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Editorial: International Consensus Recommendations to Replace the Terminology of Non-Alcoholic Fatty Liver Disease (NAFLD) with Metabolic-Associated Fatty Liver Disease (MAFLD)

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Abstract In 2020, international consensus guidelines recommended the renaming of non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD), supported by diagnostic criteria. MAFLD affects up to 25% of the global population. However, the rates of MAFLD are likely to be underestimated due to the increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity. Within the next decade, MAFLD has been projected to become a major cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide, as well as the most common indication for liver transplantation in the US. This transition in terminology and clinical criteria may increase momentum and clinical evidence at multiple levels, including patient diagnosis, management, and care, and provide the basis for new research areas and clinical development for therapeutics. The diagnostic criteria for MAFLD are practical, simple, and superior to the existing NAFLD criteria for identifying patients at increased risk of developing progressive liver disease. This Editorial aims to present the historical evolution of the terminology for fatty liver disease and the advantages of diagnosis, patient management, and future research on MAFLD.

Keywords: **Editorial • Terminology as Topic • Non-alcoholic Fatty Liver Disease • Fatty Liver • Diabetes Mellitus, Type 2**

Background

The evolution of medical terminology has included renaming to remove confusing, outdated, or inaccurate nomenclature and remove eponyms. For example, Wegener's granulomatosis is now more commonly termed, granulomatosis with polyangiitis, which is more pathophysiologically relevant [1]. Recently, primary biliary cholangitis has been recommended to replace primary biliary cirrhosis to reduce the social stigma associated with the word, cirrhosis [2]. More recently, Allen et al. [3] suggested that the medical term, non-communicable disease, which includes cancer, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and mental health conditions, was inadequate. These authors have suggested that renaming this broad collective medical name would improve awareness and management of specific diseases [2]. Non-alcoholic fatty liver disease (NAFLD), which is now called metabolic-associated fatty liver disease (MAFLD), affects up to 25% of the global population [4]. In Latin America, MAFLD affects 31% of the population, including 35.2% in Brazil, 23% in Chile, 17% in Mexico, and 26.6% in Colombia [5]. However, the prevalence of MAFLD is likely to be underestimated due to the increasing incidence of type 2 diabetes mellitus (T2DM), obesity, and chronic liver disease, including liver cirrhosis [6], and hepatocellular carcinoma (HCC) in these countries [7].

MAFLD is now predicted to become a major cause of cirrhosis and HCC worldwide [8]. In the US, the prevalence of HCC has been predicted to increase by 122% by 2030 [8]. In the US, MAFLD is predicted to become the most common indication for liver transplantation within the next decade [9]. A major concern is that in South America, almost 60% of patients with MAFLD have also been diagnosed with progressive non-alcoholic steatohepatitis (NASH), with an overall prevalence of NASH in the Latin American population reported to be between 6-18% [10]. In 2020, an International Consensus Panel proposed the new terminology of MAFLD, based on published evidence [11]. This new terminology highlights the importance of metabolic factors in the development and progression of this disease [11]. MAFLD is diagnosed on clinical criteria that are routinely evaluated in

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high-prevalence populations [11.12]. In contrast, the diagnosis of NAFLD has been a diagnosis of exclusion, which has the disadvantages of challenging diagnostic services and reducing disease awareness [12]. In Mexico, the lack of awareness of MAFLD by physicians has been associated with misdiagnosis and inappropriate treatment and has underestimated the serious consequences of this disease [12]. There has been a high level of acceptance of the new name among patients [13], primary care physicians [14], nurses, and allied health professionals [15]. This acceptance of the use of MAFLD as a medical term may be due to its clinical relevance and its value in clinical communication [15]. The acceptance of renaming NAFLD to MAFLD has importance for improving patient care as MAFLD his now increasingly used by clinical multidisciplinary medical teams [16].

