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Comparison Between MAFLD and NAFLD; From Nomenclature to Clinical Outcomes: A Review Article.

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Abstract

As a result of the obesity epidemic, Nonalcoholic fatty liver disease (NAFLD) and its complications have increased among millions of people. Consequently, a group of experts recommended changing the term NAFLD to an inclusive terminology more reflective of the underlying pathogenesis; metabolic-associated fatty liver disease (MAFLD). This new term of MAFLD has its own disease epidemiology and clinical outcomes prompting efforts in studying its differences from NAFLD. This article discusses the rationale behind the nomenclature change, the main differences, and its clinical implications.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a well-established terminology that was first ¹³ coined by Ludwig and colleagues in 1980 (1) to describe fatty liver disease arising in the absence of significant alcohol intake. Over the last four decades, there has been a rapidly growing global burden of NAFLD and its subtype nonalcoholic steatohepatitis (NASH) (2) which has ¹ a potentially progressive course that can lead to cirrhosis, hepatocellular carcinoma, liver transplantation, and potential death (3). Currently, it is

one of the most common causes of liver disease worldwide affecting nearly a quarter of the population (4,5), with increased recognition and diagnosis in younger individuals (6).

The rising body of research on NAFLD/NASH has led to a better understanding of its underlying pathophysiology and its relationship with metabolic syndrome (7). Indeed, obesity and diabetes are the strongest risk factors associated with NAFLD/NASH. The public health and economic impacts of fatty liver disease have provoked extensive clinical trial activity targeted toward finding treatments for NASH among patients, regulators, and the biotechnology and pharmaceutical industries (8). Despite this rapidly evolving activity, NASH resolution, and fibrosis regression rates are only 20-30% (9).

In an effort to recognize the importance of metabolic abnormalities in an inclusive rather than an exclusive diagnosis, a group of international experts suggested a change of the name from NAFLD to metabolic-associated fatty liver disease (MAFLD) (10-12). The criteria to diagnose MAFLD are based on evidence of hepatic steatosis in addition to one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. Hence, MAFLD is more reflective of the heterogeneous pathogenesis of metabolic fatty liver diseases than NAFLD.

Immediately after the reappraisal of the nomenclature, multiple studies have been carried out to better understand the epidemiologic impact of this new terminology and its differences from NAFLD. For example, in a US population-based study by Donghee *et al*, it was found that MAFLD was associated with an increased risk of all-cause mortality after adjusting for metabolic risk factors, while NAFLD was not (13). Interestingly, insulin resistance and stage of fibrosis were predictors of increased liver mortality in NAFLD but not MAFLD whose liver-associated mortality is primarily driven by alcohol-associated liver disease (ALD) (14). However, an awareness of the

differences between these conditions and their early recognition remains poor among general practitioners (15). Given patients with fatty liver disease are usually asymptomatic, a high index of suspicion is required to make the diagnosis. Additionally, the clinical guidelines of MAFLD and NAFLD need to be updated on a rolling basis to keep up with the most recent management practices to prevent disease progression.

In this article, we will discuss the rationale and history behind the nomenclature change, as well as the core differences between MAFLD and NAFLD with respect to various clinical aspects in contemporary practice.

NOMENCLATURE AND HISTORY

"Fatty liver" was first described by Thomas Addison in 1836, who noted alcohol-related steatotic changes in liver histology (16,17). A couple of decades later in 1857, George Budd noted similar histology in inactive, obese patients with a high-fat diet and alcohol intake (18). Subsequently, Austin Flint observed a correlation between high carbohydrate intake with worsening steatosis and interval cirrhosis (19).

By the early 1900s, fatty liver changes unrelated to alcohol were well established but the mechanism of injury remained unclear. The role of diabetes as a risk factor for fatty liver began to be recognized by Pfluger in 1905 who noted an increase in hepatic steatosis in dogs who developed diabetes following total pancreatectomy (20). These findings were later extrapolated to humans in 1936 when diet and newly discovered insulin were suggested as treatments for hepatomegaly secondary to steatosis in patients with juvenile diabetes (21).

In 1979, Adler and Schaffner developed a schema for fatty liver disease in overweight non- and light drinkers which included "fatty liver", "fatty hepatitis", "fatty fibrosis", and "fatty cirrhosis" (22). A year later, fatty hepatitis would be designated "nonalcoholic steatohepatitis" (NASH) when Dr. Ludwig coins the term during characterizations of 20

Liver biopsies in primarily female patients with obesity and/or diabetes harboring lobular hepatitis, focal necrosis, and Mallory bodies on histology (1). Not long after in 1986, NASH was included in the spectrum of "non-alcoholic fatty liver disease" NAFLD by Schaffner and Thaler (23,24). Because the histology of alcohol-related and NAFLD steatosis is nearly indistinguishable from each other, NAFLD is a diagnosis of exclusion. Despite its name, NAFLD ironically includes patients with alcohol consumption of less than 14 and 7 drinks per week for men and women, respectively (25). Further blurring the lines between NAFLD and alcoholic liver disease are studies recognizing that heavy alcohol drinkers who are obese are more likely to develop cirrhosis than non-obese heavy drinkers (25,26).

As more studies on NAFLD arose in the 21st century, NASH reappeared consistently as part of a syndrome including obesity, arterial hypertension, insulin resistance, dyslipidemia, and/or cardiovascular disease (27,28). To better capture this syndrome, terms like "metabolic syndrome", "Syndrome X", "Insulin Resistance syndrome", and "the deadly quartet" were used (29). The need for a more unified definition was reiterated in 2005, considering that the name "NAFLD" in no way highlighted the underlying metabolic etiologies, associated risk factors, or the phenotypic heterogeneity of the disease (30). This paved the way for the introduction of the term "metabolic-associated fatty liver disease" (MAFLD) in 2011 and was subsequently adopted in 2020 by international consensus (10,12). Whereas NAFLD is defined as the presence of steatosis in > 5% of hepatocytes in the absence of other liver disease etiologies, MAFLD is defined by hepatic steatosis and components of the metabolic syndrome. MAFLD recognizes the positive determinants of the disease rather than defining the disease as the absence of other diseases, akin to the transition from "Non-Hepatitis A/Hepatitis B" to formally recognizing that entity as "Hepatitis C" (17). Just as simultaneous alcohol-related liver disease and viral hepatitis can vary in disease behavior and prognosis from either entity alone, MAFLD can analogously exist with other liver diseases, including

alcohol-related liver disease as patients with concomitant liver disease causes may have different outcomes than those of either disease apart (31–33).

