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REVIEW ARTICLE

MAFLD: Exploring the Systemic Effects Beyond Liver

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a growing global health concern which is driven by the increasing prevalence of diabetes and obesity. MAFLD is characterized by excessive fat accumulation in the liver, which encompasses a range of conditions, from simple hepatic steatosis to more severe forms. This condition is associated with various complications, including chronic kidney disease (CKD), Cardiovascular Disease (CVD), liver cirrhosis, and even malignancy. Recent research has highlighted a potential connection between gut dysbiosis and MAFLD, particularly in relation to CKD. This has underscored the significance of the gut-liver-kidney axis in understanding MAFLD's pathogenesis. Inflammation triggered by MAFLD increases the risk of CVD through multiple mechanisms linked to metabolic dysfunction. These mechanisms include heightened oxidative stress, systemic and hepatic insulin resistance, low-grade inflammation, and endothelial dysfunction. Hepatic steatosis and metabolic dysfunction are major diagnostic criteria for MAFLD, often coexisting with other liver ailments. This prospective review emphasizes the intricate associations between MAFLD, cardiovascular complications, renal issues, and hepatic diseases. Understanding the underlying pathophysiological pathways is crucial in comprehending the increased risk of CKD, CVD, and other hepatic complications in individuals with MAFLD.

Keywords: MAFLD, NAFLD, NASH, Metabolic syndrome, CVD, CKD

1. Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a panorama of hepatic disorders consisting of benign nonalcoholic fatty liver to the more severe nonalcoholic steatohepatitis characterized by steatosis, hepatocellular ballooning, and lobular inflammation. In extreme cases, this may lead to cirrhosis and liver cancer, and is also predicted to become the most frequent indication for liver transplantation by 2030.[1,2] Over the past decade, it has become more coherent that MAFLD is a complex multisystem disorder with increased morbidity and mortality from other extrahepatic complications, such as Cardiovascular Disease (CVD), Type-2 Diabetes Mellitus (T2DM), and Chronic Kidney Disease (CKD). With the advent of the expanding epidemic of obesity, diabetes, and hypertension, the prevalence of MAFLD rose from 16% in 1988 to 37% in 2018 in the United States of America (USA).[3] At the same time, global prevalence rose from 15% to 33% in 2005 to 25% and 59.1% in 2010. Current global MAFLD prevalence is 50.7% among overweight or obese adults, with

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males (59.0%) having a significantly higher prevalence than females (47.5%).[4,5] In early 2020, an international panel of experts, through a consensus-driven process, coined the term "metabolic dysfunction-associated fatty liver disease" (MAFLD) to end a long ongoing discussion to rename the term Non-alcoholic associated fatty liver disease (NAFLD) to reflect the disease process and establish the disease as a metabolic disorder. MAFLD is diagnosed when patients have hepatic steatosis identified through histology, imaging, blood markers, or evidence of fat accumulation and one of the following: being overweight or obese (based on ethnicity-specific cutoffs), having type 2 diabetes mellitus (T2D) or showing signs of metabolic dysregulation. The latter is defined as having two or more of the following conditions:[6] [Fig. 1].

2. Metabolic risk abnormalities

1. Waist circumference of >102/88 cm in Caucasian men and women and >90/80 cm in Asian men and women.
2. Blood pressure of 130/85 mmHg or treatment for hypertension
3. Plasma triglycerides of 1.7 mmol/L or specific drug treatment.
4. Plasma high-density lipoprotein <1.0 mmol/L for men and <1.3 mmol/L for women or specific treatment.
5. Conditions for prediabetes: fasting plasma glucose 5.6–6.9 mmol/L, 2-h post-load glucose levels 7.8–11.0 mmol/L, or HbA1c 5.7%–6.4%.
6. Homeostasis model assessment of insulin resistance score >2.5. [7]

As various physiological, biochemical pathways and risk factors undermine the process of MAFLD as the new epitome of metabolic syndrome, this review aims to cover the clandestine role of MAFLD with other systemic disorders, including cardiovascular and chronic kidney disease.