This Editorial aims to present the historical evolution of the medical terminology for fatty liver disease to the current debates surrounding the renaming of NAFLD to MAFLD and the evidence that supports the new terminology (**Figure 1**) [16,17]. An understanding of the medical history of the evolution of these medical terms may improve the understanding of the pathophysiology of liver disease and improve research. The role of consensus guidelines from international experts in hepatology has an important role in advancing clinical practice and research, even during a time when international meetings and discussions are held remotely and online [11].

The Historical Evolution of the Terminology of Fatty Liver Disease and the Current International Consensus on the Renaming of NAFLD to MAFLD

In 1979, during the 30th Annual Meeting of the American Association for Study of Liver Diseases (AASLD) [18], a study group that included Miller, Ishimaru, and Klatskin presented their observations on the non-alcoholic liver [19]. After several weeks, Adler and Schaffner showed that fatty liver, fatty hepatitis, fatty fibrosis, and fatty cirrhosis were equally prevalent in overweight patients, and T2DM was commonly diagnosed [19,20]. Also, the terminology for fatty liver, hepatitis, and cirrhosis and their assessment were established [20]. Several months later, Ludwig and colleagues at the Mayo Clinic described the condition of non-alcoholic steatohepatitis (NASH) [21]. In 1986, the medical term, NAFLD, was proposed by Schaffner [22]. The definition of NAFLD remained almost unchanged since 1986, as hepatic steatosis that affects at least 5% of the liver cells in individuals who consume minimal or no alcohol without a secondary cause of hepatic steatosis, such as viral hepatitis, medications, or lipodystrophy [23].

In 2002, during the AASLD Clinical Single Topic Conference on NASH, the alternative term, metabolic forms of NASH,

