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Review Article

Unmet needs of metabolic dysfunction – Associated "fatty or steatotic" liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD), first named in 1980, is currently the most common chronic liver disease, imposing significant health, social, and economic burdens. However, it is defined as a diagnosis of exclusion, lacking a clear underlying cause in its diagnostic criteria. In 2020, metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed as a replacement for NAFLD, introducing additional criteria related to metabolic dysfunction. In 2023, metabolic dysfunction-associated steatotic liver disease (MASLD) was suggested to replace NAFLD, aiming to avoid the stigmatizing term "fatty" and incorporating cardiometabolic criteria for metabolic dysfunction. This divergence in nomenclature and diagnostic criteria between MAFLD and MASLD presents challenges to medical communication and progress. This review outlines the pros and cons of both terminologies, based on current research evidence, in the hope of fostering global consensus in the future.

Keywords: *Metabolic-associated fatty liver disease, Metabolic dysfunction-associated steatotic liver disease, Nonalcoholic fatty liver disease*

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease, primarily due to the westernization of diet and lifestyle, leading to an increasing prevalence of obesity and diabetes [1]. Current research shows that patients with NAFLD have higher mortality rates, with the main causes including cardiovascular diseases, liver diseases, and cancer [2,3]. Direct antiviral agents have a very high successful rate for chronic hepatitis C. Due to vaccination against the hepatitis B virus (HBV) and oral antiviral agents for suppression of HBV and eradication of hepatitis C virus (HCV), the pandemic of NAFLD become the most common cause of liver diseases with increasing health, social, and economic burden [4]. The term NAFLD has been used since it was proposed in 1980 [5]. However, there are still some issues with its clinical use. First, it is a diagnosis of exclusion, mainly to rule out alcohol consumption and other causes of chronic liver disease [6]. Second, it does not clearly indicate the possible pathogenic mechanisms [7]. It is now known that NAFLD is significantly associated with metabolic syndrome, with diabetes, obesity, and hyperlipidemia being the important risk factors [8-11]. In 2020, a new term, metabolic dysfunction-associated fatty liver disease (MAFLD), was proposed to replace the previous diagnosis of NAFLD [12]. Along with the name change, the diagnostic criteria for metabolic abnormalities were also specified and thousands of studies related to MAFLD have been published over the past few years. Although MAFLD is widely used, it has not achieved global consensus. In 2023, a new diagnostic name and criteria for metabolic dysfunction-associated steatotic liver disease (MASLD) was proposed by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Liver (ALEH) [13-15]. Despite the difference of only one word between MAFLD and MASLD, this has led to a lack of uniformity in names and diagnostic criteria worldwide. This discrepancy is expected to cause differences in future research and communication [Table 1]. Therefore, this paper attempts

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Table 1: Diagnostic criteria of nonalcoholic fatty liver disease, metabolic-associated fatty liver disease, and metabolic-associated steatotic liver disease

	NAFLD	MAFLD	MASLD
Proposed time	1980	2020	2023
Hepatic steatosis definition	Image, serum biomarker, or histology		
Alcohol consumption	Excluded if >3 drinks/day in men or >2 drinks/day in women	Any level can be included	Included if <30 g/day in men or <20 g/day in women
Other liver diseases	Excluded	Included	Excluded
Definition of metabolic dysfunction	Nil	If obesity or type 2 diabetes→MAFLD	≥1 of 5 cardiometabolic risk factors
		If no DM and normal weight→need ≥2 out of 7 metabolic risks	BMI ≥25 (23 Asia) or WC >94 cm (men) and 80 cm (women) or ethnicity adjusted
		WC ≥102/88 cm in men/women (≥90/80 in Asians)	FPG ≥100 mg/dL or 2-h postload glucose level ≥140 mg/dL or HbA1c ≥5.7% or type 2 diabetes or treatment for type 2 diabetes
		Prediabetes (HbA1c 5.7%−6.4%, or FPG 100–125 mg/dL, or 2-h postload glucose levels 140–199 mg/dL)	Blood pressure ≥130/85 mg/dL or specific antihypertensive drug treatment
		Blood pressure ≥130/85 mmHg or specific antihypertensive drug treatment	TG ≥150 mg/dL or lipid-lowering treatment
		HDL-c <40/50 mg/dL for men/women	HDL-c <40/50 mg/dL for men/women or lipid-lowering treatment
		TG ≥150 mg/dL or lipid-lowering treatment	
		HOMA-IR score ≥2.5	
		hs-CRP level >2 mg/L	
Name	Nonalcoholic; unable to reflect the nature of disease	Fatty; colloquial but stigmatizing	Steatotic; professional but unpopular use
Parameter of insulin resistance and hs-CRP	Not applicable	Needed for neither overweight/obese nor having diabetes subjects	No need

