6] According to a systematic review and meta-analysis conducted on more than 13 million individuals, the prevalence of NAFLD in Asia increased from 25.3% between 1999 and 2005 to 33.9% between 2012 and 2017 (ref.[6]) and is projected to grow further in the future.

Although the overall picture is of a global increase, the prevalence may vary significantly from one region to another based on the genetic background of the population, nutrition, physical activity, lifestyle and tendency to sedentary behaviour.[7] In fact, whilst the prevalence of MAFLD is quite high in some Far East countries, such as Japan (23–26%), Korea (27.3%) or Bangladesh (33.86%), it is remarkably low in other areas, such as rural India (9%) or Taiwan (11.4%).[8] Considerable differences in MAFLD prevalence and growth are also detected within single countries such as in different regions in China. Estimates vary in sub-populations, such as elderly individuals (50.1%), those with obesity (60.5%) or specific workers that tend to have a very inactive lifestyle (e.g. taxi drivers, 66.4%).[8] Interestingly, Asians tend to develop NAFLD and other metabolic complications at a lower body mass index, making it the region with the highest prevalence of non-obesity-related MAFLD.[2]

Pathogenesis of MAFLD and the role of oxidative stress

The most important pathological event in MAFLD aetiopathogenesis is oxidative stress. Oxidative stress refers to an imbalance between the production and accumulation of reactive oxygen species (ROS) and the ability of antioxidant defences to detoxify the reactive products. This imbalance is seen in many diseases, especially those with low-grade chronic inflammation, and has been found in patients with different cardiometabolic diseases, such as obesity, metabolic syndrome, T2D, dyslipidaemia, insulin resistance and atherosclerosis.[9]

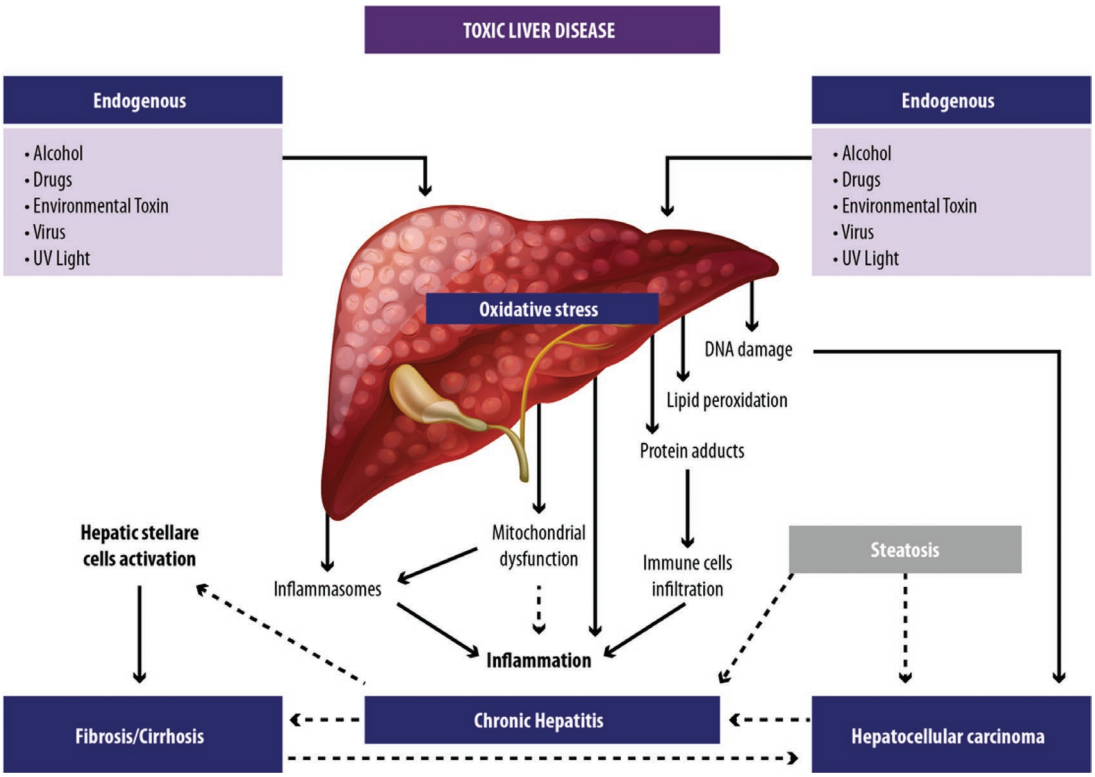
Causes of oxidative stress include smoking, obesity, unhealthy diet and genetic predisposition.[9] Once present, the imbalance leads to the overproduction of ROS, which can damage cellular proteins, lipids and nucleic acids, causing cellular and tissue injury. Additionally, oxidative stress can interfere with the normal function of hepatocytes, triggering the inflammatory and fibrogenic pathways contributing to MAFLD progression. Kupffer cells, activated by exposure to ROS, are the main effectors responsible for the generation of ROS. They contribute to the inflammatory response by generating chemokines, cytokines, and adhesion molecules and they mediate injury and fibrogenesis, affecting both hepatocytes and hepatic stellate cells. Damaged hepatocytes not only lose their normal function but also amplify the paracrine inflammatory and fibrogenesis responses, whilst the transformation of hepatic stellate cells leads to an alteration in the extracellular matrix component that contributes to the progression of liver fibrosis and cirrhosis (Figure 1).[10,11] Overall, the oxidative imbalance leads to functional and structural abnormalities in the liver that both initiate liver damage and represent the hallmark between simple steatosis and non-alcoholic steatohepatitis (NASH).

