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Review

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Risk of cardio-nephro-metabolic disease from NAFLD to MAFLD: fact or fiction?

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is emerging as the most common etiology for chronic liver disease. Despite this, our understanding of this illness is lacking. The previous paradigm is that central adiposity, hyperlipidemia, hypertension, and insulin resistance, also known as metabolic syndrome, lead to NAFLD, and this relationship is unidirectional. However, recent evidence clearly shows that the clinical burden of this illness extends well beyond liver-related morbidity and mortality and is associated with multiple extrahepatic complications, particularly metabolic consequences. Due to this, the professional consensus has proposed using the term metabolic associated fatty liver disease (MAFLD) to more accurately reflect pathogenesis and help in patient stratification for management. This review discusses the shared pathophysiological mechanisms that link these diseases and how this can be leveraged to prevent these complications in individuals with NAFLD/MAFLD.

Keywords: Nonalcoholic fatty liver disease, metabolic associated fatty liver disease, cardiovascular disease, diabetes, insulin resistance, chronic kidney disease

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases defined by the presence of hepatic fat accumulation in the absence of secondary causes of liver disease, such as significant alcohol

use[1,2]. Early-stage NAFLD, also known as non-alcoholic fatty liver, is characterized by isolated hepatic steatosis[1,2]. As the disease progresses, isolated hepatic steatosis leads to inflammation and hepatocyte injury [non-alcoholic steatohepatitis (NASH)], fibrosis (NASH cirrhosis), and hepatocellular carcinoma[1,2].

NAFLD is the most common chronic liver disease worldwide[3]. The burden of NAFLD on society continues to increase as a direct result of changes in dietary habits and sedentary lifestyles[3-5]. Recent estimates suggest a prevalence of up to 45% in the United States and 25% worldwide[3-5]. The prevalence of NAFLD in obese and diabetic individuals is as high as 75%, in contrast to a prevalence of 15%-30% in the general population[3-5]. NAFLD was previously thought to be the hepatic manifestation of metabolic syndrome, as is suggested by its increased prevalence in those with obesity and type 2 diabetes mellitus (T2DM); however, recent data suggest that the impact of NAFLD is not limited to liver-related mortality and outcomes, but rather is a multi-system disease that can lead to multiple complications including coronary artery disease and cardiomyopathies, chronic kidney disease (CKD), and insulin resistance[6].

Due to these changes in our understanding of NAFLD, Eslam *et al.*[7] called for consensus to address the nomenclature of NAFLD so that it can more accurately reflect pathogenesis and help in patient stratification for management. After applying a carefully designed Delphi method, a representative panel of experts suggested metabolic associated fatty liver disease (MAFLD) as a more appropriate overarching term [Table 1].

NAFLD/MAFLD AND INSULIN RESISTANCE

NAFLD and T2DM often co-exist as they share many common risk factors, particularly obesity and insulin resistance. In fact, recently proposed diagnostic criteria for MAFLD recommends the following definition: detection of steatosis with one of the different modalities (imaging, blood biomarker, or histology) with the presence of one of three criteria, overweight or obesity, T2DM, or evidence of metabolic abnormalities[7].

A recent meta-analysis of 19 studies with about 300,000 patients estimated that individuals with NAFLD had a 2-fold higher risk of developing T2DM and a 5-fold increase in the presence of advanced fibrosis[8]. In addition, one study examined that the risk of developing T2DM in patients with biopsy-proven NAFLD and found that approximately 80% of patients developed T2DM within 14 years[9].

The relationship between NAFLD and T2DM is quite complex as insulin resistance is associated with both intrahepatic and extrahepatic lipid accumulation and promotes liver injury and fibrosis. Under normal physiologic conditions, insulin suppresses hepatic glucose production. However, when intrahepatic fat accumulates, this physiological response is blunted as a result of insulin resistance. This results in poorer glycemic control in patients with both T2DM and NAFLD compared to patients with only T2DM[6].

