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Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes Mellitus: A Review and Position Statement of the Fatty Liver Research Group of the Korean Diabetes Association

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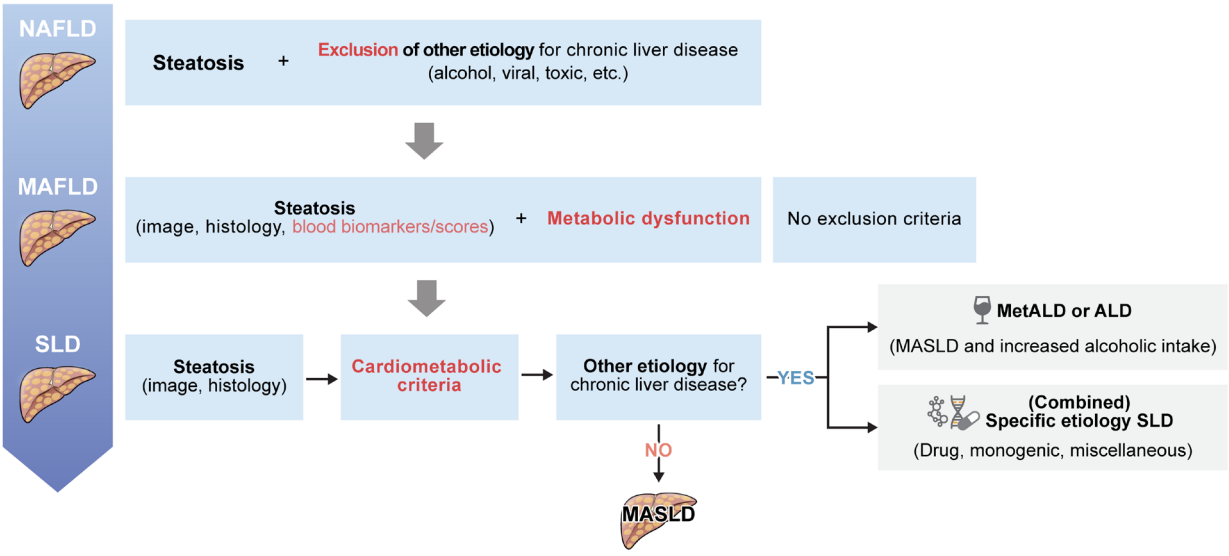

Highlights

- **The shift to MAFLD/MASLD stresses metabolic abnormalities as key factors in SLD/FLD.**
- **MAFLD diagnosis requires metabolic dysfunction, regardless of other FLD causes.**
- **MASLD also has cardiometabolic criteria but reclassifies based on other causes.**
- **MASLD better reflects metabolic dysfunction and overlaps more with NAFLD than MAFLD.**
- **We advocate for MASLD to reduce stigma, emphasize metabolism, and ensure data compatibility.**

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Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes Mellitus: A Review and Position Statement of the Fatty Liver Research Group of the Korean Diabetes Association

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Since the role of the liver in metabolic dysfunction, including type 2 diabetes mellitus, was demonstrated, studies on non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) have shown associations between fatty liver disease and other metabolic diseases. Unlike the exclusionary diagnostic criteria of NAFLD, MAFLD diagnosis is based on the presence of metabolic dysregulation in fatty liver disease. Renaming NAFLD as MAFLD also introduced simpler diagnostic criteria. In 2023, a new nomenclature, steatotic liver disease (SLD), was proposed. Similar to MAFLD, SLD diagnosis is based on the presence of hepatic steatosis with at least one cardiometabolic dysfunction. SLD is categorized into metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related/-associated liver disease, alcohol-related liver disease, specific etiology SLD, and cryptogenic SLD. The term MASLD has been adopted by a number of leading national and international societies due to its concise diagnostic criteria, exclusion of other concomitant liver diseases, and lack of stigmatizing terms. This article reviews the diagnostic criteria, clinical relevance, and differences among NAFLD, MAFLD, and MASLD from a diabetologist's perspective and provides a rationale for adopting SLD/MASLD in the Fatty Liver Research Group of the Korean Diabetes Association.

Keywords: Diabetes mellitus, type 2; Metabolic dysfunction-associated steatotic liver disease; Non-alcoholic fatty liver disease

INTRODUCTION

Identifying people at risk of progressing to steatohepatitis, fibrosis, advanced fatty liver disease (FLD), or steatotic liver disease (SLD) is crucial for reducing the incidence of both liver disease and extrahepatic complications, such as cardiovascular diseases and cancer. International academic associations and societies have published guidelines for diagnosing and managing FLD or SLD. Over the past 4 years, two international expert consortiums have advocated for changing the terminology from non-alcoholic fatty liver disease (NAFLD), a diagnosis of exclusion, to more proactive terms, such as metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) [1-3]. However, some of those strategies may not be fully applicable to people with type 2 diabetes mellitus (T2DM).