NAFLD: Nonalcoholic fatty liver disease, MAFLD: Metabolic-associated fatty liver disease, MASLD: Metabolic-associated steatotic liver disease, DM: Diabetes mellitus, WC: Waist circumference, HbA1c: Glycated hemoglobin, FPG: Fasting plasma glucose, HDL-c: High-density lipoprotein cholesterol, TG: Triglyceride, HOMA-IR: Homeostatic model assessment for insulin resistance, hs-CRP: High sensitivity C-reactive protein, BMI: Body mass index

to present the pros and cons of both terms according to current research evidence, hoping to aid in achieving a unified name in the future.

The difference in disease name

The difference between MAFLD and MASLD comes down to just one word (F vs. S) in disease nomenclature. Each of these names has its pros and cons. "Fatty liver" is more colloquial and commonly used, but it can be somewhat discriminatory due to the stigmatizing word "fat." "Steatotic liver" is typically used in histological descriptions and tends to be a specialized medical term that is not commonly used in everyday English.

Difference of diagnostic criteria for metabolic dysfunction

For the term MAFLD, the diagnostic criteria of metabolic dysfunction require meeting one of three conditions: being overweight/obese, having diabetes, or for those neither overweight/obese nor having diabetes, meeting two out of seven metabolic abnormalities. Any of these three conditions directly qualifies for a diagnosis of MAFLD [12]. As for the term MASLD, its definition follows the cardiometabolic criteria, which consists of five items, any one of which qualifies for a diagnosis of MASLD [13-15]. When delving into the differences, there are only actually two minor variations. One variation is that MAFLD includes high-sensitivity C-reactive protein (hs-CRP) and insulin resistance as indicators for lean/normal weight subjects. While these two indicators are closely related to the mechanisms of metabolic fatty liver disease, the downside is that they are not routinely tested in clinical settings. Another variation is that for patients who are of lean/normal weight and do not have diabetes, MAFLD requires two metabolic abnormalities, while MASLD requires only one. Stricter diagnostic criteria naturally screen for more severe patients, while looser criteria screen for more patients. As for how to choose between them, it should be confirmed through the evidence from subsequent research. According to our previous research, cryptogenic steatotic liver disease (SLD) accounts for approximately 3.5% of NAFLD cases. Compared to patients with MASLD, those with cryptogenic SLD have a lower risk of liver-related complications and arteriosclerosis [16]. Another study, which has been accepted and is in press, shows that 94.9% of patients with MASLD and MAFLD overlap if other causes of chronic liver disease are excluded, making it difficult to discern differences between the two groups. However, if we use cryptogenic SLD as a control group and define patients who meet the criteria for MASLD but not for MAFLD as a "missing group," we find that this "missing group" has a higher risk of liver fibrosis and arteriosclerosis. Therefore, MASLD misses fewer high-risk patients than MAFLD [17]. Based on our research results, it is recommended to use the cardiometabolic criteria to determine

metabolic dysfunction. As for hs-CRP and insulin resistance, it is suggested they might be used as optional tests in clinical settings.

The difference in populations

MAFLD does not exclude the groups with other causes of liver disease [Figure 1]. Clinically, MAFLD encompasses a broader patient population than NAFLD, making it a more general term. The downside is that because it includes groups with other chronic liver diseases, it can introduce some confounding factors for the studies focusing solely on liver issues. In contrast, MASLD excludes groups with other causes of liver disease [Figure 2]. Individuals with concurrent conditions such as alcohol-related, viral, or autoimmune liver diseases are assigned new diagnostic names including MASLD with increased alcohol intake (MetALD) or MASLD with combinatory other diseases [Figure 3]. In short, it is a narrower definition. The downside is that it includes a smaller patient population, but the upside is that it reduces the influence of other causes of liver disease, making it more suitable for liver disease research and drug development. The different populations covered by these diagnostic terms also lead to differences in epidemiological data [18,19].