Insulin resistance and elevated blood glucose lead to many downstream effects and result in the many extrahepatic manifestations observed with NAFLD; however, the exact mechanism is yet to be elucidated. Multiple chemical mediators have been identified, some that have also been implicated in the development of cardiovascular disease (CVD) and CKD, including interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), ceramides, diacylglycerols, gut microbiome dysbiosis, and mitochondrial dysfunction. Serum levels of adiponectin, an adipocytokine that protects against insulin resistance by promoting fatty acid oxidation and glucose utilization, were found to be reduced in patients with NAFLD compared to their control cohorts[10,11]. A low level of adiponectin was associated with higher levels of low-density lipoproteins and triglycerides and lower levels of high-density lipoproteins[12,13]. Elevations in lipid metabolites, particularly ceramides and diacylglycerols, have been found to occur in models of NAFLD and have been

Table 1. Comparison of diagnostic criteria for NAFLD and MAFLD

NAFLD	MAFLD
Diagnosis requires the following:	**Must have hepatic steatosis (imaging or histology) AND one of the following:**
(1) Evidence of hepatic steatosis (imaging or histology) AND	(1) Overweight (BMI > 25kg/m^2 in Caucasians or > 23kg/m^2 in Asians)
(2) Absence of secondary causes of liver disease (alcohol consumption, hereditary disorder, medication)	(2) Normal weight (BMI < 25kg/m^2 in Caucasians or < 23kg/m^2 in Asians) AND at least 2 of the following: (a) Waist circumference > 102/88 cm in Caucasians or > 90/80 cm in Asians (b) Blood pressure > 130/85mmHg or on anti-hypertensive medication (c) Triglycerides > 150mg/dL or on treatment (d) HDL-cholesterol < 40mg/dL for men or < 50mg/dL for women or on treatment (e) Prediabetes (f) Insulin resistance score > 2.5 (via homeostasis model assessment) (g) High-sensitivity C-reactive protein > 2mg/L
	(3) Type 2 diabetes mellitus

NAFLD: Nonalcoholic fatty liver disease; MAFLD: metabolic associated fatty liver disease.

linked to insulin resistance[14]. Gut microbiota is emerging as an important mediator in the natural progression of T2DM in patients with NAFLD[15]. The gut microbiota in NAFLD is often in a state of dysbiosis with an increase of deleterious microorganisms in relation to beneficial ones. Studies have shown that restoration of gut microbiota in patients with NAFLD with treatment with antibiotics, probiotics, or fecal microbiota transplantation led to an increase in insulin sensitivity[16,17]. Mitochondrial dysfunction is commonly seen in NAFLD, likely due to excessive beta-oxidation of free fatty acids in the early stages of the disease, which leads to excess production of reactive oxygen species[18]. As NAFLD progresses, fatty acid beta-oxidation is downregulated, and lipotoxic intermediates accumulate, which may directly impact insulin signaling[19].

It appears that the relationship between T2DM and NAFLD is bi-directional; not only does T2DM promote NAFLD progression to cirrhosis, increase all-cause and liver-related mortality, but NAFLD also leads to insulin resistance and poor glycemic control[20]. In addition, microvascular complications, including retinopathy and nephropathy, are more prevalent in individuals with T2DM and NAFLD than those with T2DM alone, and this relationship was independent of traditional confounding risk factors[21,22]. A study of individuals with NAFLD and type 1 diabetes demonstrated the same findings, suggesting that the common mechanism may be the release of pro-inflammatory mediators such as advanced glycated end-products, reactive oxygen species, TNF-α, and transforming growth factor-beta[23,24].

Due to the similar pathophysiologic mechanisms of NAFLD and T2DM, several anti-diabetic drugs have been trialed in patients with NAFLD. Metformin has been shown to be beneficial in patients with NAFLD by decreasing the amount of fat deposition in the liver and improving metabolic parameters, including the normalization of serum levels of aminotransferases[25,26]. A prospective trial on 42 NAFLD patients without T2DM demonstrated that metformin and dieting led to significant reductions in hepatic steatosis and fibrosis after 5 months, compared to patients treated with diet alone[27]. Interestingly, a meta-analysis of 17 randomized controlled trials showed that up to 12 months of metformin and lifestyle intervention did not improve liver histology or aminotransferases in patients with both NAFLD and T2DM[28]. Another promising class of drugs includes thiazolidinediones (TZD), which increase insulin sensitivity by activating peroxisome proliferator-activated receptors. Multiple randomized controlled trials have evaluated the efficacy of TZDs and demonstrated that these drugs provide a beneficial effect on lobular inflammation. However, their effect on steatosis and fibrosis is unclear[29-31]. Newer drugs such as the glucagon-like peptide-

1 analogues have emerged as attractive therapeutics in patients with NAFLD[32]. After 48 weeks of treatment with liraglutide, patients with biopsy-proven NAFLD showed significant improvement in steatosis and hepatocyte ballooning; however, no significant differences were seen in regard to lobular inflammation and fibrosis-4 score[33]. A recent study showed that patients with NASH treated with semaglutide resulted in a significantly higher percentage of patients with resolution of NASH compared to placebo. However, the trial did not show a significant difference between groups in the percentage of patients with an improvement in the fibrosis stage[34]. A meta-analysis of 11 randomized controlled trials showed that use of GLP-1 agonists (including liraglutide, exenatide, dulaglutide, or semaglutide) when compared to placebo or reference therapy, resulted in significant reductions in the absolute percentage of hepatic adipose content on magnetic resonance imaging and serum enzymes, in addition to the histological resolution of NASH[35].