EPIDEMIOLOGY

The adoption of the new inclusive nomenclature and diagnostic criteria for MAFLD (10) has called for multiple studies and (34–40) several meta-analyses estimating the prevalence of the disease under the new diagnostic criteria in the setting of rising numbers of patients with overweight, obesity and type 2 diabetes mellitus (41). These studies have estimated a global prevalence of 24.2% to 39.22% for MAFLD, comprising half of the overweight and obese adults (42), compared to a 15.3% to 33.86% for NAFLD (43).

MAFLD and NAFLD patients share clinical and pathogenic features leading to similarities in their overall prevalence. However, there are differences based on the presence of other liver diseases (i.e., alcoholic liver disease) that would still meet the criteria for MAFLD but not for NAFLD.

Compared to NAFLD, MAFLD is more likely to be diagnosed in Europe and Asia (44,45). In addition, a non-statistically significant trend toward increased MAFLD in Hispanic ethnicity was reported (13). Male sex, higher body mass index, lower high-density lipoprotein, higher triglyceride levels, and elevated aminotransferases carry a more significant correlation with MAFLD. Additionally, patients with MAFLD are more likely to have hypertension, diabetes mellitus, and chronic kidney disease (45). Higher aminotransferases and the presence of advanced liver fibrosis in ultrasound elastography and liver biopsy are more common in patients with MAFLD+/NAFLD- when compared to a similar population with MAFLD-/NAFLD+. Mild alcohol consumption has been noted to be associated with a higher prevalence of significant fibrosis in those patients (46).

An analysis of ³⁵ the National Health and Nutrition Examination Survey (NHANES)

database of the United States from 2017 to March 2020 found that the sample of patients with MAFLD had a higher prevalence of malignancies, coronary artery disease, myocardial infarction, heart failure, chronic pulmonary diseases, and psychiatric disorders, including sleep problems and depression when compared to the sample of patients with NAFLD; with the majority of these conditions being present in patients with more significant liver fibrosis (47).

PATHOPHYSIOLOGY AND RISK FACTORS

The exact pathophysiology of MAFLD\NAFLD remains largely unknown but a combination of genetic and environmental factors plays a crucial role. A contributing mechanism appears to be overnutrition and an increase in visceral adipose tissue (48) . Macrophages invade adipose tissue creating a pro-inflammatory state that promotes insulin resistance and excessive lipolysis enhancing the delivery of free fatty acids to the liver. An increased intrinsic lipogenesis overwhelms the liver's capacity to metabolize fatty acids resulting in dysfunction of the hepatocytes' mitochondria and endoplasmic reticulum (49). This dysfunction creates excessive oxidation of fatty acids and production of reactive oxygen species leading to hepatocyte death which promotes further inflammation and a vicious cycle (50)

Risk Factors

Figure 1 summarizes the risk factors involved in the development of MAFLD.

Role	of	Gut	Microbiota:
Gut microbiotas affect pro-inflammatory and anti-inflammatory balance in the liver by their effect on gut barrier function. Increased fructose intake leads to increased permeability of enteric cells. Fructokinase is an enzyme in the liver that is also highly expressed in the gut. Metabolism of fructose by fructokinase in the intestine can result in increased permeability of enteric cells' tight junctions. This leads to increased absorption of endotoxins into the portal circulation (51). Endotoxemia activates the			

innate immune system and the resulting inflammation ²² has been shown to have a role in the transition from steatosis to steatohepatitis and cirrhosis (52). Co-occurrence of fatty liver/NASH and alteration of gut microbiota and disruption of epithelial barrier do not prove causation. The cause or consequence relationship between gut microbiota and NAFLD remains unclear. Some authors have hypothesized that liver damage might precede alteration in gut microbiota and permeability of tight junctions of enteric cells (53).

Gut microbiota also plays an important role in the metabolism of carbohydrates. Gut microbacteria can ferment dietary sugars into alcohol that can enter the portal circulation increasing oxidative stress and inflammation in the liver (54). Studies have shown that in patients with MAFLD/NAFLD, there are significantly more gut bacteria associated with increased alcohol levels in the blood as compared to obese controls. Furthermore, some bacterial species like Escherichia, Enterobacter, Proteobacteria, and Bacteroides were found to be higher in NASH patients as compared to healthy controls(55–57).

Genetic

Factors:

□ PNPLA3 (patatin-like phospholipase domain containing 3) genetic variation has been associated with MAFLD/NAFLD independent of metabolic syndrome. This gene codes for I148M that hydrolyzes triglycerides ³⁶ in adipose tissue resulting in increased delivery of free fatty acids to the liver (58).

□ TM6SF2 (transmembrane 6 superfamily member 2) encodes E167K which is a lipid transporter on the endoplasmic reticulum. Genetic variation in this protein causes loss of function and increased deposition of triglycerides in the liver (59).

□ Upregulation of genes coding for SREBP1c ¹⁸ (sterol regulatory binding protein-1c), chREBP(carbohydrate responsive element binding protein), and PPAR-c (peroxisome proliferator-activated receptor gamma) results in increased de-novo lipogenesis (60) .

□ Other genes associated with MAFLD/NAFLD, and NASH are GCKR, MBOAT7, FAT/CD36, IGFBP2, PGC1alpha, SIRT1, miR-122, and miR-34. HSD17B13 appears to have a protective role (61).