Interestingly, oxidative imbalance seems to appear quite early in patients with MAFLD. Pastori et al. reported that patients with simple steatosis have reduced serum levels of vitamin E (a biomarker of (anti)oxidative status) in relation to those observed in NASH and are lower than those of in individuals with non-MAFLD, suggesting a potential role for antioxidant therapy in the early stages of the disease.[12]

Definitions and spectrum of MAFLD

MAFLD is an overarching term that encompasses a broad range of clinicopathological findings.[13] The histological presentations of the disease range from non-alcoholic fatty-liver, which is characterized by steatosis, to

Figure 1. General mechanism of oxidative stress induced by various factors on liver disease.



Adapted from ref.[10]

NASH, where fat accumulation in the liver is accompanied by liver cell damage (ballooning) and inflammation, with or without fibrosis. NASH can further evolve into severe forms of liver injuries, leading to fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[13] MAFLD is also associated with an increased risk for cardiovascular disease, representing the first cause of death in this clinical setting.[14]

The diagnosis of MAFLD requires evidence of steatosis in >5% of hepatocytes (according to histological examination) and the exclusion of known causes (i.e. alcohol consumption, use of steatogenic medication or hereditary disorders) for secondary hepatic fat accumulation.[15] To differentiate between MAFLD and NASH, a liver biopsy is the gold standard to assess the presence of steatohepatitis (steatosis with lobular and portal inflammation and hepatocellular ballooning). However, this invasive procedure should be performed only in individuals with suspected advanced fibrosis or doubts about the aetiology of the liver disease.[15,16] Non-invasive tests, such as abdominal ultrasonography, transient elastography and MRI, may also be useful to detect and quantify the amount of hepatic steatosis and fibrosis to diagnose MAFLD.[17] Moreover, the fibrosis-4 (FIB-4) score and the NAFLD fibrosis score are two major simple and well-validated scores used to non-invasively rule out or rule in significant liver fibrosis (F2–F3).[18]

Socio-economic burden of MAFLD

MAFLD represents a large and growing healthcare problem worldwide, especially due to the increase in obesity and diabetes worldwide.[19–21] The rise of MAFLD is leading to a remarkable increase in cirrhosis, HCC, hepatic decompensation and liver-related mortality associated with MAFLD and its extrahepatic manifestations, mainly cardiovascular disease.[19]

Growing evidence indicates that the disease negatively impacts the quality of life (QoL) of patients, with reduced physical and mental well-being and increased fatigue scores.[22–24] Additionally, comorbidities contribute to the disease burden, especially in patients with obesity and/or T2D, which further reduces their QoL.[25]

The healthcare costs of MAFLD are also quite impactful and are expected to grow in the future.[21] Costs include direct costs (medical and non-medical) and indirect costs, which refer to premature mortality, disability and reduced work productivity resulting from NAFLD and related complications. Direct costs mostly arise from hospitalization and testing; they are es-

pecially high at the time of MAFLD diagnosis (due to increased healthcare utilization in terms of imaging, hospitalizations, liver biopsies, laboratory tests and outpatient office visits) as well as in the advanced stages of the disease (likely due to the evaluation and management of complications related to end-stage liver disease).[21]