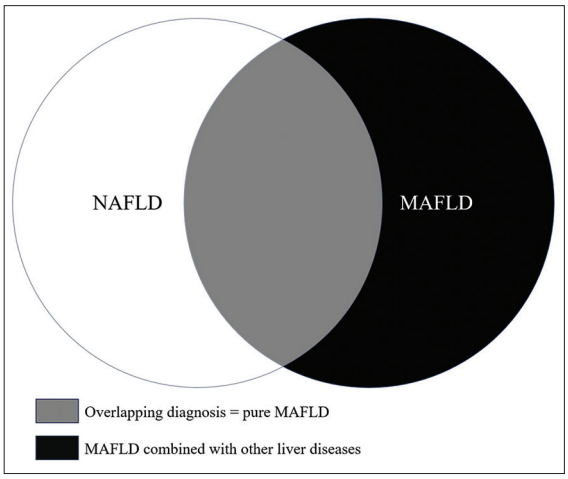

Figure 1: Relationship between metabolic-associated fatty liver disease and nonalcoholic fatty liver disease. NAFLD: Nonalcoholic fatty liver disease, MAFLD: Metabolic-associated fatty liver disease

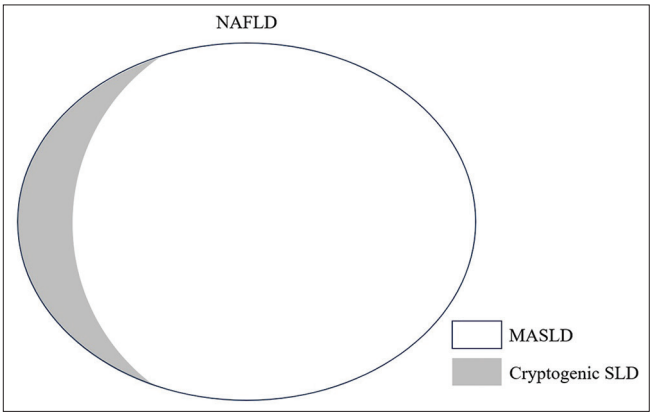

Figure 2: Relationship between metabolic-associated steatotic liver disease and Nonalcoholic fatty liver disease. NAFLD: Nonalcoholic fatty liver disease, MASLD: Metabolic-associated steatotic liver disease, SLD: Steatotic liver disease

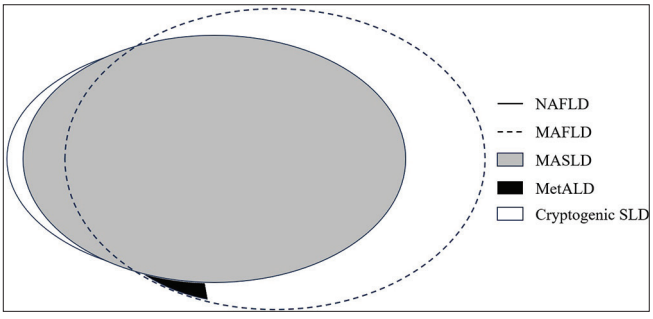

Figure 3: Relationship among nonalcoholic fatty liver disease, metabolic dysfunction-associated fatty liver disease, metabolic-associated steatotic liver disease (MASLD), and MASLD with increased alcohol intake. NAFLD: Nonalcoholic fatty liver disease, MAFLD: Metabolic dysfunction-associated fatty liver disease, MASLD: Metabolic-associated steatotic liver disease, MetALD: MASLD with increased alcohol intake, SLD: steatotic liver disease

Metabolic dysfunction-associated fatty liver disease/metabolic dysfunction-associated steatotic liver disease combined with viral hepatitis

Unlike NAFLD, patients with MAFLD or MASLD can have concurrent HBV or HCV infection. In a meta-analysis, the prevalence of hepatic steatosis was 29.6% and 60% in HBV and HCV patients, respectively [20]. By definition, MAFLD may affect understanding of the liver disease outcomes of hepatic steatosis combined with viral hepatitis, since it includes other etiologies of liver diseases, such as increased alcohol intake or autoimmune hepatitis. In our previous, large population-based studies from Taiwan Biobank dataset, concurrent MAFLD with chronic HBV infection (MAFLD-HBV) and MASLD combined with chronic HBV infection (MASLD-HBV) patients are associated with lower risk of dyslipidemia and hepatic steatosis but higher risk of liver fibrosis, compared with those with MAFLD or MASLD, respectively [21,22]. Patients with MAFLD-HBV have a lower risk of atherosclerosis, compared with MAFLD patients but there was no difference in the risk of atherosclerosis between MASLD-HBV and MASLD patients [20,21]. Both MAFLD-HBV and MASLD-HBV could have synergistic effects on the risk of liver fibrosis, cirrhosis, and HCC [23,24].