Lifestyle and dietary habits
There is a close association between eating habits, obesity, and NAFLD. Increased consumption of refined carbohydrates, animal proteins, soft drinks, a high-fat diet, and fructose are closely associated with the development of MAFLD/ NAFLD (51). Carbohydrates with high glycemic index led to increased liver glycogen and fat content and increased serum triglycerides. The predominant mechanism is increased de Novo Lipogenesis (62). Saturated fatty acids and a diet high cholesterol in diet are associated with advanced fibrosis in MAFLD.

Patients with obesity and MAFLD/NAFLD have a more sedentary lifestyle (63,64). Finally, another modifiable factor associated with advanced fibrosis in MAFLD/ NAFLD is a smoking history of > 10 pack-years although the exact mechanism is unknown (65).

HISTOPATHOLOGY OF MAFLD/NAFLD AND NASH

The presence of >5% steatotic hepatocytes on liver biopsy is considered the minimum histologic criteria to diagnose fatty liver disease. Macrovesicular steatosis is the most common pattern although a mixed macro/microvesicular steatosis is seen in some cases as well. Pure microvesicular steatosis is not common. In MAFLD/NAFLD, small areas of lobular and portal inflammation and lipogranulomatous changes can be seen but features of hepatocyte injury and fibrosis are absent. Steatosis in adults has predilection to start in acinar zone 3 (perivenular) (66). During the histological examination, the involvement of hepatocytes is assessed in percentages: 0-33%-mild, 33-66%-moderate, and >66% hepatocyte involvement is categorized as severe steatosis (67).

On the other hand, histological features of NASH include steatosis and more severe

inflammation than mentioned above along with hepatocyte injury and fibrosis. Ballooning, apoptosis, and/or necrosis are typical features of hepatocyte injury. Ballooning is of particular ¹⁰ importance in NASH as its presence has been associated with a more aggressive disease and higher progression to cirrhosis (68). However, the recognition of hepatocyte ballooning has significant inter-observer variation (69). Hepatic apoptosis appears as acidophil bodies on liver biopsy. The Acidophil body index (acidophil bodies per mm² of tissue) serves as further confirmation of NASH when the diagnosis is uncertain.

¹⁰ Fibrosis in NASH typically starts in zone 3 and has a "chicken wire" pattern which entails the deposition of fibrotic material along sinusoids of zone 3 and around hepatocytes. As the disease progresses, bridging fibrosis and features of macronodular or mixed cirrhosis are seen (70). Other histological features that may be seen in the fatty liver include megamitochondria, iron deposition, glycogenated nuclei, and Mallory-Denk bodies (71).

DIAGNOSIS

With recently published guidelines, experts have refined the criteria for the diagnosis of MAFLD. The new criterion involves the presence of hepatic steatosis in adults and the presence of ⁵ one of the following: Type 2 diabetes mellitus, overweight/obesity, or metabolic dysregulation. Proposed diagnostic criteria for MAFLD are outlined in Figure 2.

Various modalities can be used to evaluate for the presence of hepatic steatosis including ultrasound, ultrasound elastography (i.e., transient elastography, acoustic radiation force impulse imaging, strain elastography), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), MRI-derived proton density fat fraction, histology and serum biomarkers (i.e., fatty liver index, hepatic steatosis index, NAFLD liver fat score). Recently, ultrasound

elastography has been increasingly used in clinical practice as compared to ultrasound. Ultrasound has limited sensitivity for detecting liver steatosis < 20% and performance may be suboptimal in patients with higher BMI >40 kg/m² (72–74).

Patients with normal body weight can still develop MAFLD. It was demonstrated in a recent study that patients with BMI <23 kg/m² have the same disease severity on histology when compared to patients with BMI >25 kg/m² (75). It is also known that metabolically unhealthy patients who are not obese and have MAFLD are at increased risk for cardiovascular morbidity and liver damage as compared to metabolically healthy individuals (76). Moreover, hepatic fat can be an early indicator of metabolic dysfunction. Therefore, in the new criteria in addition to diabetes mellitus and overweight/obesity, patients with lean/normal weight with metabolic dysregulation are included. In these patients, the presence of at least two metabolic risk factors is needed for diagnosis. The various risks include waist circumference ≥102/88 cm in caucasian men and women, blood pressure ≥130/85 mmHg, serum triglycerides ≥150 mg/dL, serum HDL cholesterol <40 mg/dL for men, and <50 mg/dL for women, prediabetes, serum high-sensitivity C-reactive protein level >2 mg/L and homeostasis model assessment of insulin resistance score ≥2.5. Patients who meet the criteria for MAFLD and also have one or other chronic liver condition causing fatty liver should be classified as having dual etiology (or more) fatty liver disease.

The experts have also suggested that disease severity in MAFLD should be defined by grade of activity and fibrosis stage similar to NAFLD and NASH. Patients without typical histology of steatohepatitis but have cirrhosis can be defined as MAFLD-related cirrhosis if there is past or present evidence of metabolic dysregulation risk factors for MAFLD with at least one of the following: MAFLD on a previous liver biopsy or documentation of steatosis by hepatic imaging (77).

MANAGEMENT

Despite the high worldwide prevalence, significant healthcare burden, and costs, there are currently no FDA-approved treatments for NAFLD. The 2018 AASLD practice guidelines on the treatment of NAFLD are based on the following four principles: (1) Effective diet and lifestyle modifications to achieve weight loss, (2) Identification and correction of underlying cardiometabolic risk factors, (3) Pharmacological therapy primarily aimed at improving hepatic steatosis/fibrosis and (4) Close monitoring and prevention of complications of NAFLD (78).

Obesity and diabetes mellitus constitute the major pathophysiological risk factors for NAFLD, and drugs that modify or alter glucose metabolism and/ or body weight comprise the current mainstay therapies focused on improving clinical outcomes, such as the degree of hepatic inflammation and/or fibrosis (3). Over the past several years, multiple potential treatment options have been extensively investigated in this regard. These include insulin sensitizers and ⁵ glucose-lowering drugs (such as pioglitazone, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose co-transporter-2 (SGLT-2) inhibitors), antioxidants (such as vitamin E), lipid-lowering drugs (statins), farnesoid X activated receptor (FXR) agonists and others.