Estimates on healthcare costs associated with MAFLD are available primarily for Europe, the USA and Hong Kong, whereas data from other regions are lacking. These estimates are quite variable depending on the assumptions made in the model and how the impact of metabolic comorbidities is incorporated into the analysis. In 2016, the annual cost for NASH-attributable healthcare was estimated at approximately €35 billion (from €354 to €1,163 per patient) in Europe and US$103 billion (US$1,613 per patient) in the USA.[26] Data from 2018 reported total NASH-related economic costs in Europe ranging between €8,548 and 19,546 million, including €619–1,292 million for healthcare-related costs and €41,536–90,379 million for indirect costs.[27] Interestingly, Younossi et al. estimated that, by 2039, the NASH-attributable healthcare cost per patient will increase in the USA from US$3636 to US$6968, most likely driven by the growing number of patients with NASH and advanced fibrosis.[28] Regarding the Asia-Pacific region, only one modelling study conducted in Hong Kong is available and suggests a total cost of NASH of US$1.32 billion with an average per-person cost of US$257.[29]

Given the economic impact of the disease, awareness, early recognition and early intervention are key to improving clinical outcomes and reducing the socio-economic and healthcare burden of MAFLD.

Expert opinion 1

Experts agree that oxidative stress is central to the development of MAFLD, and there is a strong association between fatty liver disease and metabolic conditions such as obesity, insulin resistance, T2D and dyslipidaemia. Experts also recognize that the increasing prevalence of fatty liver disease, both worldwide and in Southeast Asian countries, may represent a growing health problem in both developed and developing countries. According to experts, the increased prevalence of MAFLD will not only increase the financial burden of families but also have a major impact on the healthcare systems of the countries involved.

Evolving concept of MAFLD

Need for a new definition

The term NAFLD was initially coined in 1980 but has progressively shown limitations that have prompted clinicians to question its validity. One of the main issues is that the definition of 'NAFLD' is based on exclusion rather than inclusion, forcing clinicians to exclude other well-known causes of steatosis before confirming the diagnosis. This is challenging as alcohol consumption and known causes of fat accumulation may coexist with other independent metabolic risk factors, making it difficult to identify only one leading cause of the disease.[30,31] Forcing a highly heterogeneous population of patients into a restrictive category may affect clinical decision-making, with the risk of an incomplete and ineffective treatment plan. In addition, the term 'alcoholic' was considered too stigmatizing for patients,[30] and physicians recognized that determining the level of alcohol consumption could be difficult and arbitrary.[31]

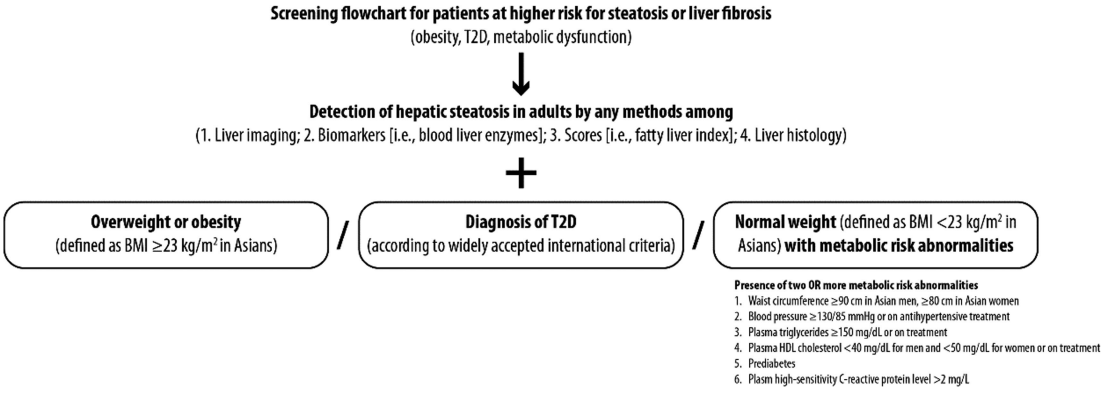
To tackle this issue, an international panel of experts has sought a consensus on a new definition that could better summarize the current understanding of disease pathogenesis whilst providing a clear and simple tool to categorize patients. The new terminology is 'metabolic-associated fatty-liver disease' or MAFLD. Diagnosis is based on the presence of liver steatosis, as detected by serum biomarker scores, imaging methods or histology, together with at least one of three criteria that include overweight or obesity, T2D or evidence of at least two signs of metabolic dysregulation (e.g. increased waist circumference, abnormal lipid or glycaemic profile) (Figure 2).[31] In addition, experts propose surpassing the dichotomous categorization of 'NASH' *versus* 'non-NASH' disease, opting for a more detailed assessment and stratification of disease severity.[31]