3. Mechanism of MAFLD effect on cardiovascular system

MAFLD is a multisystem disorder that affects various extrahepatic organs, including the cardiovascular (CV) system. The congruency between the risk profile of MAFLD and metabolic syndrome, in addition to increased oxidative stress, systemic/hepatic insulin resistance, low-grade inflammation, and endothelial dysfunction, contributed to the link between MAFLD and cardiac disease. This established MAFLD as an independent risk factor for developing cardiovascular diseases like myocardial infarction, subclinical coronary or carotid atherosclerosis, and valvular heart disease.[6,8]

The liver plays a pivotal role in fatty acid oxidation and metabolism of lipids and lipoproteins by synthesizing and removing different lipoprotein particles. Inadequate lipid uptake coupled with an aberrant fatty acid oxidation leads to the accumulation of fatty substances in the liver hindering its physiological role of clearing inflammatory cytokines.[9] Patients suffering from MAFLD generally have increased hyperinsulinemia with insulin resistance, resulting in increased lipolysis and free fatty acids (FFA) in the bloodstream. These free fatty acids taken up by the liver are synthesized into Very low-density lipoprotein (VLDL) particles by esterification and combining with ApoB-100 particles.[10] Overproduction of VLDL-1 by hepatic cells and changes in hepatic lipid metabolism result in increased plasma triglyceride, remnant lipoprotein cholesterol, and small dense LDL particles levels,

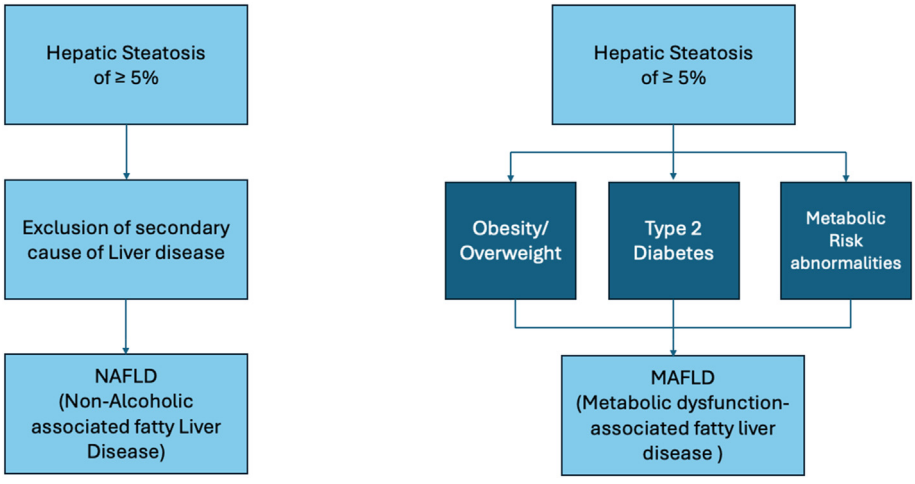

Fig. 1. NAFLD and MAFLD diagnostic criteria.[7]

which damages the endothelium layer and forms atherosclerotic plaques.[11–13] MAFLD patients generally has hyperinsulinemia with insulin resistance due to associated systemic inflammation, visceral obesity, and ectopic fatty tissue. In patients with MAFLD, the accumulation of fat in the liver and pancreas leads to insulin resistance and beta-cell dysfunction with decreased insulin clearance.[9] In addition to these, hyperinsulinemia also promotes de novo lipogenesis (DNL) through sterol regulatory element-binding protein (SREBP1c), which activates the transcription of PPARgamma, a nuclear receptor required for normal adipocytes to achieve differentiation and is involved in hepatic steatosis development.[14] The DNL pathway increases malonyl CoA, inhibiting Carnitine palmitoyl transferase I (CPT1) and, thus, fatty acid oxidation.[15] The combination of hepatic fat accumulation increased saturated fatty acids, and persistent hyperglycemia is central to the altered metabolic profile of MAFLD, which is linked to the development of CVD. This persistent hyperglycemia leads to the formation of advanced glycosylation end products (AGEs), which damage the vascular endothelial lining, stimulating the proliferation of smooth muscle cells (SMCs), increasing thrombogenic properties of platelets, and inducing Reactive Oxygen Species production. These effects can lead to the oxidation of LDL-cholesterol, which may promote the transformation of macrophages into foam cells.[9] LDL, VLDL, and triglyceride-rich lipoproteins with ApoC3 triggers Toll Like Receptor 2/4 dimerization and activating the NLRP3 inflammasome. This activation leads to caspase-1 formation, which boosts proinflammatory cytokines (IL-1, IL-6, CRP), further damaging endothelial cells and promoting atherosclerosis.[16] In addition, the hepatic DNL pathway results in the increased saturated fatty acid formation, and VLDL particles, which causes upregulation TLRs 2 and 4, further triggering the endothelial inflammation, contributing to vascular injury and plaque formation. Over time, these plaques undergo further lipid deposition, inflammation, fibrosis, and calcification, causing severe atherosclerotic disease.[9] In patients with MAFLD, disarranged hepatic function also results in altered conjugation of S-adenosylmethionine (SAM), resulting in high levels of homocysteine, oxidative damage to platelets, endothelial cell dysfunction.[17] Also, high levels of homocysteine results in reduced nitric oxide bioavailability by disrupting the uncoupling of nitric oxide synthase activity, aggravating the endothelial function.[18] In addition, Patients with MAFLD often have increased levels of asymmetric dimethyl arginine (ADMA), a natural antagonist to nitric oxide synthase. This leads to over-inhibition of nitric oxide synthase and a subsequent increase in vascular stress and damage. Overall, the combination of increased homocysteine levels and decreased nitric oxide levels dramatically accelerates the development of atherosclerotic plaques in patients with MAFLD.[19–21] [Fig. 2].