The following section focuses on the different available treatment strategies for NAFLD highlighting our understanding of key elements regarding therapy.

Lifestyle modifications

Lifestyle modifications in the form of diet, exercise, and weight loss remain the cornerstone and first-line recommendation for treating patients with NAFLD/MAFLD (79). Weight loss has by far the best evidence thus far as an independent predictor for improvement in histopathological features of NASH. The best likelihood for sustained weight loss appears to be a combination of a hypocaloric diet (decrease in caloric intake by 500-1000 kcal/ day) and moderate-intensity exercise (80–82). While weight loss of a minimum of 7%-10% of body weight is required to improve a majority of histopathological features of NASH, losing body weight by at least 3%-5 % results in improved hepatic steatosis (83). These findings were observed in a 12-month

prospective study that revealed a dose-response curve with significant improvement in histopathology with a greater degree of weight loss. Patients who achieved greater than 10 % weight loss had improvement in all features of NASH, including portal inflammation and fibrosis. Importantly, patients who lost at least 5% of body weight stabilized or improved fibrosis in 94% of the cases (84). Other lifestyle modifications may result in benefits as physical activity of more than 150 minutes/week or an increase in activity level by more than 60 minutes/week have been associated with a decrease in serum aminotransferases independent of weight loss (85). On the other hand, a Mediterranean diet containing low saturated fat and high polyunsaturated and monounsaturated fats is found to be beneficial (86).

Insulin sensitizers

Pioglitazone, a peroxisome proliferator-activated receptor agonist, is a thiazolidinedione derivative that modulates glucose and lipid metabolism. It ameliorates insulin resistance in addition to creating positive effects on vascular biology, adipose tissue function, and inflammation (80). These unique properties of pioglitazone led to immense interest among researchers in exploring its potential role in patients with NAFLD/MAFLD. A single-center clinical trial performed almost a decade ago suggested that pioglitazone at a dose of 45 mg daily in addition to a hypocaloric diet improved histological findings of steatosis, ballooning necrosis, and inflammation. However, the degree of fibrosis was no different from that of the placebo group (87,88). More recently, in another study by Cusi *et al*, pioglitazone treatment not only improved the NAFLD activity score and metabolic parameters but also caused significant regression of liver fibrosis. These effects were observed after 36 mo of therapy with no significant difference in adverse events except for net weight gain of > 5.0 kg when compared to patients who did not receive pioglitazone (89).

Apart from the diabetic population, pioglitazone has also proven to be quite effective in NASH patients without DM. In the Pioglitazone vs Vitamin E vs Placebo for the

Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, a substantially higher percentage of patients who received pioglitazone achieved resolution of NASH. However, the primary endpoint of at least ≥ 2 -point improvement in NAFLD activity score did not reach predetermined statistical significance (90). Hence, although pioglitazone is advocated for T2DM patients with biopsy-proven NASH, its use in the non-diabetic population still remains a debate among hepatologists.

Antioxidants

A key mechanism of hepatocellular inflammation and injury in patients with NASH is oxidative stress. Vitamin E is an antioxidant that has been investigated in multiple studies as a potential treatment option for NAFLD. Initial studies demonstrated improved steatosis and inflammation with vitamin E administration but most of these were underpowered. Furthermore, it was challenging to compare data among the available studies largely due to significant heterogeneity regarding the dose and formulation of vitamin E, inclusion criteria, and concomitant use of other antioxidants or drugs.

More recently, the PIVENS clinical trial revealed that oral α -tocopherol, administered at a dose of 800IU/day, results in considerable improvement in liver histology at 96 wk in non-diabetic biopsy-proven NASH patients (91). These findings are substantiated by another US-based (TONIC) clinical trial that reported a significantly higher percentage of resolution of steatohepatitis in pediatric patients with NAFLD (92). Despite similar convincing data from a few other studies, a high dose of vitamin E has been associated with increased all-cause mortality and a higher risk of prostate cancer with no improvement in fibrosis (93,94). As such, the general consensus at this time includes consideration of vitamin E therapy in non-diabetic NAFLD/MAFLD patients following a patient-centered individualized approach. It is currently not recommended for treating NASH patients with DM or cirrhosis.

Statins

NAFLD/MAFLD are associated with metabolic syndrome that constitutes HTN, T2DM, dyslipidemia, and obesity. Current society guidelines recommend treating associated comorbidities in NAFLD patients in addition to treating the liver disease itself. Treatment with statins was associated with lower steatosis, inflammation, and fibrosis in NASH patients (95–98). Moreover, ⁵ patients who received statins had substantially lower cardiovascular mortality without any significant liver-related adverse events. A nationwide nested case-control study from South Korea including 11,593,409 patients from a nationwide database suggested that statins lower the risk of occurrence of NAFLD independent of accompanying T2DM (99). In addition to the noted benefit in reducing the incidence of NAFLD, this study also highlighted that statin usage also prevented the progression to advanced fibrosis in patients with pre-existing fatty liver disease with an adjusted odds ratio of (AOR) of 0.43; 95%CI 0.42–0.44). It is therefore reasonable to initiate anti-lipid therapy for patients that meet treatment criteria. While the concern for statin-induced hepatotoxicity prevails, severe liver injury from statins is extremely rare regardless of baseline elevation of transaminases or the presence of underlying chronic liver disease.