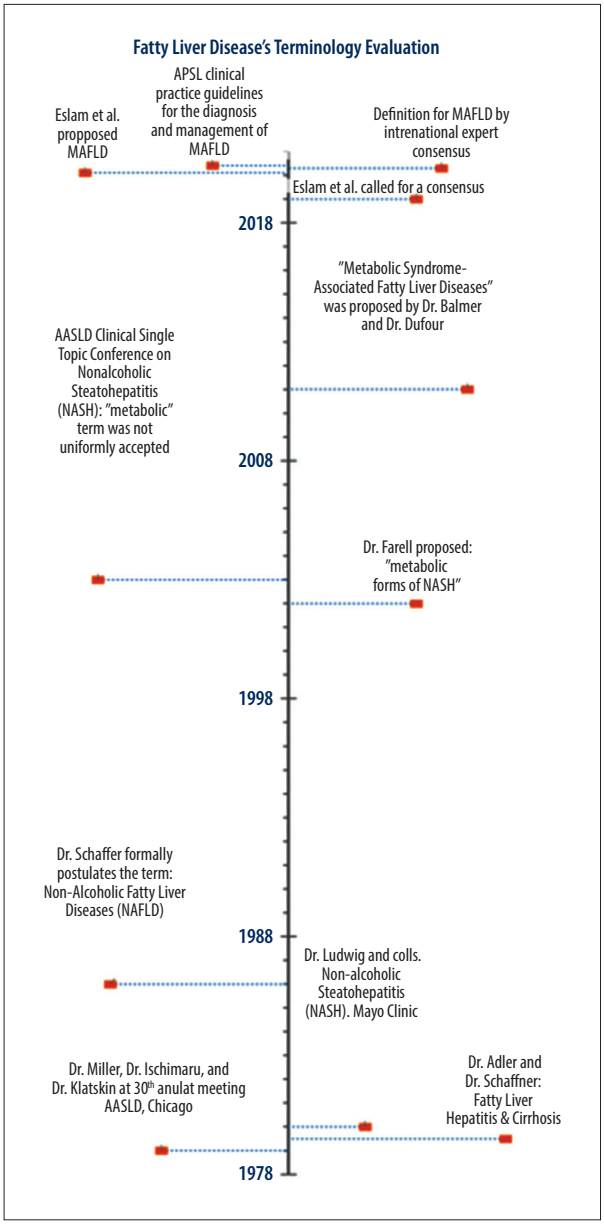

Figure 1. Evolution of the terminology of fatty liver disease from 1978 to 2021. AASLD – American Association for the Study of Liver Disease; ALEH – Asociación Latinoamericana para el Estudio del Hígado; AMAGE – African Middle East Association of Gastroenterology; APASL – Asian Pacific Association for Study of the Liver, BMI – body mass index; CSH – Chinese Society of Hepatology; EASL – European Association for Study of the Liver; MAFLDL – metabolic-associated fatty liver disease; NAFLD – non-alcoholic fatty liver disease; NASH – non-alcoholic steatohepatitis; T2DM – type 2 diabetes mellitus.

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was discussed but not uniformly accepted [24,25]. In 2011, the medical term, metabolic syndrome-associated fatty liver disease, was proposed by Balmer and Dufou to describe the pathophysiological characteristics of the disease, almost a decade ahead of its time [26]. In 2019, Eslam and colleagues expressed their concern for the need for a specific diagnostic approach rather than merely exclusion criteria for the diagnosis of NAFLD [27]. In 2020, they published the International Consensus Panel proposed nomenclature for MAFLD to provide a rationale for phenotyping the disease [11]. Later in 2020, an international expert consensus endorsed the change in terminology and recommended that the diagnostic criteria for MAFLD included the presence of hepatic steatosis with one of three following criteria: overweight or obesity; T2DM; or evidence of metabolic dysregulation [28]. Clinical inclusion criteria were developed for patient care and included the design of research protocols to facilitate evidence-based studies [28]. The results have increased cross-sectional and prospective clinical studies to assess the renaming impact, with main agreement on the benefits [28].

There is an understandable concern whenever there are changes to medical terminology and uncertainty on whether renaming will affect basic, clinical, epidemiological, and even translational research [29]. However, the past 19 years of debate on the metabolic' concept of fatty liver disease and the lack of international consensus may have had a negative impact on the progression of research in this area of hepatology. In contrast, in 2020, the Asia Pacific Association for Study of Liver (APASL) developed a clinical practice guideline for the diagnosis and management of MAFLD [30]. Recently, the Chinese Society of Hepatology (CSH) joined APASL in endorsing the renaming of MAFLD [31]. Also, the African Middle East Association of Gastroenterology (AMAGE) expert panel reached an almost uniform consensus in endorsement of the MAFLD diagnostic criteria [32].

In Latin America, on the occasion of the International NASH Day on June 10, 2021, Arab and colleagues provided an update on the key challenges for MAFLD in South American countries [33]. They identified a lack of disease awareness, health system fragmentation, and a lack of effective strategies for preventing and treating disease risk factors [33]. The authors concluded that extensive collaboration between scientific societies, governments, non-governmental organizations (NGOs), the pharmaceutical industry, and other stakeholders was mandatory [33]. Importantly, the Latin American Association for the Study of the Liver (Asociación Latinoamericana para el Estudio del Hígado) (ALEH) released their positional statement endorsing the MAFLD criteria proposal in January 2021 [11]. On 16th and 17th September 2021, the European Association for Study of the Liver (EASL) will launch the Digital NAFLD Summit 2021 to define fatty liver disease and compare the advantages of using NAFLD compared with MAFLD [34]. Future debate on the renaming proposal may continue into and beyond 2021 [34].