History of changing nomenclature for FLD

Ludwig et al. [4] first introduced the concept of nonalcohol-associated steatohepatitis (NASH) and published a collection of findings of 20 patients' steatohepatitis of "unknown cause" in 1980. In 1986, Dr. Fenton Schaffner coined NAFLD, which includes nonalcohol-associated fatty liver (NAFL) and NASH, and was described as having an alcohol-related liver disease (ALD)-like histologic pattern but without clinically significant alcohol consumption or other liver diseases. Since then, interest in NAFLD has dramatically risen, with research spanning its natural history, pathophysiology, epidemiology, and socioeconomic impact. Defined as hepatic fat accumulation evidenced by radiologic or histologic examination without other liver disease or secondary causes of steatosis, including drugs, significant alcohol consumption, or inherited metabolic states, NAFLD is now the most prevalent chronic liver disease. However, in the past decade, researchers have come to agree that the name should be changed to better convey the disease's characteristics instead of simply deeming it the opposite of ALD [5,6]. Criticisms of NAFLD's stigmatizing terminology and exclusionary criteria which is challenging in patients with coexisting etiologies such as viral hepatitis or ALD, and heterogeneous mixture of pathogenesis prompted a search for better nomenclature [7,8].

To overcome these concerns, a consortium of international experts suggested a consensus-driven process to rename NAFLD. Following a survey and two-stage Delphi process, "MAFLD" was proposed in 2020 to incorporate the context of systemic metabolic dysfunction [1]. However, despite acceptance of the term, MAFLD still faced concerns over mixed etiologies and stigma associated with the term "fatty."

In 2023, a 36-member steering committee developed a four-part Delphi survey to determine a new FLD nomenclature, with five essential areas of consideration: (1) concerns with the current nomenclature and whether the issues can be addressed; (2) the importance of steatohepatitis in disease definitions and endpoints; (3) the role of alcohol intake; (4) the impact of the term change on disease awareness, clinical trials, and regulatory approval processes; and (5) the possibility for the new name to reduce heterogeneity and facilitate future advancements [3]. Finally, the new term, SLD, and its subtype, MASLD, were introduced. NAFLD was supposed to approach the opposite of alcoholic FLD. The concept of MAFLD was introduced to cover the limitation of NAFLD compromising the dual etiologies and the terminology's stigma. The umbrella

term of SLD was proposed to avoid another potentially stigmatizing term (i.e., fatty), further reduce heterogeneity in the classification of various liver disorders, and facilitate the creation of a new entity—metabolic dysfunction- and alcohol-related/-associated liver disease (MetALD) [3].

Need for opinion on changing nomenclatures for people with T2DM

The evolution from NAFLD to MASLD reflects a deeper understanding of the metabolic underpinnings of the disease rather than the simple exclusion of alcohol as a cause. Although NAFLD was initially useful for distinguishing liver damage not caused by alcohol, it did not fully capture the complex metabolic dysfunction associated with the disease. The more proactive and metabolically oriented diagnostic terms of MAFLD and MASLD have almost identical populations when using the term MASLD instead of NAFLD [9-11]. From a diabetologist's perspective, understanding the metabolic underpinnings of FLD or SLD and differentiating between MAFLD and MASLD in the context of T2DM are crucial for precise diagnosis, management, and research to facilitate the development of personalized therapeutic approaches for people with T2DM. The Fatty Liver Research Group (FLRG) of the Korean Diabetes Association (KDA) recognized a need for a position statement on changing the nomenclatures for people with T2DM and offer its rationale behind adopting these optimal nomenclatures to emphasize the link between cardiometabolic risk and all-cause mortality for people with T2DM.

Preparation of the guidance opinion

The last position statement by the FLRG of the KDA on NAFLD in people with T2DM was published in 2020, but the concept and nomenclature of FLD have progressed considerably since then [12]. Consequently, the FLRG has decided to deliver a new, comprehensive position statement on FLD or SLD focusing on the spectrum, rationale, and nomenclature for people with T2DM. Core researchers of the FLRG were initially consulted and unanimously agreed to form the MASLD Working Party consisting of 25 members. Multiple virtual meetings were held in January to September 2024, and MASLD Working Party members attended two off-site conferences, where they presented their opinions and supporting literature. These presentations were first made to the entire MASLD Working Party group, which then ratified the statements after detailed discussions.

The shift from NAFLD to MAFLD and MASLD has been paralleled in the last decade by significant advancements in knowledge of the mechanisms linking FLD or SLD with systemic pathogenic pathways leading to increased cardiometabolic risk. This article reviews the differences between NAFLD, MAFLD, and MASLD, discusses the clinical relevance and a diabetologist's perspective of these terminological changes, and suggests reasons for advocating for the SLD/MASLD approach.

DISEASE DEFINITION

All three terms are based on the presence of hepatic steatosis (Fig. 1).

NAFLD is diagnosed by excluding all non-metabolic etiologies

NAFLD includes individuals with liver diseases not derived from alcohol, drugs (e.g., valproic acid, tamoxifen, aromatase inhibitors, corticosteroids), viral infection (i.e., hepatitis B or C), autoimmune disorders (e.g., autoimmune hepatitis, celiac disease), or genetic disorders (e.g., hemochromatosis, Wilson's disease, α1-antitrypsin deficiency, lipodystrophy). A greater-than-moderate amount of alcohol consumption (≥210 g/week or ≥30 g/day for men and ≥140 g/week or ≥20 g/day for women) is also an exclusion criterion [13,14]. NAFLD compromises from simple steatosis and NASH to advanced liver fibrosis or cirrhosis. NAFL is characterized by macrovesicular hepatic steatosis (≥5% fat in the liver) that may be accompanied by mild inflammation, and NASH is characterized by the presence of NAFL and additional hepatocyte injury (inflammation, ballooning), regardless of fibrosis.