Gastrointestinal hormones (Incretins) and newer antidiabetic agents

³³ ⁹ Glucagon-like peptide (GLP)-1 is a gut-derived incretin hormone secreted in response to oral food intake. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) constitute a novel class of well-established anti-diabetic drugs with encouraging data on the utility of these agents in treating obesity, preventing cardiovascular diseases, improving kidney function, and lowering mortality in patients with T2DM (99). A growing body of evidence suggests that GLP-1RAs exert anti-NASH activity through several mechanisms such as increased insulin secretion, delayed gastric emptying, modulation of appetite, promoting fat redistribution, and reduced fat accumulation in the hepatocytes. A landmark UK-based 48-week multicenter RCT (LEAN) revealed that NASH patients treated with liraglutide had a higher resolution of biopsy-proven

steatohepatitis with no worsening of fibrosis when compared with placebo. Of those patients treated with liraglutide, 39% achieved resolution of NASH as opposed to only 9% in the placebo group. (Relative risk 4.3 [95%CI 1.0–17.7]; $P = 0.019$). These findings were supported by a Japanese pilot study (LEAN-J) where treatment with liraglutide was associated with significantly improved liver function and histological features in NASH patients with glucose intolerance (100).

Semaglutide, another GLP-1RA is currently approved for the treatment of T2DM and under extensive evaluation for weight loss (101). Although semaglutide shares its mechanism of action with liraglutide, it has gained rapid recognition for its more pronounced metabolic effects with regard to improved glycemic control, reduced cardiovascular risk, and effective weight loss (102). A placebo-controlled 72-week trial suggested that once-daily subcutaneous semaglutide administered at a dose of 0.4 mg results in a higher likelihood of NASH resolution without worsening of underlying fibrosis in addition to a dose-dependent weight loss (103–105). Despite these encouraging results, the rate of fibrosis regression was comparable between the treatment and placebo groups, and a higher number of patients treated with semaglutide experienced gastrointestinal side effects such as nausea and vomiting (106). More refined data on histological outcomes and adverse effects will be required before the widespread use of semaglutide in routine clinical practice for the sole treatment of NAFLD/MAFLD.

Renal sodium-glucose co-transporter 2 (SGLT2) inhibitors are another class of anti-diabetic agents that work through the inhibition of glucose reabsorption in the kidneys in combination with enhanced urinary excretion of excess glucose. The consequent glucosuria results in lower blood glucose levels and eventual weight loss. A Malaysian open-label pilot study demonstrated that empagliflozin significantly improved steatosis, hepatocyte ballooning, and fibrosis in a small cohort of biopsy-proven NASH patients with T2DM. Interestingly, these effects were noted after a short duration of

treatment (6 months) and remained significant when compared with a historical placebo group at 48 wk (107). Another meta-analysis of six RCTs including 309 patients by Xing *et al* reported a positive effect of SGLT2 inhibitors in patients with NAFLD and T2DM. Patients treated with SGLT2 inhibitors achieved significant weight loss in addition to lower liver fat and improved alanine transaminase levels (108). Apart from the encouraging evidence on anti-NASH metabolic effects, several other studies have demonstrated improved cardiovascular outcomes in T2DM patients treated with SGLT2 inhibitors. CVD currently remains ²⁴ the most common cause of death in patients with NAFLD, thus highlighting the added benefit of reduced cardiovascular deaths on the overall prognosis of NAFLD patients. Based on the aforementioned data, GLP-1 RAs, and SGLT2 inhibitors, either as monotherapy or combination therapy appear to be promising treatment options for NAFLD/MAFLD.

Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin, vildagliptin, and saxagliptin; ¹ slow the inactivation of incretin hormones such as GLP-1 and glucose-dependent insulintropic polypeptide (GIP) by selective inhibition of DPP-4 enzymes. As such, these agents indirectly increase insulin synthesis and lower glucagon levels through the prolonged action of GLP-1. Despite the observed benefit in early studies, these drugs have failed to significantly alter the histological profile in diabetic patients with NAFLD/MAFLD (110). Possible explanations for the lack of clinical benefit postulated thus far in the literature include non-selective inhibition of both GLP-1 and GIP enzymes that could result in counterproductive effects on weight and fatty liver, questionable need for higher dosages in human models, and short study duration (3-6 mo). DPP-4 inhibitors are currently not recommended as therapies for patients with hepatic steatosis or steatohepatitis.

¹ Farnesoid X receptor (FXR) agonists

The Farnesoid X receptor is a ligand-activated nuclear receptor that is a key regulator for bile acid signaling and metabolism (109). In recent years, FXR has gained

considerable interest as a potential therapeutic target for the treatment of NASH. FXR activation leads to the inhibition of bile acid synthesis and increased conjugation, transport, and excretion of bile acids. These changes ultimately result in decreased cholestasis with protection of the liver from the deleterious effect of bile accumulation (110).

²⁷ Obeticholic acid (OCA), a synthetic 6 α -ethyl derivative of natural human bile acid, chenodeoxycholic acid regulates lipid and glucose metabolism through stimulation and upregulation of FXR activity. The FLINT trial for the treatment of NASH revealed that OCA administered at a dose of 25 mg daily improved multiple liver histology parameters in nearly half (45%) of the patients at 72 wk follow-up (111). These findings were noted despite the study including a significant proportion of patients with T2DM and vitamin E non-responders. This landmark study underscored the clinical relevance of FXR agonists in improving hepatic insulin sensitivity and inhibition of lipogenesis in the NASH population. These findings were later corroborated by another phase 3 study (REGENERATE) that evaluated the efficacy of OCA in ⁹ 2400 patients with NASH including 2100 patients with stage 2 or 3 Liver fibrosis. This study revealed that a significantly higher proportion of patients treated with either 10 mg or 25 mg of OCA achieved regression of fibrosis compared to placebo but there was no difference between the groups in regards to complete resolution of steatohepatitis (112). While the most common adverse event was mild to moderate pruritis, the incidence of serious adverse events was similar across the groups.

Tropifexor is a novel non-bile acid agonist of FXR that has demonstrated potent *in vivo* activity in animal models. This drug is believed to be highly efficacious in upregulating FXR target genes even at very low doses and has currently progressed into clinical development. Several phase 2 human clinical trials on the safety and efficacy of Tropifexor in patients with NASH are under evaluation (113,114).