Based on this data, it is beneficial to screen patients with NAFLD for T2DM with yearly serum glycated hemoglobin (HgbA1c) and encourage weight loss and lifestyle changes, including dietary avoidance of fructose. In addition, due to their increased risk of complications, patients with NAFLD and established T2DM should be regularly screened for both microvascular and macrovascular changes.

NAFLD/MAFLD AND RENAL DISEASE

CKD, defined as loss of kidney function as estimated by glomerular filtrate rate (GFR) less than 60 mL/min/1.73m^2 or presence of overt proteinuria, is present in up to 50% of individuals with NAFLD[23]. The most common causes of CKD are hypertension and T2DM, which are closely intertwined with metabolic syndrome, and have a strong association with NAFLD as well. However, studies have shown that NAFLD may accelerate the development and progression of CKD, regardless of hypertension or diabetes status[36,37]. The increased risk of CKD in NAFLD is further highlighted by the fact that NASH cirrhosis is the leading and most rapidly growing indication for simultaneous liver and kidney transplantation[38]. Individuals who receive a liver transplant for NASH cirrhosis remain at risk for developing CKD during the post-transplant follow-up[39,40].

A meta-analysis of over 20 studies with more than 60,000 patients evaluated the prevalence and incidence of CKD in patients with fatty liver, NASH, and advanced fibrosis and found that incidence of CKD increased with more advanced NAFLD, suggesting that the severity of NAFLD is linked to CKD[37]. In addition, a randomized controlled trial with patients with biopsy-proven NASH demonstrated that GFR improved after one year of lifestyle intervention and resolution of NASH, while no improvement in GFR was observed in individuals that did not have lifestyle intervention[41].

The pathological mechanisms linking NAFLD and CKD are thought to include dysregulation of angiotensin-converting enzyme (ACE)-2, impaired antioxidant mechanisms, hyperuricemia, and gut microbiota dysregulation[42]. The renin-angiotensin-aldosterone system is upregulated in obese patients due to adipocyte production of ACE-1[43]. ACE-1 is responsible for converting the inactive hormone angiotensin-2 to the active hormone angiotensin-2. Angiotensin-2 has detrimental effects on both the liver and kidney by promoting insulin resistance, lipid production and deposition, mitochondrial oxidative stress, inflammation, and fibrosis[44,45]. Under normal physiologic conditions, ACE-2 degrades active angiotensin-2 to inactive angiotensin-1, which limits its activity. Although not studied in humans, experimental animal models of NASH showed that ACE-2 levels were significantly depressed[46].

Multiple studies have shown that increased intake of dietary fructose was associated with worsening liver fibrosis and renal function[47,48]. This mechanism is thought to be secondary to fructose metabolism in hepatocytes, which leads to adenosine triphosphate depletion and consequently an increase in adenosine

monophosphate conversion to uric acid. Hyperuricemia is associated with mitochondrial oxidative stress in hepatocytes and inhibits nitric oxide generation in endothelial cells, which is detrimental to the kidney[49].

The relationship between CKD and NAFLD appears to be bi-directional. CKD leads to the build-up of uremic toxic metabolites, which can induce gut microbiota dysbiosis, which in turn promotes NAFLD. In particular, ammonia and ammonium hydroxide cause alterations in intestinal tight junctions and provide substrates to urea metabolizing microbiota[50,51]. These alterations subsequently allow the passage of lipopolysaccharides and activate inflammasome pathways in the liver, triggering liver injury and progression of NAFLD. Resolution of urea-induced disruption of colonic epithelial tight junctions by using oral activated charcoal in mouse models of CKD attenuated associated endotoxemia, oxidative stress, and inflammation[52].