MAFLD is diagnosed based on the presence of metabolic dysfunction, regardless of other FLD etiologies

Unlike NAFLD, MAFLD has positive diagnostic criteria. After confirming hepatic steatosis through imaging, histology, or blood biomarkers, MAFLD is diagnosed if one or more of the following criteria are met, regardless of the etiology of FLD: (1) overweight/obesity (body mass index [BMI] ≥25 kg/m^2 in Caucasian individuals and ≥23 kg/m^2 in Asian individuals); (2) diabetes mellitus; or (3) metabolic disorder (at least two of the following metabolic risk components: waist circumference ≥102/88 cm in Caucasian men and women, ≥90/80 cm in Asian men and women; blood pressure ≥130/85 mm Hg or

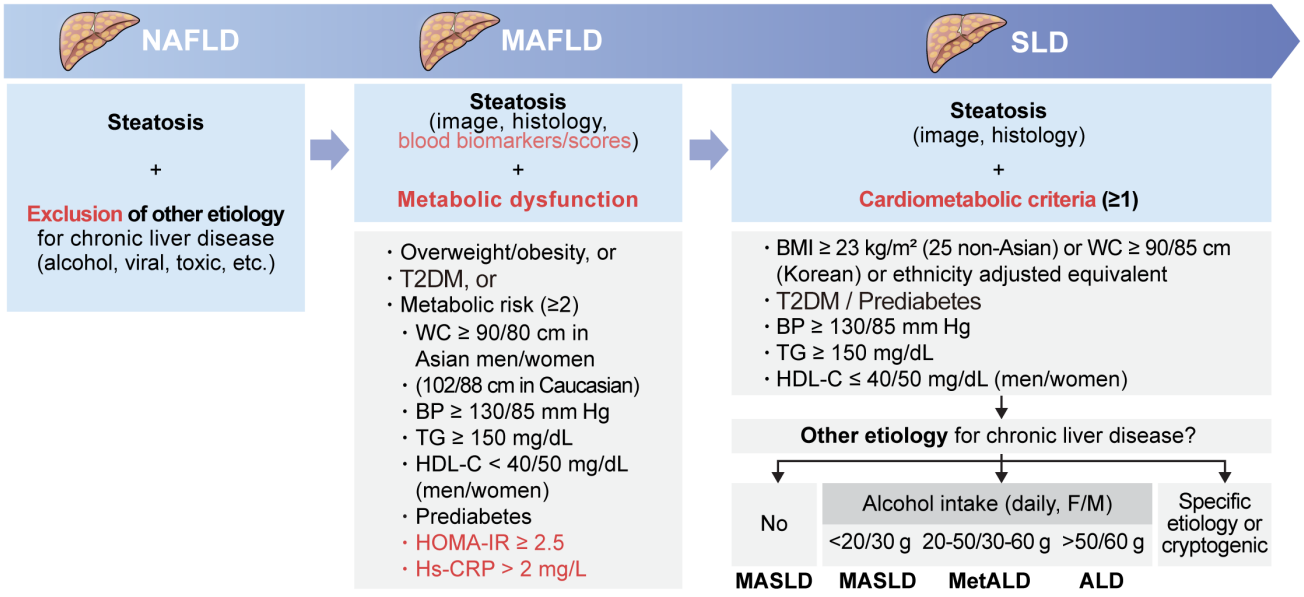

Fig. 1. Diagnostic criteria of non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), and metabolic dysfunction-associated steatotic liver disease (MASLD). SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; MetALD, metabolic dysfunction– and alcohol-related/-associated liver disease; ALD, alcohol-related liver disease.

taking anti-hypertensive medications; plasma triglycerides ≥150 mg/dL or taking triglyceride-lowering agents; plasma high-density lipoprotein cholesterol [HDL-C] <40 mg/dL for men or <50 mg/dL for women; prediabetes, defined as fasting blood glucose of 100–125 mg/dL, 2-hour post-load glucose of 140–199 mg/dL, or glycosylated hemoglobin [HbA1c] of 5.7%–6.4%; homeostasis model assessment of insulin resistance score ≥2.5; plasma high-sensitivity C-reactive protein level >2 mg/L) [1]. Notably, MAFLD is a single overarching term that does not consider further classification of steatosis versus steatohepatitis.

MASLD has similar criteria to MAFLD, focusing on metabolic dysfunction

For SLD, only imaging or histological methods are accepted as detection methods for hepatic steatosis, and the cardiometabolic criteria are more concise, requiring more than one of the following five criteria: (1) overweight/obesity (BMI ≥25 kg/m^2 in Caucasian individuals or ≥23 kg/m^2 in Asian individuals, or waist circumference ≥94/80 cm in Caucasian men/women or ethnicity-adjusted equivalent 90/85 cm in Koreans [15]); (2) prediabetes/T2DM (presence/treatment of T2DM, fasting serum glucose ≥100 mg/dL, 2-hour post-load glucose ≥140 mg/dL, or HbA1c ≥5.7%); (3) hypertension (blood pressure ≥130/85 mm Hg or anti-hypertensive drug treatment); (4) plasma triglycerides ≥150 mg/dL or treatment with lipid-lowering agents; and (5) HDL-C <40 mg/dL for men or <50 mg/dL for women, or treatment with lipid-lowering agents [3]. The SLD diagnostic criteria consider waist circumference to be equivalent to BMI as an adiposity index and further consider prediabetes as a single independent factor. SLD also has pediatric criteria. When SLD is identified, categorization should take place according to the causes of steatosis. SLD comprises five groups: MASLD, MetALD, ALD, specific etiology SLD, and cryptogenic SLD. MetALD and ALD are distinguished based on the quantity of alcohol intake (140–350 g/week or 20–50 g/day for women and 210–420 g/week or 30–60 g/day for men). MetALD can be identified as MASLD- or ALD-predominant. In addition, metabolic dysfunction-associated steatohepatitis (MASH) has been proposed as the replacement term for NASH.