Bariatric Surgery

Weight loss through lifestyle modifications is often challenging to achieve or sustain due to the substantial need for strict adherence and patient compliance. Bariatric surgery may be opted to achieve weight loss in select patients as it helps improve lipid metabolism and inflammatory pathways involved in the pathophysiology of NAFLD. National Institute of Health consensus criteria currently recommends bariatric surgery for patients with a BMI of 35 to 39.9 kg/m² with any severe obesity-related comorbidity such as T2DM, HTN, NAFLD/MAFLD, and/or NASH.

A systematic review appraising 29 studies by Bower *et al* showed significant improvement in several histological (steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis) and biochemical parameters of NAFLD following bariatric surgery. A more recent meta-analysis spanning 21 studies with a total of 2374 patients reaffirmed the noted benefit of bariatric surgery in patients with NAFLD with almost 88 % of patients achieving improvement in steatosis and 30% having an improvement or resolution in liver fibrosis (115).

Apart from the long-term sustained weight loss, bariatric surgery also ameliorates NAFLD/MAFLD through multiple other mechanisms including but not limited to enhanced secretion of satiety hormones, variation in dietary habits, improvement in T2DM, alterations in bile acid homeostasis, modification of gut microbiome (116). Further longitudinal controlled studies are needed to delineate the benefits and type of bariatric surgery as a therapy for those with NAFLD/MAFLD.

Although a few case series on bariatric surgery suggest an acceptable safety profile of these procedures in patients with cirrhosis, a vast majority of these studies included patients with well-compensated cirrhosis. More recently, evolving data demonstrated a modest but nonnegligible risk of complications following bariatric surgery in patients with more advanced cirrhosis. The common complications reported in such patients undergoing bariatric surgery include anastomotic leak, prolonged hospital stay, prolonged intubation, ileus, higher need for blood transfusion, and less commonly sepsis and fulminant hepatic failure (117–120). As such, bariatric surgery is currently

preferred for patients with Child A cirrhosis due to the acceptable risk of complications from surgical and hepatic factors (121–123).

Gut Microbiome

Several gut microbiota is known to interact with carbohydrate and lipid metabolism by regulating homeostasis, immunity, and several metabolic pathways. Gut microbiome dysbiosis increases gut permeability thereby increasing exposure of hepatocytes to endotoxins that eventually can lead to hepatocyte inflammation and fibrosis (124). Studies from animal models suggest that oral administration of prebiotics, probiotics, and synbiotics improves lipid metabolism, dysbiosis, insulin resistance, and hypercholesterolemia associated with hepatic inflammation by altering multiple genes involved in B-oxidation and lipogenesis.

A randomized controlled trial by Vrieze *et al* suggested that FMT improved insulin resistance in Caucasian males with metabolic syndrome thus raising a potential therapeutic option for NAFLD/MAFLD (125). Needless to say, there is a dire need for more improved and standardized methods of gut microbiome analysis along with a better ¹ understanding of interactions between diet, dysbiosis, and environmental factors and their impact on the gut-liver axis to help devise effective and targeted treatment options.

Emerging Therapies and Future Directives

Multiple other studies recently evaluated anti-fibrotic and anti-apoptotic therapies as unique treatment options for patients with NAFLD (126). Albeit the intriguing preliminary results, these studies failed to show considerable clinical benefit in phase 2/3 clinical trials largely due to the limited utility of these drugs in the early stages of NAFLD. The introduction of MAFLD and its diagnostic criteria appear promising as it would potentially allow the incorporation of pharmacotherapeutic agents used in the treatment of metabolic syndrome at an earlier stage in the development of NAFLD.

OUTCOMES

Advanced

fibrosis

If left untreated, patients with NAFLD are at risk of advanced fibrosis. A meta-analysis encompassing 11 studies with 411 patients with biopsy-proven NASH showed that 33.6% of patients have eventual fibrosis progression. ² The annual fibrosis progression rate in patients with NAFLD and stage 0 fibrosis at baseline was 0.07 stages (95%CI, 0.02-0.11 stages), compared with 0.14 stages in patients with NASH (95%CI, 0.07-0.21 stages). These findings correspond to 1 stage of progression over 14.3 years for patients with NAFLD (95%CI, 9.1-50.0 y) and 7.1 years for patients with NASH (95%CI, 4.8-14.3 y) (127,128). While baseline demographics such as BMI, age, history of alcohol use, and T2DM play a major role in determining progression to advanced fibrosis, disease-related risk factors such as elevated baseline transaminases, presence of necroinflammation, ballooning degeneration, and Mallory hyaline on histology are also known to contribute to disease progression (70,129-132).

Advanced fibrosis eventually leads to hepatic decompensation from the development of cirrhosis and end-stage liver disease (2.69 events per 100 person-years). ²⁹ Liver-related mortality is the third cause of death in patients with NAFLD (133).

Hepatocellular

Carcinoma

(HCC)

Cirrhosis secondary to NAFLD/MAFLD does confer a higher risk of HCC than those without cirrhosis (134). Interestingly, the presence of fatty liver disease also confers a higher risk of HCC even in the absence of cirrhosis. Past data suggests that patients with non-cirrhotic NAFLD have a modest risk of HCC when compared to the general population (135,136). This risk is notably higher in male patients > 65 years with a smoking history, co-existing DM, and/or baseline elevation of ALT (137-144). As such, performing routine periodic surveillance of these patients with abdominal imaging and measuring alpha-fetoprotein levels could be considered.