These findings suggest that a strong association exists between NAFLD and CKD, including a relationship that corresponds with NAFLD severity. Therefore, the management of CKD and its sequelae should be addressed early and incorporated in the care of patients with NAFLD. Given this relationship, it is likely that improvement in NAFLD may improve CKD, and the management of CKD may ameliorate the clinical outcomes in NAFLD.

NAFLD/MAFLD AND CARDIOVASCULAR DISEASE

CVD accounts for approximately 20% of death in individuals with NAFLD, making it the leading cause of mortality in this population[53]. NAFLD has been associated with traditional cardiometabolic risk factors, including obesity, hyperlipidemia, hypertension, and insulin resistance; however, the relationship between NAFLD and CVD is not entirely clear. Recent evidence appears to suggest that NAFLD, independent of the above risk factors, leads to additional risk for premature CVD[54,55]. In addition, new studies have identified non-traditional risk factors, such as pro-inflammatory cytokines (e.g., IL-6, TNF-α), gamma-glutamyl transferase (GGT), fibrinogen, plasminogen, vascular adhesion molecules, C-reactive protein, adiponectin, and uric acid, which may link these two processes[56-58]. Interestingly, many of these molecules that link CVD and NAFLD are synthesized in the liver. A better understanding of this relationship is important, as it would allow us to target therapy for the treatment of liver disease to further ameliorate the risk of CVD.

NAFLD is linked with increased subclinical atherosclerosis and increased coronary artery calcium (CAC) deposition, as well as CVD itself[59]. Studies have demonstrated a link between NAFLD and increased carotid intima-media thickness, a well-validated tool for assessing atherosclerosis in asymptomatic patients that independently predicts CVD events[60-63]. A meta-analysis demonstrated that NAFLD was independently associated with a 3.7-fold higher likelihood of having carotid plaques[64]. Arterial stiffness, measured using the cardio-ankle vascular index, is closely associated with coronary atherosclerosis and stroke and was found to be increased in patients with NAFLD[65-68]. Computed tomography-based quantification of coronary atherosclerosis or CAC score has recently been demonstrated to be perhaps the most reliable non-invasive biomarker for cardiovascular health[69]. CAC scores in individuals with ultrasound confirmed NAFLD was found to be elevated compared to their control counterparts[70]. A longitudinal study demonstrated that NAFLD plays a role in the initial development of coronary artery calcification without any baseline calcification. As seen by liver ultrasound, the severity of NAFLD is positively associated with CAC in a dose-dependent fashion[71]. Another study that screened patients scheduled to undergo coronary angiogram with abdominal ultrasounds observes that fatty liver was associated with significant coronary stenosis independent of other metabolic factors[72].

Epidemiological studies clearly establish an association between NAFLD and the risk of cardiovascular events. In a large study of almost 20,000 patients without known liver disease, ultrasound-detected NAFLD was associated with an elevated 10-year risk of CVD events as estimated by the Framingham risk score, independent of traditional risk factors typically associated with metabolic syndrome[73]. Prospective studies have shown that the risk of CVD events is correlated with the extent of biopsy-proven fibrosis of NAFLD rather than other histological factors[74]. When adjusted for traditional CVD risk factors, fibrosis stage was the strongest predictor for CVD-related mortality in patients with NAFLD even after 33 years of follow-up[74]. Furthermore, it was observed that patients with NAFLD and advanced fibrosis had CVD events predominantly, while those with NAFLD cirrhosis had liver-related events predominantly over a mean follow-up of 5.5 years[75].

As the primary etiology of cirrhosis prior to liver transplant, NASH has been shown to infer a higher long-term risk for CVD mortality compared to those transplanted for other causes of cirrhosis[76]. Furthermore, the long-term risk was affected, and CVD risk within one year of liver transplantation was increased in patients transplanted for NASH cirrhosis compared to patients transplanted for alcohol-induced cirrhosis[77,78].

One proposed mechanism linking NAFLD and CVD is serum GGT. GGT is frequently elevated in patients with NAFLD, and it has been reported to be associated with cardiovascular death, as well as increased non-fatal cardiovascular events, even in individuals with low to moderate cardiovascular risk[79]. In addition, Serum GGT undergoes redox reactions and is deposited in atherosclerotic plaques, likely leading to their progression[80]. In fact, serum GGT was validated as a potential biomarker for future cardiovascular disease risk[81].