Keynotes
- SLD can be categorized as MASLD, MetALD, ALD, specific etiology SLD, and cryptogenic SLD according to its causes. MASLD has criteria similar to those for MAFLD, focusing on metabolic dysfunction.

EPIDEMIOLOGY

MAFLD is more prevalent than NAFLD

NAFLD is the most common chronic liver disease worldwide, affecting 25% to 32% of the adult population [16,17]. In the general Korean population, the prevalence of NAFLD is approximately 22% to 35% [17-19]. Its prevalence has increased in recent decades, parallel to the increasing prevalence of obesity and obesity-related diseases. More surprisingly, Korea has among the fastest-increasing prevalence and incidence of NAFLD in the Asia-Pacific territories, reaching similar figures as those of European countries [17]. In addition, the prevalence of NAFLD among T2DM is higher than that of the general population, reported to be over 65% [20,21].

The prevalence of MAFLD is higher than that of NAFLD, largely due to its definition, which includes other liver diseases with metabolic abnormalities, especially ALD and viral hepatitis. In Korea, its prevalence is reportedly 25% to 38% [22-24]. The studies reporting this prevalence commonly suggested that most of the NAFLD population overlapped that of MAFLD, and only a few NAFLD individuals (~5%) did not have metabolic dysfunction or meet the criteria for metabolic abnormalities [8,25]. The discrepancy in the prevalence of NAFLD and MAFLD in Korea was around 10% [24,26,27], which was slightly less than that of global reports (15%) [25]. This might be due to the negative association between liver steatosis and chronic hepatitis B (CHB) infection [28] and the higher prevalence of CHB in the middle-aged population [19,29]. The individuals with MAFLD but not NAFLD were more frequently men and had a higher BMI [24,25].

MASLD has a closer overlap with NAFLD than with MAFLD

Epidemiologic studies have demonstrated the overlap between SLD and MAFLD. In National Health and Nutrition Examination Survey data, the prevalence of MAFLD and SLD evaluated by vibration-controlled transient elastography were identical, showing a high degree of concordance between those two terms [30]. Studies have also shown the overlapping prevalence of MASLD and NAFLD. Based on proton-magnetic resonance spectroscopy results in Hong Kong data, the MASLD diagnostic criteria include individuals previously diagnosed with NAFLD [10]. Moreover, the MASLD definition can better capture lean patients with NAFLD compared with the MAFLD definition [31]. The prevalence of SLD is reportedly 34% to 38% in Korea [26,32,33], similar to United States reports [34]. Most of the SLD population (80%) has MASLD, whereas MetALD (10% to 15%) and SLD with other etiologies explain the rest. The prevalence of NAFLD, MAFLD, and MASLD were 26.8%, 34.1%, 26.6%, respectively, according to a study utilized data from the Korea National Health and Nutrition Surveys [32]. The proportion of MetALD is higher in young (20 to 39 years) and middle-aged (40 to 64 years) age groups than in older adults (65 to 79 years) and is higher in men than in women. Considering the increasing alcohol consumption and rapid expansion of SLD in Korea [35,36], the currently low prevalence of MetALD is expected to grow.

Keynotes
- The prevalence of MAFLD is higher (25% to 38% in Korea) than that of NAFLD due to its inclusion of other etiologies, such as ALD and viral hepatitis. The prevalence of SLD is similar to that of MAFLD, but MASLD has a closer overlap with NAFLD. Nevertheless, the MASLD definition better captures lean NAFLD patients.

PATHOPHYSIOLOGY

Although NAFLD was first described with a histologic pattern reminiscent of ALD, they have important pathologic differences. The concepts of MAFLD and MASLD are based on the assumption that FLD and SLD are regarded as hepatic manifestations of metabolic diseases. Each diagnostic criterion is involved in inducing metabolic-associated changes in the liver. In addition, over-nutrition, dysbiosis, genetic predisposition, and immune dysregulation can directly trigger the disease mechanisms in liver tissue [37,38].

Histopathology of SLD

In general, when >5% of hepatocytes is shown steatosis, we can call fatty degeneration and when >50% of hepatocytes with steatosis is detected, FLD or SLD can be defined [39]. Steatosis is the accumulation of fat droplets in the hepatocyte cy-

toplasm and can be categorized as macrovesicular or microvesicular according to the lipid droplets' size. In macrovesicular steatosis, a large fat droplet pushes the hepatocyte nucleus to the periphery, whereas microvesicular steatosis is characterized by multiple small lipid droplets in the cytoplasm with a central nucleus (Fig. 2) [40].