4. Clinical cardiac implications of MAFLD

According to a large meta-analysis of involving 34,043 adult individuals, patients with MAFLD have a higher odds ratio (OR) of 1.64 (95% CI: 1.26–2.13)

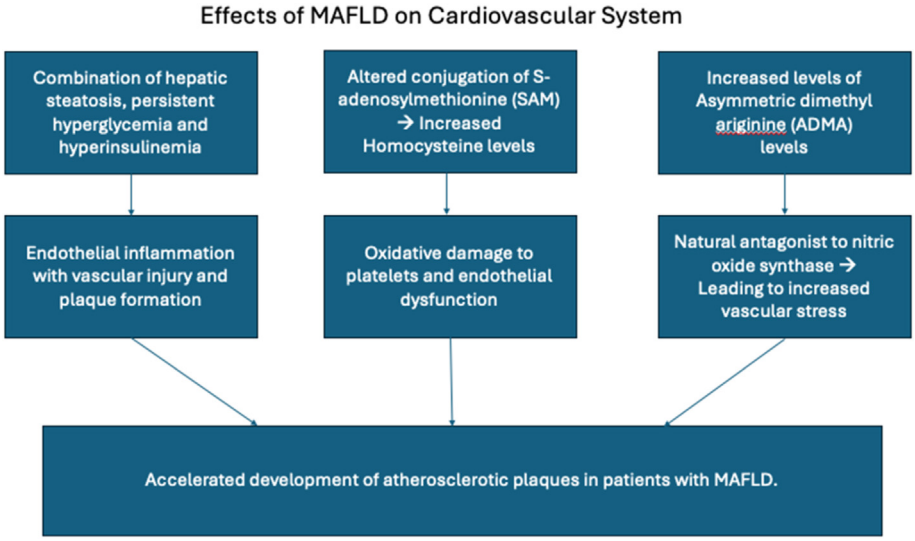

Fig. 2. Effects of MAFLD on Cardiovascular system.

for fatal and non-fatal CVD events and the risk further increases with the progression of the disease, leading to an OR of 2.58 (95% CI: 1.78%−3.7%) in those with the most severe MAFLD phenotype.[2,22] A study by Zhou YY found that MAFLD is linked to a higher risk of developing atherosclerotic cardiovascular disease with a meta-analysis of 26 studies involving 85,395 participants showing that individuals with MAFLD had a significantly higher risk of subclinical atherosclerosis (OR 1.60; 95% confidence interval, 1.45−1.78). Further analysis showed that individuals with MAFLD had a higher risk of carotid artery intima-media thickness/plaques, arterial stiffness, coronary artery calcification, and endothelial dysfunction with OR (95% confidence interval) of 1.74 (1.47−2.06), 1.56 (1.24−1.96), 1.40 (1.22−1.60), and 3.73 (0.99−14.09), respectively 26. Another study by Noda et al. revealed that MAFLD and inadequate physical function tests independently predicted the likelihood of adverse cardiovascular disease outcomes. These findings suggest that MAFLD may increase the chances of unfavorable CVD outcomes.[23]

5. Mechanism of MAFLD effect on the renal system

Patients with MAFLD are reported to have a higher risk of chronic kidney diseases (CKD), and the two can be associated with several pathophysiological explanations. The most important one is the presence of inflammation in MAFLD.[24] Type 2 diabetes and arterial hypertension are the primary risk factors for the development of CKD. The same can be claimed for obesity, dyslipidemia, prediabetes, and insulin resistance. Numerous studies have found a correlation between the aforementioned risk factors and the occurrence of CKD.[25] In addition to being a risk factor shared by MAFLD and CKD, obesity plays a critical role in the progression of both diseases. Through the release of adipokines, adipose tissue is recognized as an endocrine organ. Further, it also has some important regulatory activities on insulin sensitivity, satiety, and inflammation and plays a significant role in the renin-angiotensin system.[26]