NAFLD *versus* MAFLD: advantages of the new definition

The main benefit of the new term 'MAFLD' is the shift towards a 'positive' categorization that recognizes metabolic dysfunction as the key pathogenetic driver of the disease. The exclusion of significant alcohol intake or other chronic liver diseases as a prerequisite for the diagnosis allows physicians to identify patients with dual aetiology and include alcohol consumption or other co-existing liver diseases as factors in MAFLD severity and progression.[8,31,32] The new definition may also facilitate understanding of the disease and patient–physician communication, shifting patient's focus from the stigma of alcohol consumption towards the important role of metabolic factors.[32]

The new term will help unify the terminology (e.g. for ICD coding), facilitate the identification of a more homogeneous group of patients, and possibly set the basis for a further stratification effort for individuals with MAFLD.[8] For example, Lin et al. have recently shown that the term MAFLD may help identify patients with a high risk of disease progression more practically and accurately compared with NAFLD.[33] Ultimately, the new term could help

Figure 2. Management algorithm for patients with MAFLD.



LOW RISK	INTERMEDIATE RISK	HIGH RISK
Can be managed by non-liver specialist (primary care physician, endocrinologist, internist)	Multidisciplinary management, including liver specialist	Multidisciplinary management, including liver specialist
Periodic non-invasive assessment for fibrosis every 2–3 years	Yearly assessment for fibrosis progression	Yearly assessment for cirrhosis and cardiovascular disease
The risk factors, such as diabetes, obesity, hypertension and dyslipidemia, should be managed properly	The risk factors, such as diabetes, obesity, hypertension and dyslipidemia, should be managed properly	The risk factors, such as diabetes, obesity, hypertension and dyslipidemia should be managed properly
Initiate treatment (lifestyle change)	Initiate treatment (lifestyle change)	Treat to prevent liver cirrhosis and cardiovascular complications

MAFLD, metabolic-associated fatty liver disease; T2D, type 2 diabetes.

improve clinical care for patients with MAFLD and move the clinical and scientific field of liver research forward.[8]

More recently, a multi-society consensus statement proposed another improvement in the nomenclature and the term metabolic dysfunction-associated steatotic liver disease (MASLD) replaced the term NAFLD. The new definition aimed at reducing stigma around the disease and improving awareness and patient identification. Of note, it was agreed that patients with steatosis and any one of the cardiometabolic criteria (overweight or obesity, insulin resistance or T2D or treatment for T2D, hypertension or treatment for hypertension, high triglyceride levels, low-HDL-cholesterol levels, or treatment for dyslipidaemia) would be considered to have MASLD, reinforcing the strong link between this liver disease and cardiometabolic abnormalities. Both MAFLD and MASLD terms are introduced to replace the existing term NAFLD. Overall, there is a substantial overlapping between the metabolic criteria used for the definition of MAFLD and MASLD; however, the two terms may identify slightly different groups of patients, which may not be clinically significant.[34]

MAFLD beyond hepatology: a multidisciplinary approach

Besides liver damage, individuals with MAFLD frequently present multiple extrahepatic manifestations, including cardiovascular disease, T2D, chronic kidney disease, hypothyroidism, polycystic ovarian syndrome and psoriasis. Cardiovascular diseases and malignancies, in particular, are the main causes of mortality in individuals with MAFLD and should therefore be promptly screened and treated to avoid progression to end-organ damage.[35,36]

Overall, MAFLD can be regarded not as a single-organ disease but as the hepatic component of the metabolic syndrome. Metabolic syndrome is a cluster of disorders of metabolism, including visceral obesity, T2D, dyslipidaemia and hypertension.

Therefore, the multi-dimensional complexity of MAFLD management requires careful screening for possible comorbidities and complications and a multidisciplinary approach to improve liver injury whilst treating the associated systemic metabolic dysfunction and avoiding further organ damage.[8,37]

Expert opinion 2

According to experts, the new terminology of MAFLD accurately reflects the pathogenesis of the disease. It better explains the disease itself, which is a multisystemic clinical condition with a wide spectrum of extrahepatic manifestations. Therefore, clinicians should be aware of these associations to ensure early screening and use a multidisciplinary approach involving general practitioners and non-hepatologist specialists. These clinicians play a pivotal role in identifying MAFLD at an early stage,

treating associated comorbidities, and prompting referral to the hepatologist when needed.