The Evidence to Support the Change in Terminology from NAFLD to MAFLD

The observed interindividual heterogeneity in the clinical course and severity of fatty liver disease has hindered the development of holistic recommendations for the diagnosis, staging, and stratification of disease based on noninvasive tests and liver biopsy to enable more personalized patient management. There is no current consensus on the concept of metabolic health or diagnostic and stratification criteria [33]. Studies on patients with fatty liver disease have been contradictory regarding the effects of obesity and insulin sensitivity [35]. Also, drug development has presented a high risk of bias due to variations between individuals for treatment targets during liver disease and the use of arbitrary study endpoints [29]. Recently, it has been unhelpful to divide fatty liver disease into potentially nonprogressive NAFLD and potentially progressive NASH subtypes [36]. Therefore, it would be more accurate to consider fatty liver disease as a continuum from simple hepatic steatosis with different risks of chronic liver complications, such as cirrhosis and HCC, based on different grades of steatohepatitis and stages of liver fibrosis [36,37]. Steatohepatitis is defined by the extension of the inflammatory process and features of injured hepatocytes. Although it is unclear how to accurately define all the potential subtypes, future clinical trials will improve knowledge on the pathogenesis of MAFLD disease progression based on updated protocol designs with reduced selection bias [37].

As an example of the potential improvements in clinical research and trials, Semmler and colleagues performed MAFLD phenotyping according to the body mass index (BMI) to stratify patients into lean, overweight, and obese, with and without MAFLD [38]. Although overall survival was similar between the patient groups, lean and overweight patients with MAFLD had worse clinical outcomes [38]. During the 7.5-year median follow-up, cancer, cardiovascular disease, and liver disease were the main causes of death [38]. Recently, Angelico and colleagues applied MAFLD diagnostic criteria to a prospective cohort study (clinical trial: NCT04036357), which showed that 96% of patients initially diagnosed with NAFLD fulfilled the criteria for MAFLD, and 25.5% of patients who did not fulfill the NAFLD criteria fulfilled the MAFLD criteria [39]. Patients with NAFLD who did not fulfill the MAFLD criteria had an increased prevalence of severe liver fibrosis [39]. However, recent real-world study data have shown contradictory results [40]. Lean subjects with MAFLD were shown to be under-diagnosed according to classical risk factors [35,39]. The MAFLD phenotype has been associated with worse hepatic outcomes, independent

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of commonly associated genetic variations [41]. The MAFLD clinical criteria are easily applicable and validated for the entire spectrum of disease phenotypes [42].

The renaming of MAFLD is intended to detect and assess the multiple factors associated with the pathogenesis and progression of this liver disease, including the synergistic effect of more than one chronic liver disease or metabolic abnormality in a single patient [37]. Therefore, patients affected by MAFLD with other chronic liver diseases caused by different etiologies, such as alcohol, viral infection, or medications, who were initially excluded as having NAFLD-negative criteria, are now considered one of the MAFLD subtypes [40]. In 2020, Fouad and colleagues showed that in patients with MAFLD and chronic hepatitis C virus (HCV) infection, the presence of MAFLD was significantly associated with liver fibrosis detected by the FIB-4 score [OR, 3.77 OR; P<0.005)] [42]. Initially, Eslam and colleagues supported the new terminology by highlighting that NAFLD overemphasized the absence of alcohol use [11,28]. It is now recognized that patients with MAFLD with alcohol consumption tend to be male, younger, and have fewer metabolic disorders but higher liver enzymes and are at an increased risk of advanced liver fibrosis [43].

In pediatric patients with MAFLD, fatty liver disease constitutes a rare condition mainly associated with genetic factors or congenital metabolic diseases [44]. According to the IDF consensus, metabolic syndrome should not be diagnosed in children below the age of 10 years, and the adult criteria should be used for patients older than 16 years [44]. In this context, Flisiak-Jackiewicz and colleagues have proposed pediatric diagnostic criteria for MAFLD in children aged 10-16 years, based on the presence of hepatic steatosis and either abdominal obesity (waist circumference ≥90th percentile adjusted for age and gender) or fasting blood glucose >100 mg/dl, or known T2DM, or at least two metabolic risk factors in lean patients [45].