Distinct histologic differences between ALD and metabolic dysfunction-associated liver disease

Alcoholic steatosis is usually macrovesicular or has a mixed micro and macrovesicular pattern. Pure microvesicular steatosis may be observed in alcoholic foamy degeneration, not MASH [40]. Steatosis begins in pericentral hepatocytes surrounding the central vein (zone 3) and progresses toward the periportal region (zone 1). MASLD also has a typically macrovesicular pattern, accompanied by patches of small-droplet steatosis, and initially develops in the perivenular region (zone 3) and progresses outward [41]. Zone 3 hepatocytes are responsible for glycolysis and lipogenesis and are involved in β-catenin/Wnt signaling, whereas periportal hepatocytes in zone 1 are responsible for gluconeogenesis and β-oxidation [42].

Inflammatory cell infiltration is commonly seen in zone 3 in both alcoholic steatohepatitis (ASH) and MASH. However, in ASH, portal inflammation, including neutrophils, tends to be

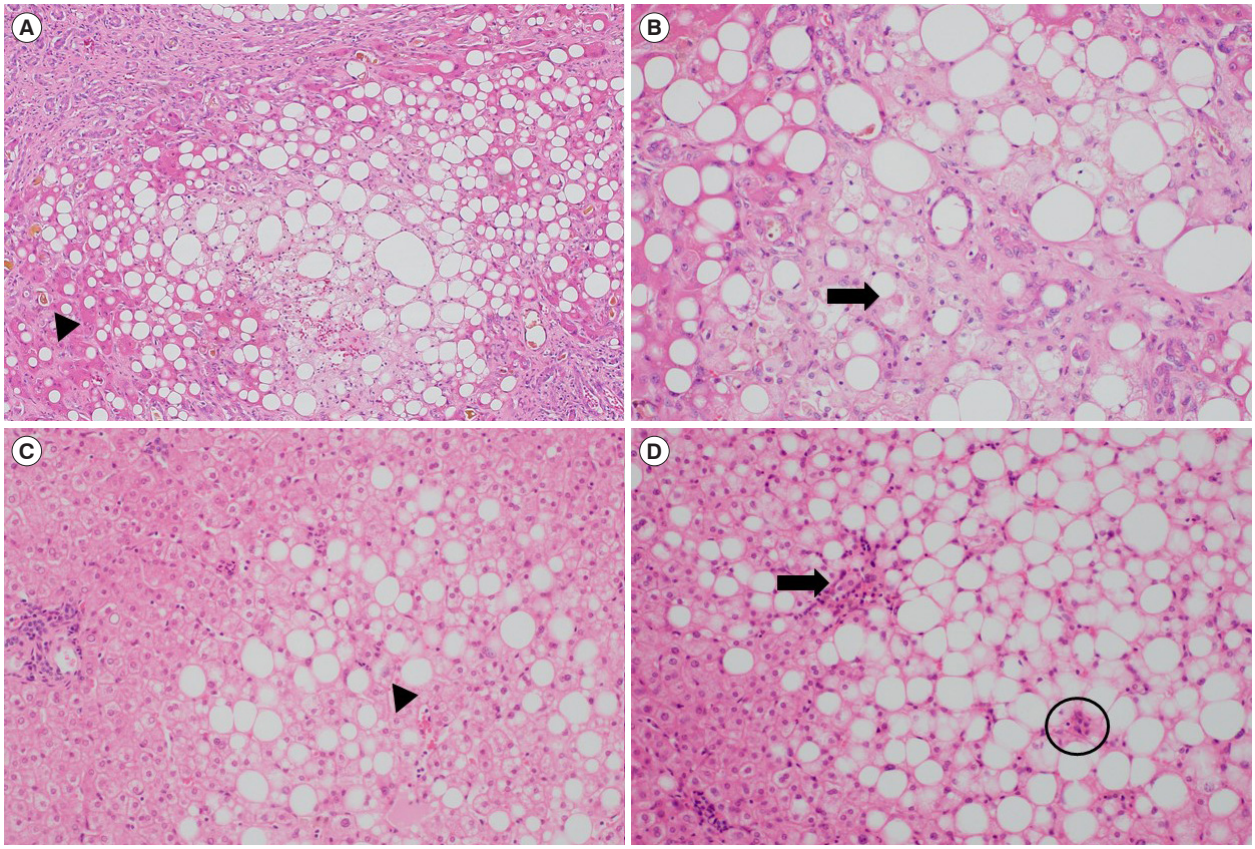

Fig. 2. Liver pathology of alcoholic steatohepatitis (ASH) and metabolic dysfunction-associated steatohepatitis (MASH). (A, B) The liver biopsy specimens in the top row came from a patient with alcoholic cirrhosis during liver transplantation. They show (A) cholestasis (arrowhead), (B) ballooned hepatocytes containing Malloy-Denk bodies (arrow), and focal necrosis associated with prominent inflammatory cell infiltration and fibrosis (hematoxylin and eosin stain [H&E]). (C, D) The liver biopsy specimens in the bottom row came from a patient with obesity during bariatric surgery. It shows macrovesicular zone 3 steatosis accompanied by lobular inflammation. (C) Ballooning degeneration (arrowhead) is observed, it is characterized by enlarged and swollen hepatocytes with granular material in the cytoplasm, which represents collapsed cytoskeleton. (D) Neutrophilic satellitosis (circle) and Mallory's hyaline, clumps of ropy eosinophilic material in hepatocyte cytoplasm representing misfolded and aggregated keratin filaments (arrow), are also present. ASH and MASH are pathologically difficult to distinguish (H&E; A and C, 100×; B and D, 200×).

more pronounced. Conditions such as sclerosing hyaline necrosis (perivenular hepatocyte necrosis with fibrosis), phlebosclerosis (narrowing of the hepatic vein lumen), and canalicular cholestasis (presence of bile thrombi in bile canaliculi) are more prevalent in ASH (Fig. 2A) [40]. In MASLD, hepatic injury may be seen as the concentration of mononuclear cells and polymorphonuclear leukocytes [41]. Although both MASH and ASH exhibit hepatocyte ballooning, ASH typically presents a more severe histological form (Fig. 2B and C). Mallory's hyaline (Mallory-Denk body) is usually well-formed in ASH and poorly formed in MASH (Fig. 2B and D) [40].