MAFLD journey, disease management and role of oxidative stress

The journey of patients with MAFLD

The presence of obesity, T2D or metabolic risk factors is the main factor that could direct a patient to screening for MAFLD (Figure 2). The first step of disease assessment includes collecting medical history and physical examination to determine an individual's dietary intake, lifestyle, BMI, abdominal girth and body shape. Non-invasive investigations are also performed, such as blood tests and abdominal ultrasound to detect hepatic steatosis, and clinical and laboratory assessments, including simple fibrosis scores, to determine the degree of fibrosis. Determining the risk of advanced fibrosis by measuring hepatic fibrosis biomarkers or liver stiffness is crucial to deciding a patient's path. Patients are identified as being at low, intermediate or high risk for advanced fibrosis for each score according to the following cut-offs: AST to platelet ratio index (0.5 and 1.5), FIB-4 (1.30 and 2.67), FIB-8 (0.88 and 1.77) and NAFLD fibrosis score (<–1.455 and >0.67611).[8,38] Once the risk level is established, guidelines suggest that patients at low risk are treated by general practitioners or non-hepatologists with follow-up visits every 2–3 years and non-invasive testing. Patients at intermediate or high risk should be referred to a hepatologist for further evaluation. They may need to perform a liver biopsy to better assess the fibrosis stage, disease activity and possible presence of cirrhosis.[8,16,39]

Therapeutic options include lifestyle interventions (healthy diet and physical activity) to reduce the risk of metabolic and cardiovascular events and improve liver health.[8] In terms of medication, no treatment is specifically approved for MAFLD; however, patients may benefit from antioxidant therapy, antidiabetic medications or lipid-lowering drugs.[8,16,39]

Common problems in diagnosis and treatment of MAFLD

Experts agreed on the importance of fibrosis assessment as a key step to determine the level of risk of individual patients and the need for specialist referrals. Non-invasive techniques, such as transient elastography and ultrasound, are considered useful to assess the condition of the liver, determine the level of risk and rule out the presence of HCC, which is a known complication of MAFLD.

Experts discussed three hypothetical cases of MAFLD to highlight the most common problems in MAFLD diagnosis and treatment. The three cases included one individual with MAFLD and progressive fibrosis, one with MAFLD and metabolic syndrome with increased CV risk factors (dyslipidaemia and hypertension), and one with MAFLD and familial hypercholesterolaemia.

According to experts, early diagnosis is essential for patient management. However, this may prove challenging, especially if the healthcare system lacks sufficient integration between different specialists and a solid network for a multidisciplinary approach. Considering that patients with MAFLD have a high chance of presenting concomitant diseases such as T2D, dyslipidaemia, hypertension, metabolic syndrome and CVD, it is crucial that specialists, such as diabetologists, endocrinologists and cardiologists, are appropriately educated about MAFLD screening and early management and can identify these patients and refer them to a specialist if needed. Despite the importance of the multidisciplinary approach, experts also recognize that visiting different specialists may be difficult for some patients, especially in resource-limited countries and for individuals with financial constraints.

Regarding treatment, experts recognize that no approved medication is available for the treatment of MAFLD, and the best approach consists of lifestyle modification and management of comorbidities such as T2D, hyperlipidaemia and hypertension. Antioxidant therapy is a useful option to improve overall biochemistry and liver health status. According to the panel experts, most healthcare practitioners prescribe antioxidants like silymarin to treat patients with MAFLD, achieving good results after 3–6 months of treatment. However, many countries do not reimburse antioxidant therapy by the healthcare system, leading to additional financial burden on patients and likely negatively influencing treatment adherence given the need for long-term use to achieve the maximum effect and reduce liver enzymes. Healthcare practitioner education, especially amongst non-liver specialists and general practitioners, is therefore important to prompt the correct use of antioxidant therapy.