The effect of NAFLD on heart disease extends beyond the vascular disease to include cardiomyopathies, valvopathies, and arrhythmias[82]. NAFLD has been found to be a risk factor for the development of atrial fibrillation (AF)[83,84]. In large cohort studies of patients with NAFLD with and without T2DM, NAFLD was found to be independently associated with AF[85,86]. A meta-analysis involving over 200,000 patients showed that NAFLD was associated with a two-fold increased risk of incidence of AF[87]. In addition, NAFLD has been shown to be independently associated with valvular disease, particularly aortic valve sclerosis and mitral annular calcification, which can subsequently lead to increased cardiovascular mortality and cardiac arrhythmias[88,89].

Additionally, studies have linked NAFLD and diastolic dysfunction[90]. Compared to those without NAFLD, patients with NAFLD had alterations in cardiac remodeling, manifested by increased left ventricular mass index, left ventricular end-diastolic diameter, and left atrial volume index[90]. Both hepatic steatosis and fibrosis were significantly associated with increased left ventricular filling pressure, reflective of diastolic dysfunction, independent of other common cardiovascular risk factors[91]. In addition, those with NAFLD had impaired myocardial glucose uptake measured using fluorodeoxyglucose-positron emission tomography compared to those without NAFLD[92]. Further studies demonstrated that the severity of myocardial dysfunction was linearly correlated with the severity of biopsy-proven NAFLD. Interestingly, it was noted that myocardial alterations occurred prior to cirrhosis, suggesting that these changes may not be a consequence of portal hypertension[93,94]. The fibrosis-4 index, a marker of liver stiffness, was an independent predictor of left ventricular diastolic dysfunction, larger atrial volume, and higher all-cause mortality in patients with heart failure[95].

As demonstrated by multiple studies, there is a higher prevalence of clinically significant cardiac disease in patients with NAFLD than in the general population. This requires greater attention as their risk for CVD, including carotid and coronary atherosclerosis, appears to be increased unproportionally to traditional cardiometabolic risk factors, including metabolic syndrome and T2DM. Due to this elevated risk, this group of patients should undergo careful cardiovascular surveillance by screening for metabolic risk factors and intervening in modifiable risk factors.

DIFFERENCES BETWEEN NAFLD AND MAFLD

The above-presented data was gathered in patients diagnosed under the previously established NAFLD criteria. One would assume that patients diagnosed using the newly proposed MAFLD would show the same results; however, this may not entirely be the case. Recent studies have compared the characteristics of patients diagnosed by MAFLD and NAFLD criteria and found that the MAFLD population had higher liver enzymes and more glucose and lipid metabolism-related disorders[96,97]. MAFLD individuals had a lower GFR and higher prevalence of CKD compared to patients with NAFLD even after adjusting for sex, ethnicity, age, alcohol intake, and diabetes[98]. Patients with MAFLD were found to have a higher risk for cardiovascular adverse outcomes and a higher incidence of all-cause mortality compared to those with NAFLD[97,99]. Furthermore, patients with concomitant MAFLD and viral hepatitis, but not NAFLD and viral hepatitis, had a significantly increased cardiovascular risk as assessed by cardiovascular disease risk estimator and atherogenic indices[100]. Tsutsumi *et al.*[101] recently used a generalized estimating equation approach to investigate the difference in atherosclerotic cardiovascular disease (ASCVD) risk between patients with MAFLD and NAFLD. Using this approach, they found that MAFLD better identifies patients with higher ASCVD risk, and this was due to the presence of metabolic dysfunction rather than moderate alcohol consumption. Another study showed that MAFLD was significantly associated with a higher risk of developing subclinical atherosclerosis as measured with carotid intima-media thickness and brachial-ankle pulse wave velocity[102]. A study of middle-aged Korean adults found that a considerable proportion of patients were found to have MAFLD without satisfying the former definition of NAFLD, and these individuals had a higher risk of CVD events[103]. Similar results have been reported from a community-based cohort study in suburban Sri Lanka[99].