Considering the differences between ALD and MASLD mentioned above, it seemed to be reasonable to categorize the etiologies of SLD.

Keynotes
- Despite the overlap in histologic features between MASH and ASH, distinct differences exist.

TREATMENT APPROACH

Refining treatment for MAFLD and MASLD in the context of metabolic dysfunction and risks

As previously described, both the MAFLD and MASLD criteria were established to more accurately reflect the role of metabolic dysfunction in the development and progression of FLD or SLD compared with NAFLD. This is evident in the diagnostic process for MAFLD, which involves assessing BMI, diabetes status, and metabolic risk abnormalities, and for MASLD, which includes evaluating cardiometabolic criteria. Consequently, therapeutic strategies targeting metabolic dysfunction that were previously utilized for NAFLD are also applicable for MAFLD and MASLD.

Similarities and differences in treatment approaches for NAFLD, MAFLD, and MASLD

Initially, weight loss through diet and physical activity is a fundamental therapeutic strategy that ameliorates hepatic steatosis, inflammation, and fibrosis through metabolic mechanisms [12,43-47]. Weight reduction via surgery or endoscopic procedures is also deemed effective in this context. Pharmacological treatments formerly recommended for NAFLD, such as thiazolidinedione, glucagon-like peptide-1 (GLP1) receptor agonists, GLP1-glucose-dependent insulinotropic polypeptide dual agonists, and sodium-glucose cotransporter 2 inhibitors, are anti-hyperglycemic drugs that improve steatosis or steatohepatitis by mitigating metabolic dysfunction [48-53], although the level of evidence varies across these drugs. Thus, these medications may be advised for patients with diabetes and SLD, irrespective of their classification as MAFLD or MASLD. Given that novel medications, including thyroid hormone receptor-β selective agonist, possess metabolic mechanisms [54], it is plausible that this assumption can also be applied to the novel agents for MASLD.

However, if a patient exhibits additional factors beyond metabolic dysfunction contributing to SLD, the aforementioned therapeutic approaches may have limited effectiveness in improving the patient's condition, potentially leading to a poorer prognosis. For instance, in patients with significant cardiometabolic risk and alcohol consumption history, a diagnosis of MetALD within the SLD system can be made; MetALD is recognized as a distinct entity with a graver prognosis than MASLD [55]. In treating MetALD, management strategies must address both ALD and metabolic dysfunction. The greater a patient's alcohol consumption, the more essential the therapeutic focus on ALD becomes. The most crucial factor in the treatment of ALD is abstinence from alcohol [56]. In cases where liver damage has already progressed, the treatment approaches resemble those used for cirrhosis caused by other etiologies. Although some staged treatments for severe alcoholic hepatitis are known to be beneficial, most other treatments have limited efficacy. Consequently, for patients with MetALD, it may be challenging to apply the treatment guidelines or recommendations based on the definition of NAFLD. In both MetALD and ALD, addressing the accompanying metabolic disorders is known to help improve the prognosis, yet the primary treatment focus remains on reducing alcohol consumption, differing from the approach for NAFLD. Therefore, the treatment guidelines for NAFLD cannot be directly extended to MetALD.

On the other hand, MASLD, which excludes other etiologies such as alcohol, viruses, and autoimmune diseases, allows us to focus on the metabolic aspects of SLD. Furthermore, recent studies have reported very high concordance between NAFLD and MASLD [57,58], indicating that the previous guidelines for NAFLD can be applied to MASLD interchangeably. The recently published clinical practice guidelines on MASLD management by the European Association for the Study of the Liver, Diabetes, and Obesity (EASL, EASD, and EASO) incorporate the treatment sections from the previous NAFLD guidelines [59].

By contrast, for MAFLD, which encompasses MASLD and MetALD, greater caution must be exercised in using the existing NAFLD treatment guidelines. In some cases of MAFLD, treatment for ALD or other liver diseases may be more crucial for the patient's prognosis.

Keynotes
- Although MAFLD and MASLD treatment strategies largely align with those for NAFLD, MASLD allows for a more straightforward application of NAFLD guidelines due to the exclusion of other etiologies. By contrast, MAFLD requires more caution in applying existing guidelines.

PROGNOSIS

Poorer prognosis of MAFLD compared with NAFLD

NAFLD is associated with increased all-cause mortality and an increased risk of extrahepatic diseases, such as cardiovascular diseases, chronic kidney disease, and sleep apnea [60-63]. Hepatic steatosis is known to have a modest impact on liver-related outcomes in the general population [59,64]. However, NASH is significantly associated with liver-related outcomes, including increased liver-related mortality and hepatocellular carcinoma [64,65]. The stage of fibrosis is reported to be the most significant predictor of liver-related outcomes [66].