Cardiovascular disease is the most common cause of death among NAFLD/MAFLD patients followed by extrahepatic malignancies (145). MAFLD is the hepatic manifestation of metabolic syndrome; as such, a vast majority of these patients have additional cardiometabolic risk factors. Indeed, when compared to NAFLD patients a nationwide database study from China demonstrated that MAFLD patients had an increased medium/high 10-year CVD risk according to Framingham risk score (1064 (29.92%) vs. 1022 (26.37%), $P < 0.005$) (146). While steatosis confers a lesser risk of CVD compared to steatohepatitis, the overall individual risk of CVD ultimately stems from the combination of the stage of fatty liver disease and the presence of other cardiometabolic risk factors. Patients with steatohepatitis and /or advanced fibrosis and those with co-existing T2DM are considered special risk groups for significant cardiovascular events and mortality (147).

In addition to coronary atherosclerosis, NAFLD/MAFLD patients are at a higher risk of cardiac arrhythmias such as atrial fibrillation and ventricular arrhythmias. Furthermore, many NAFLD patients have left ventricular systolic and/or diastolic dysfunction, aortic valve sclerosis, and mitral calcifications (148-153). While several studies have revealed a higher burden of cardiorenal disease in patients with MAFLD, a recent meta-analysis by Wen *et al* evaluating ten studies suggested a 1.95 times higher incidence of CVD or CVD-related mortality in the MAFLD patients than in the control group (146,154,155). Therefore, a thoughtful risk assessment of CVD, evaluation for subclinical atherosclerosis, and presumptive diagnostic studies and interventions for high-risk patients are needed to lower the high global disease burden of CVD in NAFLD/MAFLD patients. Studies evaluating the association of NAFLD/MAFLD, and CVD are listed in Table 1 for further review.

Table 1. Studies evaluating the risk of CVD in patients with NAFLD and MAFLD

Study

Number of patients

Type of Study

Outcome measure

Results

Liang *et al* (168)

6873

Cohort Study with a 4.6 year follow up

Associations of MAFLD and NAFLD with DM, CKD, and CVD

⁸

MAFLD was associated with higher risks of CVD (hazard ratio 1.44; 95%CI, 1.15-1.81)

Similar associations were observed for NAFLD, except for a higher incidence of DM in

MAFLD patients with HBV infection and excess alcohol consumption

Wang *et al* (169)

12183

Cross-sectional study

(SPECT – China)

Compare the cardiovascular and renal burden between MAFLD and NAFLD patients.

The odds ratio of previous CVD was higher in patients with MAFLD. (male 1.50 (1.22,1.85) vs 1.35 (1.1,1.66); female 1.58 (1.33,1.87) vs 1.45 (1.22,1.72)

Zhang *et al* (170)

19,617

Nationwide database study

¹

The burden of CKD and CVD in adults with MAFLD and NAFLD.

The cardiorenal burden may be greater for MAFLD than for NAFLD.

Lee *et al.* (171)

8,962,813

Cohort study with a 10.1 year follow up

Association of MAFLD and NAFLD with CVD

MAFLD patients have a higher risk of CKD when compared to NAFLD (1.43 (1.41 – 1.45) vs. 1.09 (1.03 – 1.15)

Yoneda *et al* (172)

2,452,949

Nationwide database study

Association of MAFLD and NAFLD with CVD

The incidence rates of CVD were 2.82 (95%CI 2.64-3.01) per 1000 person-years in the NAFLD groups and 2.69 (95%CI 2.55-2.83) per 1000 person-years in the MAFLD groups.

Guerreiro *et al* (173)

1233

Retrospective cross-sectional study

Compare CVR and risk of CVD between patients with NAFLD and MAFLD.

In patients with MAFLD and NAFLD, CVR was intermediate/high (36.4 and 25.7%, $P = 0.209$) and CVD occurred in 20.1 and 12.8% ($P = 0.137$) of the cases, respectively, with no influence of liver injury severity.

Zhang *et al* (156)

11,673

Retrospective study

Compare the risk of CVD between patients with NAFLD and MAFLD.

MAFLD was more significant than NAFLD in medium/high 10-year CVD risk (according to Framingham risk score) (1064 (29.92%) vs. 1022 (26.37%), $P < 0.005$).

Wen *et al* (146)

Meta-analysis

Investigate the risk of CVD incidence or CVD-related mortality in patients diagnosed with MAFLD and NAFLD

The incidence of CVD or CVD mortality was 1.95 times higher in the MAFLD group than in the control group.

4

The risk of CVD or death from CVD was significantly higher in the MAFLD-only group than in the NAFLD-only group, with an RR of 2.57 (95%CI 1.41-4.71; I² = 78%, P = 0.002)

Guo *et al* (174)

12,794

Cohort study

Study the relationship between MAFLD and incident CVD.

1

The incidence of CVD in the patients with MAFLD was significantly higher than that in the non-MAFLD patients (18.38% vs. 9.02%, $p \leq 0.001$; aHR = 1.37, 95%CI = 1.20-1.56)

Moon *et al* (175)

8,919

Cohort study

7

Effect of MAFLD on future mortality and CVD using a prospective community-based cohort study.

7

T2DM in MAFLD increased the risk of both mortality (HR, 2.07; 95%CI, 1.52 to 2.81) and CVD (HR, 1.42; 95%CI, 1.09 to 1.85)

Zou *et al* (176)

513

Cross-sectional study

Prevalence of MAFLD and its relationship with CVD risks in RA patients

1

RA patients with MAFLD had a higher rate of CVD events (17.3 vs. 9.2%) and a higher proportion of high estimated 10-year CVD risk (55.5 vs. 26.1%) than those without.

Chronic kidney disease (CKD)

CKD is a worldwide public health problem affecting up to 10 -15% of the general population. More recently, ³² a strong association between NAFLD/MAFLD and CKD has been established independent of commonly co-existing diseases such as obesity, HTN, and T2DM. A meta-analysis by Targher *et al* suggested that NAFLD patients had a considerably higher risk of incident CKD than those without NAFLD. (OR 1.87; 95%CI

1.3-4.1) (156). Few other studies also demonstrated similar findings even after adjustment for potential confounders such as age, sex, BMI, and other well-established metabolic risk factors (157). Currently postulated etiologies include upregulation of the renin-angiotensin system and impairment of antioxidant defense. Other associated factors that link NAFLD/MAFLD and CKD include metabolic syndrome, platelet activation, dysbiosis, unhealthy eating habits, and aging (158,159). Since the advent of the new diagnostic criteria for MAFLD, numerous studies have suggested a significant association of MAFLD with CKD, particularly in patients with concomitant DM. A nationwide cohort study evaluating 268,946 patients by Jung *et al* revealed a higher adjusted hazard ratio (aHR) for incident CKD in MAFLD patients when compared to those with NAFLD (1.18 (95%CI, 1.01-1.39; *P* = 0.040) (160) . Studies evaluating the association of NAFLD/MAFLD, and CKD are listed in Table 2 for further review.