6. Gut-Liver-kidney axis

In recent years, research has emerged that suggested a possible link between gut dysbiosis and both MAFLD and CKD. The significance of the gut-liver-kidney axis has consequently increased because of this development. Alterations in the diversity of the gut microbiota can result in the production of potentially harmful metabolites, including p-cresyl sulfate, indoxyl sulfate, and trimethylamine N-oxide (TMAO).[24] In a study conducted in the Japanese population, MAFLD was reported to be a determinant of CKD. This remained constant regardless of sex, coronary artery disease, age, estimated glomerular filtration rate (eGFR), smoking, and metabolic risk factors, including hypertension, DM, obesity, and hyperlipidemia.[27] A substantial association between the diagnosis of MAFLD and the development of CKD was observed for the first time in a recent systematic review and meta-analysis.[28]

7. Clinical renal implications of MAFLD

In a study conducted in US cohort patients, MAFLD was shown to be associated with all-cause mortality among patients. In a median follow-up of 23 years, the same study reported that patients with metabolic dysfunction associated with liver disease have a 17% increased risk of all-cause mortality.[29] The research showed that compared to non-metabolic fatty liver disease individuals, MAFLD patients have an increased risk of CKD. In an analysis conducted for a median period of 5.1 years among approximately 270,000 individuals, MAFLD patients had an adjusted hazard ratio (aHR) of 1.39 compared to the non-metabolic liver disease patients.[30] In another study conducted by Hashimoto et al. among 27,371 participants, it was reported that MAFLD increases the CKD risk when compared to patients with non-metabolic dysfunction-associated fatty liver disease.[31] Interestingly, in a recent study published by Miyamori et al., it was reported that the co-existence of kidney diseases with MAFLD significantly increases the risk of ischemic heart disease.[32] As a result, one can draw the conclusion that MAFLD can predict CKD in addition to being associated with increased incidence and higher mortality rates. Levels/stages of hepatic steatosis/fibrosis and kidney function indices such as the urine ACR and the eGFR are significantly related in this group of patients. This relationship should not come as an unexpected event, given that both entities share risk factors and detrimental biological pathways such as dysbiosis of gut microbiota, oxidative stress, and inflammation. In parallel, genes and their variants that are linked to a tendency for fatty liver disease may also be responsible for propagating renal impairment.[24] Further studies are warranted that can address the prognosis of patients with MAFLD with kidney diseases and help in understanding the exact nature of this association.

8. Mechanism of MAFLD effect on liver

Non-alcoholic fatty liver disease affects 25 percent of the global population. However, the term NAFLD is limited because it relies on exclusionary criteria and does not reflect its underlying pathophysiology. A new term was proposed in 2020 by Eslam et al., which encompasses a wide range of liver conditions that are associated with metabolic dysregulation to highlight the metabolic abnormalities associated with fatty liver disease.[33] In recent times, another new term called MAFLD has been introduced. In contrast to MAFLD, the diagnosis of MAFLD requires the presence of a minimum of one out of five cardiometabolic risk factors (high BMI, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels).[34] It has been acknowledged in both attempts to rename the condition that MAFLD or MAFLD may coexist with other chronic liver diseases. In view of the frequent occurrence of both alcohol misuse and metabolic dysfunction, a clear methodology for categorizing fatty liver disease and determining the degree of alcohol consumption has been presented in this fresh consensus statement. A new classification, called MetALD, was proposed to represent MAFLD patients with higher alcohol consumption (140–350 g/week for females, 210–420 g/week for males).[35] One noteworthy thing is that clinicians should assess significant variations in clinical outcomes when considering a name change.

9. Genetic predisposition of MAFLD

Genetic variables have been found to have significant impacts on the predisposition to MAFLD, according to recent epidemiological studies. Regardless of the existence of metabolic triggers, first-degree relatives of patients with MAFLD cirrhosis have a risk of acquiring severe fibrosis that is almost twelve times higher than that of those without MAFLD.[36]

The genetic basis of MAFLD can now be better understood thanks to recent developments in high-throughput sequencing technology, which have made genome-wide association studies (GWAS) possible. Five genetic loci that may affect susceptibility to the disease were found by a GWAS-based investigation using a sizable sample of the European population to find genetic variants connected to MAFLD. These loci were found in close proximity to the genes TRIB1, TM6SF2, APOE, GCKR, and PNPLA3.[37]

Apart from hepatic fat accumulation itself, GWAS have also identified genetic variations linked to the development of MAFLD to steatohepatitis, fibrosis, and cirrhosis. Disruptions in insulin signaling, glucose metabolism, fibrogenesis, oxidative stress, cell senescence, inflammation, and lipotoxicity are some of these pathways. One of the main causes of liver damage and the advancement of MAFLD is thought to be mitochondrial dysfunction, which is defined by oxidative stress and reduced mitochondrial respiratory complex activity and oxidation.[38]