Since the concept of MAFLD was proposed in 2020, many researchers have compared the prognosis of patients diagnosed with NAFLD to that of patients diagnosed using the MAFLD criteria. Most studies showed that MAFLD has a poorer prognosis compared with NAFLD [27,67-69], suggesting that the MAFLD criteria better predict adverse outcomes, such as mortality, cardiovascular risk, and liver-related complications. Considering the causes of death among FLD patients, a higher proportion of those with NAFLD die from cardiovascular disease compared with ALD patients, a higher proportion of ALD patients die from liver-related disease [70]. MAFLD, which encompasses the mixed etiologies of FLD, including NAFLD and ALD, is inevitably associated with increased mortality and morbidity.

Similar prognosis between NAFLD and MASLD

MASLD has shown a very high concordance with NAFLD and is conceptually considered to reflect NAFLD more accurately than MAFLD. Thus, MASLD is expected to have a prognosis similar to that of NAFLD. Recently, several studies reported a similar long-term prognosis for NAFLD and MASLD [57,71], with slightly higher mortality in MASLD, likely due to the inclusion of criteria to identify cardiometabolic risk. Following the proposal of the MASLD criteria in 2023, several studies have been published comparing the prognosis of MAFLD and MASLD [72-74]. Generally, these studies reported that MAFLD included a higher proportion of high-risk patients with poorer outcomes compared with MASLD and showed a stronger association with adverse prognoses. Although this trend can be interpreted as MAFLD better identifying and predicting high-risk groups, it may indicate an overinterpretation of the risk in patients with SLD caused by metabolic dysfunction by including SLD with other etiologies. In other words, the probability that both liver-related and extrahepatic outcomes will be impacted by chronic liver diseases arising from causes other than metabolic dysfunction is higher in cases of MAFLD versus MASLD.

Furthermore, in patients who are lean or of normal weight without T2DM, the diagnostic criteria for MASLD (i.e., one or more cardiometabolic risk factors) have a higher sensitivity compared with those for MAFLD (i.e., two or more metabolic abnormalities). This may lead to the inclusion of relatively younger and leaner patients in the MASLD category, explaining this trend.

Keynotes
- MAFLD, encompassing a higher proportion of high-risk patients, generally has a poorer prognosis, including higher mortality, cardiovascular risk, and liver-related complications, compared with NAFLD and MASLD. However, MAFLD diagnosis may lead to an overinterpretation of the impact of metabolic dysfunction in patients with SLD. MASLD is expected to more clearly reflect the influence of metabolic dysfunction in terms of prognosis.

CONCLUSIONS

Advocating for "steatotic"

The stigma associated with certain terms varies between cultures and languages. Although the term "fatty" is not prominently stigmatized in the Korean language or public perception, it may be in other languages, such as English, and it is important to avoid the use of potentially stigmatizing terms whenever possible. Therefore, in this context, it is more appropriate to use "steatotic" rather than "fatty."

Advocating for "MASLD"

MAFLD and MASLD are nomenclatures proposed to reflect the metabolic dysfunction underlying SLD, previously defined as NAFLD. However, the two definitions differ significantly in (1) the exclusion of etiologies causing SLD, such as alcohol and viruses; (2) the criteria for confirming metabolic dysfunction; and (3) the allowed diagnostic strategies (blood biomarkers can be used to detect hepatic steatosis in MAFLD, whereas MASLD diagnosis relies solely on imaging or histology).

MAFLD does not exclude FLD due to other causes, such as alcohol and viral hepatitis. Taking NAFLD and ALD as examples, although NAFLD and ALD reportedly share histological similarities, their histopathology influenced by pathophysiology should not be considered identical. Furthermore, in FLD or SLD patients who have both metabolic disorders and a significant history of alcohol consumption, therapeutic approaches targeting metabolic factors may have limited effectiveness. In addition, the treatment guidelines for NAFLD clearly differ from those for ALD and other liver diseases, including viral hepatitis and autoimmune hepatitis. Therefore, the concept of MASLD, which excludes other causes, is more appropriate for applying existing NAFLD treatment guidelines focused on improving metabolic dysfunction.

These etiologic differences influence the epidemiology data on prevalence and prognosis, with MAFLD showing a higher prevalence and a larger proportion of high-risk patients, resulting in more adverse outcomes compared with MASLD. Although this may be interpreted as the MAFLD criteria better identifying and predicting high-risk patients, it could also be seen as an overestimation of the progression and prognosis of SLD due to metabolic dysfunction. Regarding the clinical relevance of the criteria for confirming metabolic dysfunction, patients who are overweight or obese or have T2DM generally satisfy both the MAFLD and MASLD criteria. However, the MASLD criteria are slightly more sensitive for patients without diabetes who are lean or of normal weight, leading to the inclusion of a higher proportion of younger and leaner individuals. This may be more useful in the Asian population, which has a relatively high proportion of patients with "lean" FLD or SLD [75]. From a diabetologist's perspective based on histopathology, epidemiology, clinical relevance, and treatment, the definition of MASLD more clearly reflects SLD induced by metabolic dysfunction. And, these advantages are more important for MASLD in T2DM, which requires an approach that focuses on metabolic causes, including insulin resistance.