Genotyping patients with MAFLD may alert clinicians to recommend close follow-up assessments that healthcare resources may be more efficiently allocated. Liu et al. showed that patients with MAFLD had an increased risk for liver cancer, cirrhosis, other liver diseases, cardiovascular disease, renal disease, and cancers [41]. They also found that the incidence of hepatic and extrahepatic events was increased by a high genetic risk score that included genetic variants in the PNPLA3, TM6SF2, and MBOAT7 genes [41]. These related genetic variations might also modulate pancreatic beta-cell function [46]. However, within the Chinese Han population with MAFLD, the minor allele TA of the rs72613567 variant in the hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) gene was associated with an increased risk of liver fibrosis [47]. The SD17B13 rs6531975 variant of the HSD17B13 gene had a protective effect in European populations with MAFLD [47]. Therefore, future research studies should be undertaken to map individual variations in phenotypes and genotypes associated with prognosis in patients with MAFLD.

In 2020, Lin et al. showed that in patients from the US National Health and Nutrition Examination Survey (NHANES) database, the prevalence of MAFLD was 31.24%, and the prevalence of NAFLD's was 33.23% [43]. Patients with MAFLD were older, had a higher BMI, multiple metabolic comorbidities, a higher homeostasis model assessment-insulin resistance (HOMA-IR), and increased serum lipid levels and liver enzyme levels [40]. Huang and colleagues reported MAFLD in 31.24% of cases from the NHANES database, of which 50.2% had two metabolic comorbidities [48]. The number of comorbid metabolic conditions was associated with older age, female gender, renal impairment, and liver fibrosis [48]. T2DM was the most important risk factor for advanced liver fibrosis [48]. Yamamura et al. showed that MAFLD was present in 79.6% of Japanese individuals, and NAFLD was present in 70.7% [49]. In this study, liver stiffness was more common in patients with MAFLD, and alcohol intake less than 20 g/day and NAFLD were independently associated with significant liver fibrosis [49]. The sensitivity of the MAFLD criteria for detecting liver fibrosis using noninvasive testing was significantly greater than the NAFLD criteria (93.9% vs 73.0%) [49]. In the Hong Kong population, the prevalence of MAFLD was slightly higher than that of NAFLD (25.9% vs 25.7%), and patients with NAFLD who did not fulfill the MAFLD criteria (5.1%) presented mild or nonprogressive disease [50]. Patients with incidental NAFLD that fulfilled the MAFLD criteria had a low incidence of liver stiffness [50]. Therefore, screening for MAFLD based on a prior diagnosis of NAFLD may not prevent the development of liver fibrosis.

A recently published systematic review and meta-analysis showed that the estimated global prevalence of MAFLD in overweight and obese adults was 50.7%, with a higher prevalence in men (59.0%) than women (47.5%) [51]. The pooled estimated prevalence of comorbidities was 19.7% and 57.5% for T2DM and metabolic syndrome, respectively [51].

Future Perspectives

Raising awareness of early screening for MAFLD and developing pharmacological strategies to improve metabolic function at the early stages of the disease may be promising future clinical approaches [52]. The planned future discussions and expert opinions on MAFLD should dedicate a special section for discussing the need for updating the guidance statements to guide international regulatory agencies for drug development in NASH and MAFLD. The effectiveness of novel treatment options for patients with different MAFLD phenotypes and genotypes should be conducted using NAFLD and MAFLD criteria as holistic approaches to patient care [53].

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Conclusions

In 2020, international consensus guidelines recommended the renaming of NAFLD to MAFLD, supported by diagnostic criteria. This transition to MAFLD may increase momentum and clinical evidence at multiple levels, including patient diagnosis, management, and care, and provide the basis for new research areas and clinical development for therapeutics. The diagnostic criteria for MAFLD are practical, simple, and superior to the existing NAFLD criteria for identifying patients at increased risk of developing progressive liver disease.

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Conflict of interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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