Multidisciplinary treatment approach

Given the multi-system nature of MAFLD, patient management requires the cooperation of numerous specialists, including hepatologists, gastroenterologists, endocrinologists, internists, cardiologists and pathologists.[37] Although a hepatologist/gastroenterologist is the main specialist involved in the diagnosis, playing a crucial role in the management of advanced fibrosis, many other specialists are necessary for the identification and management of MAFLD.[40]

According to experts, screening and treating patients with MAFLD and comorbidity requires an interdisciplinary approach for better management. General practitioners and non-hepatologists play a crucial role in identifying patients at an early stage and should therefore be appropriately educated on MAFLD-associated diseases. These specialists should also be able to treat patients at low risk for fibrosis progression, addressing the comorbidities as per their specialty and monitoring patients through regular follow-up visits to determine possible disease progression and increased risk. Patients at high risk should be promptly referred to a hepatologist for further assessment.

Despite these premises, according to the panel experts, awareness of MAFLD screening, diagnosis and treatment is still relatively low amongst endocrinologists, cardiologists and internal medicine experts, thus requiring more cross-specialty collaboration amongst these clinicians.

Role of oxidative stress management in MAFLD treatment

As previously mentioned, oxidative stress is one of the main causes of MAFLD, which may also explain the link between MAFLD and other cardiometabolic diseases. Excess ROS generation causes hepatocellular damage and contributes to the pathophysiology of T2D by disrupting pancreatic β-cell homeostasis and promoting insulin resistance.[41] Moreover, oxidative imbalance contributes to cardiovascular disease by activating monocytes/macrophages, oxidation of LDL, endothelial dysfunction and atherogenic dyslipidaemia.[42,43] Therefore, antioxidative therapy represents a reasonable therapeutic approach to treat MAFLD and associated cardiometabolic diseases.[44]

Vitamin E is recommended by international guidelines[45] to improve liver damage in selected patients with steatohepatitis without T2D; however, data do not support the antifibrotic role of vitamin E, and limited information is available on the effects of vitamin E on cirrhosis.[39] A study published in 2020 showed that vitamin E could improve liver transplant-free survival and reduce liver decompensation in individuals with bridging fibrosis and cirrhosis due to NASH.[46] According to the experts, vitamin E plays a role in reducing liver enzymes and can be considered in the early stages of the disease in certain patients, especially in those with increased liver enzymes and numerous concomitant metabolic risk factors. Furthermore, vitamin E requires a long treatment duration as the benefits reported in the literature come from long-term studies of 2 years or more and vitamin E is often used in clinical practice at low doses and combined with other antioxidants to achieve better outcomes. Nonetheless, vitamin E presents some safety concerns as it may increase the risk of bleeding, haemorrhagic stroke and mortality if used at high doses for a long duration or in combination with antiplatelet agents.[47,48]

Silymarin is another useful option in the treatment of MAFLD and its associated risk factors. Literature evidence shows that silymarin has promising effects on different components of MAFLD, with potential benefits in individuals at high risk.[49] Silymarin reduces oxidative stress in individuals with T2D,[50] decreases the level of hepatic transaminases in patients with MAFLD,[51,52] reduces inflammation and ameliorates insulin resistance.[53] Experts agree that silymarin is a safe and effective option for managing elevated liver enzymes in individuals with MAFLD, especially if used in the early stages, and the treatment lasts until the liver enzymes are normalized and stable over time. Monitoring of liver enzymes or other non-invasive tests may be useful to check the health status of patients and restart treatment if needed. However, it is important to remember that most patients with MAFLD have normal serum liver enzymes. Various studies have been conducted or are ongoing to further confirm the evidence on silymarin and improve its clinical use.[54–59]

Conclusion

The new term MAFLD more accurately reflects the pathogenesis of the disease and better captures the importance of metabolic alteration as a key driver of the disease. MAFLD is recognized as a multisystemic clinical condition involving liver damage and a wide spectrum of extrahepatic manifestations such as obesity, T2D, metabolic syndrome and cardiovascular diseases.[31]

Oxidative stress is one of the main pathological events in MAFLD pathogenesis and the hallmark between the normal liver, simple steatosis and NASH manifestation. The oxidative imbalance interferes with the normal function of liver cells, leading to the activation of inflammatory and fibrogenic pathways that ultimately cause functional and structural abnormalities in the liver, favouring MAFLD progression.

Given the complexity of MAFLD and associated concomitant diseases, implementing a multidisciplinary approach in patient screening, diagnosis and treatment is extremely important to allow early recognition of the disease and prompt referral. Increasing the awareness and education of non-hepatologists, including endocrinologists, cardiologists and internists, is therefore key for the management of MAFLD in the future.

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