Approach for MASLD detection and evaluation in people with T2DM

Some strategies for detecting and evaluating SLD may not be fully applicable to practice and research for people with T2DM. Allowing the use of blood biomarkers or scoring systems in addition to imaging and histology for identifying FLD enhanced the versatility of MAFLD in clinical settings. If robust statistical correlations with the blood biomarkers or scoring systems are established and evaluated, the SLD system might also consider allowing such biomarkers as hepatic steatosis screening methods.

Assuming that previous data on NAFLD can be interchangeably applied to MASLD, we recommend that SLD should be suspected in T2DM patients with unexplained elevations in blood liver enzyme levels, obesity, or other cardiometabolic risks as well as abnormal noninvasive scoring system results. For these patients, we recommend confirming the presence of SLD using imaging modalities, especially ultrasonography. Although ultrasonography has interobserver variability and limited sensitivity to detect mild hepatic steatosis, it is recommended as a priority for diagnosing SLD in term of accessibility, sensitivity, and safety [12,76]. These patients require evaluations for other coexisting etiologies per the SLD diagnostic flow. In addition, to assess the risk of fibrosis, which is a highly critical factor for prognosis, we recommend using scoring systems such as the fibrosis-4 (FIB-4) index, the most widely available and established noninvasive test [59,77]. FIB-4 is calculated using variables including age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count (PLT) [78], and if the calculated value exceeds 2.67, it is considered high risk. The NAFLD fibrosis score (NFS) and the AST-to-platelets ratio (APRI) have also shown moderate accuracy in predicting fibrosis [59]. The formula for the biomarkers is as follows [78-80].

- FIB-4 = age × AST/(PLT × $ALT^{1/2}$)
- NFS = −1.675+0.037 × age+0.094 × BMI+1.13 × [impaired fasting glucose or diabetes (yes = 1, no = 0)]+0.99 × (AST/ALT)−0.013 × PLT−0.66 × albumin
- APRI = 100 × (AST/upper limit of normal AST)/PLT (age in years, AST and ALT in U/L, PLT in 10^9/L, BMI in kg/m^2, albumin in g/dL)

If the risk is calculated to be intermediate or high, further evaluation of fibrosis using vibration-controlled transient elastography, the enhanced liver fibrosis score, or magnetic resonance elastography is recommended (Fig. 3).

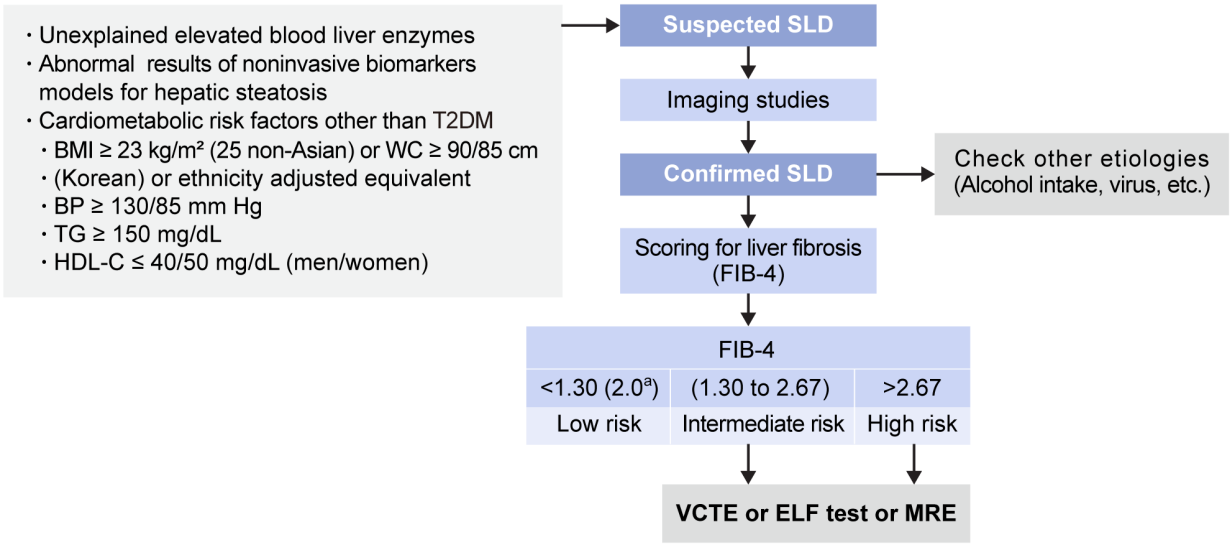

Fig. 3. Algorithm for steatotic liver disease (SLD) evaluation in patients with type 2 diabetes mellitus (T2DM). BMI, body mass index; WC, waist circumference; BP, blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FIB-4, fibrosis-4; VCTE, vibration-controlled transient elastography; ELF, enhanced liver fibrosis; MRE, magnetic resonance elastography. [a]Higher cutoffs for patients aged >65.

In conclusion, from the perspective of the diabetologist, the concept of MASLD more clearly reflects SLD induced by metabolic dysfunction. Future studies are needed to identify key factors influencing clinical outcomes of these diseases and to implement appropriate interventions. Furthermore, understanding the pathophysiology of these disorders is crucial to developing new prognostic indicators, diagnostic markers, and therapeutic targets.

CONFLICTS OF INTEREST

Kyung Mook Choi has been honorary editors of the *Diabetes & Metabolism Journal* since 2022. Kyung-Soo Kim has been associate editors of the *Diabetes & Metabolism Journal* since 2024. They were not involved in the review process of this article. Otherwise, there was no conflict of interest.

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