Table 2. Studies evaluating the risk of CKD in patients with NAFLD and MAFLD

Study
Number of patients
Type of Study
Outcome measure
Results
Sun <i>et al</i> (177)
12,571
Cross-sectional study
Association between MAFLD and NALFD with CKD
MAFLD patients had lower GFR (74.96 ± 18.21) and higher prevalence of CKD (29.6%)
Liang <i>et al</i> (168)

6873

Cohort Study with a 4.6 year follow up

Associations of MAFLD and NAFLD with T2DM, CKD, and CVD

⁸ MAFLD was associated with a higher risk of CKD (RR 1.64; 95%CI, 1.39-1.94)

Similar associations were observed for NAFLD, except for a higher incidence of DM in MAFLD patients with HBV infection and excess alcohol consumption.

Deng *et al* (178)

4869

A cross-sectional study from the NHANES database 2017 – 2018

Association between MAFLD and CKD

¹ Higher prevalence of CKD in MAFLD subjects than in non-MALFD subjects (22.2% vs. 19.1, $P = 0.048$)

Wang *et al* (169)

12183

Cross-sectional study (SPECT – China)

Compare the cardiovascular and renal burden between MAFLD and NAFLD patients.

OR of CKD was higher in males with NAFLD [CKD: 1.44 (1.05,1.96) vs. 1.56 (1.14,2.12)] than those with MAFLD

Su *et al* (179)

5,594

Cross-sectional study

Association between MAFLD and CKD

² MAFLD was independently associated with an increased risk of CKD (odds ratio [OR]: 1.35, 95% CI: 1.09-1.67)

² MAFLD with T2DM had significant associations with increased risk of CKD (OR: 2.85, 95% CI: 2.24-3.63), as well as increased eGFR and UACR

Hu *et al* (180)

15,010

Cross-sectional study

Association between MAFLD and CKD

⁶ MAFLD was significantly associated with a higher CKD prevalence (OR 1.715, 95%CI 1.389-2.117, $p < 0.001$)

MAFLD alone was not an independent risk factor for CKD

Hashimoto *et al* (181)

27,371

Cross-sectional study

Association between FLD and MAFLD with CKD

⁶ MAFLD was associated with the risk of incident CKD (adjusted hazard ratio 1.24 [1.14-1.36], $P < 0.001$), whereas FLD without MD was not (1.11 [0.85-1.41], $P = 0.433$)

Zhang *et al* (170)

19,617

A retrospective nationwide cohort study

¹ Renal burdens in adults with MAFLD and NAFLD

The cardiorenal burden may be greater for MAFLD than for NAFLD

Jung *et al* (160)

268,946

A retrospective nationwide cohort study

Association between MAFLD and NAFLD with CKD

¹ The adjusted hazard ratio (aHR) for incident CKD in MAFLD was 1.18 (95%CI, 1.01-1.39; $P = 0.040$) compared to those with NAFLD

Tanaka *et al* (182)

13,159

Retrospective single-center study

Associations of FL, NAFLD, and MAFLD with the development of CKD

¹² MAFLD (HR [95%CI]: 1.12 [1.02-1.26], $P = 0.027$), but not FL or NAFLD, was an independent risk factor for incident CKD.

Extrahepatic

malignancies

Metabolic syndrome is a well-known risk factor for colorectal cancer (161). Consequently, several studies have suggested that NASH is independently associated with a heightened risk of colorectal adenomas and advanced colonic neoplasms. Of late, Fukugana *et al* ²³ suggested that MAFLD identifies colorectal adenomas more accurately than NAFLD (OR 3.191; 95%CI 1.494-7.070; $P = 0.003$), with a particularly high risk of colonic adenomas in individuals with non-obese MAFLD (OR 3.351; 95%CI 1.589-7.262; $p \leq 0.001$) (162). Whether NAFLD/MAFLD directly contributes to colon cancer or if colon cancer occurs due to shared metabolic risk factors remains unclear. Patients with NAFLD are believed to have lower adiponectin levels that result in lesser endothelial cell apoptosis and increased proliferation of neoplastic cells, supporting the former possibility of a direct carcinogenic effect of steatohepatitis. Moreover, increased risk of other extrahepatic malignancies such as gastric cancer (163), pancreatic cancer (164), esophageal cancer (165), breast cancer (166), and prostate cancer (167) are noted in patients with NAFLD.

Others

²⁰ Other commonly associated conditions in patients with NAFLD/MAFLD include gastroesophageal reflux disease, obstructive sleep apnea syndrome, psychological dysfunction, hypothyroidism, growth hormone deficiency, and polycystic ovarian syndrome. Despite the substantial research and evidence revealing an association between NAFLD/MAFLD and the aforementioned extrahepatic complications, there are no standardized screening recommendations for these conditions in these patient populations. Careful surveillance and proactive treatment of these extrahepatic complications might improve overall outcomes, morbidity, and mortality in patients with NAFLD/MAFLD.

CONCLUSION

The change in nomenclature has impacted the current understanding of fatty liver disease and stimulated more interest from the research community to better understand and treat this silent but deadly condition. As a limitation of our review, it only provides information about what is known and has been published to date as data on MAFLD is emerging. As new evidence becomes available, practitioners will be better able to tackle this disease and prevent its deleterious complications.

17%

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