Fatty liver disease is a heterogenous disorder with different metabolic and genetic factors. Therefore, NAFLD diagnosis is based on the exclusion of other concomitant liver diseases, which does not accurately reflect the pathogenesis of this disease. On the other hand, MAFLD avoids the dichotomous view of non-alcoholic fatty liver and non-alcoholic steatohepatitis since it is based on positive criteria (see Table 1) instead of negative criteria[7]. Furthermore, this allows concomitant liver disease due to causes other than MAFLD and is called dual etiology, which was not possible under the previous definition of NAFLD[104]. For instance, a patient with a history of alcohol use disorder and criteria meeting MAFLD would have dual etiology of MAFLD and alcohol. Similarly, individuals with viral hepatitis and criteria meeting MAFLD would have dual etiology of MAFLD and viral hepatitis. Another subtype of MAFLD that merits discussion is patients with cirrhosis who fulfill the criteria for MAFLD. The proposed definition is MAFLD-related cirrhosis and to avoid the term cryptogenic cirrhosis[104]. The diagnostic criteria of MAFLD-related cirrhosis require a patient to have cirrhosis in the absence of typical histological signs suggestive of steatohepatitis with one of the following criteria: past or present metabolic risk factors, MAFLD on the previous biopsy, or previous documentation of steatosis by hepatic imaging.

As described above, MAFLD appears to better identify patients who are at higher risk of hepatic or cardiovascular outcomes. However, one drawback of this new definition is that it de-emphasizes the severity of hepatic steatosis, which has been shown to correlate with CVD outcomes and insulin resistance[105,106]. A

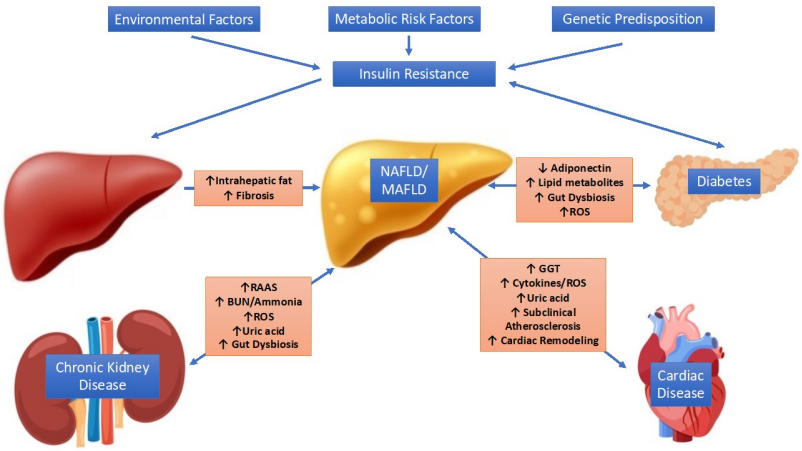

Figure 1. The proposed interplay between insulin resistance and NAFLD/MAFLD and subsequent development of diabetes, chronic kidney disease, and cardiac disease. NAFLD: Nonalcoholic fatty liver disease; MAFLD: metabolic associated fatty liver disease; ROS: Reactive oxygen species; BUN: blood urea nitrogen; RAAS: renin-angiotensin-aldosterone system; GGT: gamma-glutamyl transferase.

specific population of patients may be overlooked with this new definition, those with hepatitis steatosis and no metabolic risk factors, also previously known as lean NAFLD. A recent study using the NHANES III database compared patients with MAFLD and those with non-metabolic risk NAFLD and severe steatosis[107]. The cohort with non-metabolic risk NAFLD and severe steatosis was small, reflecting the rarity of this entity. This study showed that these patients had a similar degree of liver damage to those with MAFLD. Another study conducted in South Korea included patients with non-metabolic risk NAFLD, and while the proportion of subjects was too small to compare to patients with MAFLD, they found that patients with non-metabolic risk NALFD had an increased adjusted risk of CVD comparable to patients with MAFLD[102]. Interestingly, patients with non-metabolic risk NAFLD were significantly younger than those with MAFLD, which may suggest that these patients are being identified before overt signs of metabolic dysfunction[102,107]. These studies highlight that this is a population that may require close monitoring.

CONCLUSION

The evidence clearly shows that the clinical burden of NAFLD/MAFLD extends well beyond liver-related morbidity and mortality and is associated with multiple extrahepatic complications [Figure 1]. While most studies have been observational and retrospective, these associations require greater clinical awareness so that providers can provide multidisciplinary screening to patients with this illness. Moreover, using MAFLD criteria may be more practical for identifying patients with fatty liver disease with a high risk of disease progression. The main therapeutic interventions to manage these manifestations should include lifestyle and dietary modification as well as the early approach to pharmaceutical treatments, particularly with lipid-lowering drugs and medications that augment insulin sensitivity. Future studies continue to be needed to better understand the mechanisms of these conditions and how we may potentially prevent them.

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Authors' contributions

Performed literature review and prepared the manuscript: Hassouneh R, Bhati C
Provided critical revisions: Hassouneh R, Siddiqui MS, Bhati C

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