Metabolic abnormalities are the extrahepatic manifestations of HCV infection, especially in genotype 3. The term “viral steatosis” is used in describing the steatogenic properties of HCV genotype 3, probably due to its direct cytopathic effect on the liver [25]. On the contrary, “metabolic steatosis” is due to host metabolic derangements, such as obesity or diabetes mellitus [26]. MAFLD-HCV patients have a higher risk of advanced liver fibrosis than MAFLD patients [27]. For patients with dual diagnosis (metabolic fatty liver and viral diseases), this represents a unique genotype and is a clinically important topic. Currently, research on this is limited, especially concerning the natural history and long-term liver disease outcomes such as cirrhosis or HCC development. Further studies are needed to provide confirmation.

Unmet needs of two diagnostic criteria

For the MAFLD, since it broadly includes chronic liver diseases from other causes, it is recommended to divide it into two groups. One group is without any other liver diseases, referred to as pure MAFLD (pMAFLD), while the other group is combined with other chronic liver diseases, referred to as combinatory MAFLD (cMAFLD) [28]. The broad definition of MAFLD can be used in clinical practice and pure MAFLD for liver research or drug development according to different needs. As for the MASLD, there are several areas that need clarification. First, for SLD combined with metabolic dysfunction, there is no general term provided for the condition. Instead, it is subdivided into several new disease categories, including MASLD, MASLD with increased alcohol intake (MetALD), and MASLD combined with other liver diseases. The second area that needs clarification is the definition of the amount of alcohol consumption for the MetALD diagnosis. It should be clarified whether the upper limit definition for alcohol consumption (alcohol consumption > 350 g/week in females and > 420 g/week in males) is based on scientific evidence or merely expert opinion. In addition, for those with alcohol consumption exceeding the upper limit, there is no specific diagnostic name for these patients. If they are classified as alcohol-related liver disease (ALD), it will complicate its classification. In the era of NAFLD, ALD including alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis are typically defined by alcohol consumption levels exceeding 140 g/week for women and 210 g/week for men. However, according to the current algorithm, MASLD patients who consume more than 350 g/week for women and 420 g/week for men are classified as ALD. This redefinition makes the criteria highly complex and difficult to implement in clinical practice.

Evidence-based medicine validation

The changes in these two disease names and diagnostic criteria are based on expert opinions. In the current era of evidence-based medicine, subsequent research validation is crucial. The term of MAFLD was proposed 3 years earlier than the term MASLD, and it currently has more research reports and papers, which is relatively reasonable. Until August 2024, a search on PubMed yields approximately 20,000 research reports for the MAFLD. In contrast, the MASLD yields about 1800 results on the Internet. Besides the fewer number of studies, another concern is that the term MASLD replaces NAFLD and excludes patients who do not meet the cardiometabolic criteria, classifying them as having cryptogenic SLD [16]. This group of patients constitutes about 1%–4.23% in the literature, with most patients overlapping between NAFLD and MASLD [29,30]. This high overlap rate has led to the assertion that the findings from previous NAFLD research can be totally applied to the new diagnostic term. This claim not only goes against the scientific spirit but also hinders subsequent research and validation for the term MASLD.

Conclusion

Currently, MAFLD and MASLD, two different names and diagnostic criteria, were proposed to replace the previous NAFLD without global uniformity [31]. This situation undoubtedly hinders medical development and communication. Unifying the disease name and diagnostic criteria should be a priority. Achieving this will require broad-mindedness, mutual communication, and coordination, along with more evidence-based medical validation. Developing a universally accepted disease name and criteria will benefit clinical patient care, subsequent research, and drug development. With collaborative efforts, this goal can ultimately be reached in the future.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

There is no conflict of interest.

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