Although liver biopsy is the gold standard procedure to diagnose MAFLD, it has drawbacks because of its high cost and potential for intrusive procedure-related problems. Genetic techniques, especially single nucleotide polymorphisms (SNPs), have garnered interest recently due to their non-invasive nature. These techniques predict the risk of MAFLD by combining the effects of several SNPs into a single score. Genetic risk scores (GRS) have been demonstrated in several studies to be helpful in this regard. An increased risk of acquiring MAFLD and associated liver disorders is indicated by a higher GRS. Large populations can be screened using GRS techniques, and individuals who are at high risk can lower their risk of contracting the illness by changing their food, and increasing their physical activity, and changing their lifestyle.[39,40]

10. Clinical implications of MAFLD

Recent findings from studies have shown individuals meeting the criteria for MAFLD possess greater risk compared to those diagnosed with NAFLD. There is a high risk of mortality, which includes both all-cause mortality as well as liver-related mortality. When MAFLD is present without coexisting NAFLD (signifying fatty liver alongside factors contributing to liver disease), the susceptibility to mortality becomes even more pronounced.[41] Nyguyen et al. categorized National Health and Nutrition Examination Survey (NHANES) III participants into non-NAFLD-MAFLD, overlap NAFLD-MAFLD, and non-MAFLD-NAFLD. The study revealed a significant discrepancy in 15-year all-cause mortality rates among these groups: 26.2% for non-NAFLD-MAFLD, 21.1% for overlap NAFLD-MAFLD, and 10.6% for non-MAFLD-NAFLD ($p < 0.0001$). Remarkably, individuals with MAFLD (Metabolic Associated Fatty Liver Disease) but not NAFLD (Non-Alcoholic Fatty Liver Disease) exhibited a 2.4-fold higher mortality risk than those with NAFLD only. A study done by Younossi et al. showed liver-related mortality exhibited higher rates in MAFLD compared to NAFLD (3.01%, 95% CI 1.99–4.03 vs. 1.81%, 95% CI

0.95–2.66). While the impact of various covariates on mortality related to cardiovascular diseases (CVD) and extra-hepatic malignancies demonstrated similarity between the two groups, a notable disparity emerged in terms of liver-related mortality. While the most substantial influence over liver-related mortality for both MAFLD and NAFLD was the high risk for fibrosis (HR 17.15, 95% CI 4.55–64.65 and HR 9.26, 95% CI 1.84–46.33, respectively), other influential factors diverged. For MAFLD, these factors were alcohol-related liver disease (HR 4.50, 95% CI 1.89–10.75) and chronic kidney disease (HR 2.92, 95% CI 1.21–7.01), while for NAFLD, they were high levels of C-reactive protein (CRP) (HR 4.47, 95% CI 1.35–14.77) and insulin resistance (HR 3.57, 95% CI 1.35–9.42).[42]

11. Conclusion

This review concludes that MAFLD is significantly associated with CVD, CKD, and other liver ailments, including liver cancer. It thus can be concluded that MAFLD is linked to high incidence and mortality rates and acts as an independent predictor of chronic kidney disease (CKD). There is a correlation between the degree of hepatic steatosis and fibrosis in this group of patients and kidney function indices like the urinary albumin-to-creatinine ratio and the estimated glomerular filtration rate. On the other hand, in patients with MAFLD, an increased incidence of CVD is also reported. There is a growing interest, both in the scientific and clinical communities, in the connection between MAFLD and the risk of CVD. There is a dearth of scientific guidelines developed by cardiology professional groups that are geared toward addressing this widespread and severe liver illness. It has been acknowledged that MAFLD may coexist with other chronic liver diseases. Further, this review also stressed the point that physicians should be urged to use the new terminology for the timely medical care and management of this preventable condition and its complications. However, there is a paucity of data available at this time about the impact of the updated definition on the medical outcomes and mortality rates associated with the condition; hence, additional in-depth clinical trials are required to fill this gap in the existing body of research. In addition, there should be an increase in awareness of simultaneous metabolic disruption associated with the condition.

Ethics

No patient or confidential information is shared. This study does not include any Huma or animal subjects.

Data availability statement

All datasets on which the conclusions of the paper rely are available to editors, reviewers, and readers without unnecessary restriction.

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Conflict of interest

We declare that there is no conflict of interest regarding the publication of this review study. We have no financial or personal relationships that could potentially bias outcome. There was no financial support or conflicting interests associated with this manuscript.

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