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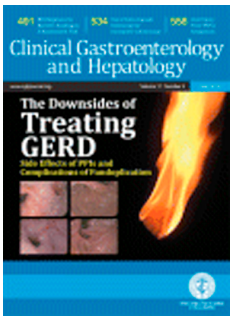

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On the proposed definition of metabolic associated fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is now the leading cause of chronic liver disease in the U.S. and globally.[1-3] NAFLD is the hepatic manifestation of the metabolic syndrome and is

closely associated with diabetes and obesity. Coinciding with large increases in metabolic syndrome, the prevalence of NAFLD in the general population has doubled in the past 2 decades with estimates as high as 30%.[2] Although NAFLD is often a non-progressive hepatic steatosis associated with few, if any, hepatic complications, at least 20–30% of patients with NAFLD develop progressive liver disease with necroinflammation and fibrosis that can result in cirrhosis in 10–20% of cases. NAFLD is the fastest growing cause of cirrhosis in the U.S. and an increasingly important risk factor for hepatocellular cancer.[4]

Despite the importance of the condition, there has been a controversy about its name, as we describe below. A consensus of international experts recently proposed the disease acronym metabolic (dysfunction)-associated fatty liver disease or 'MAFLD' *in lieu* of NAFLD.[5] This proposed shift in terminology has led to a major debate in the field. We discuss the history of the term NAFLD and its limitations, controversies around the new terminology, and our viewpoint about what lies ahead.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Brief history of the term ‘NAFLD’

Fatty liver related to alcohol use was first described by Addison in 1836.[6] Following that and over a century, pathologists pinpointed the similarities in liver histology seen in diabetic and morbidly obese individuals with those who drink excessively. In 1979, Miller, Ishimaru, and Klatskin presented the findings of their histologic study of non–alcoholic liver disease mimicking alcohol-induced hepatitis and cirrhosis, characterized by fatty infiltration, Mallory bodies, neutrophilic infiltration, severe hepatocyte injury, and fibrosis.[7] Concurrently, Adler and Schaffner, published their observations about "fatty liver hepatitis and cirrhosis" occurring in obese patients.[8] This was followed by the report from Ludwig and colleagues about their experience with what they named nonalcoholic steatohepatitis in 1980.[9] These early reports were selected from cases whose liver pathology was typical of alcohol-related liver disease but who had no history of excessive alcohol use. Over the years, the nomenclature has included many terms, from nonalcoholic fatty liver, fatty hepatitis, and nonalcoholic steatohepatitis (NASH).

Limitations of the term NAFLD

NAFLD remains a diagnosis of exclusion. By definition, it can only be diagnosed when other liver diseases, such as hepatitis C or hepatitis B virus infection, are absent. However, fatty liver due to metabolic dysfunction (and in the absence of alcohol use) can not only co-exist with viral hepatitis and other chronic liver diseases, but can also have a synergistic negative effect

on disease progression in patients with both conditions compared to those with one condition alone. Further, and since its first description, NAFLD has been considered distinct from alcohol-related liver disease based on a cutoff of daily alcohol intake of 30 g daily for men and 20 g daily for women. This dichotomy is problematic in real clinical practice. NAFLD and alcohol use are both common conditions and common conditions often co-exist. Many adults with NAFLD drink at least in moderation. There is a need to understand the influence of light and moderate alcohol use in patients who have NAFLD, but the current terminology makes it difficult to study this group of individuals. Patients who have coexisting metabolic and alcohol-related liver disease are also currently excluded from all clinical trials of NAFLD, resulting in a large unmet need about the best way to manage and treat this important subgroup of individuals.

There is also an underlying heterogeneity in individuals with NAFLD with respect to primary drivers and disease modifiers. Specifically, although hepatic steatosis is highly prevalent, only a few individuals with hepatic steatosis develop hepatic inflammation at any point in their clinical course. Indeed, natural history studies and clinical trials have clearly shown that NAFLD/NASH is a highly dynamic state with disease progression in some and improvement through lifestyle changes and pharmacological treatment in others.[14-16] There is unexplained heterogeneity in how fast fibrosis progresses from one to the next stage.[14] In summary, the

drivers of disease progression in NAFLD are likely multifactorial – suggesting that classifying all individuals as NAFLD (or NASH) *vs*. not may be too simplistic of an approach for such a heterogenous disease.

AN ALTERNATIVE TERM: METABOLIC (DYSFUNCTION)-ASSOCIATED FATTY LIVER DISEASE (MAFLD)

Given the limitations noted above, a panel of international experts recently proposed the disease acronym or 'MAFLD'.[5] This term recognizes that metabolic dysfunction can lead to or worsen liver disease in the presence of other etiological risk factors, such as alcohol use or hepatitis C virus infection. This term is also supposed to reflect the close relationship between fatty liver and overnutrition, sedentary lifestyle and metabolic conditions including type 2 diabetes, hypertension, dyslipidemia and obesity. The definition of MAFLD requires the presence of metabolic risk factors, allows the inclusion of patients with concomitant liver diseases and excludes patients with hepatic steatosis who do not fulfill the metabolic criteria. (**Table**).

The proposal to change the nomenclature from NAFLD to MAFLD is more than a change in the name; this change comes with a slight shift in the *types* of patients classified as having MAFLD *vs*. NAFLD. For example, recent studies show that there is a substantial overlap in

the two definitions, with 80-90% of patients with hepatic steatosis meeting criteria for both NAFLD and MAFLD. However, a non-negligible proportion of individuals meets the criteria for one but not the other condition (**Figure**). In a population-based study using proton-magnetic resonance spectroscopy, Wong *et al.* found that out of 277 patients with hepatic steatosis, 247 (89.2%) met both definitions, 5.8% met the definition of MAFLD but not NAFLD, and 5.1% met the definition of NAFLD but not MAFLD.[14] In another study using data from the U.S. National Health and Nutrition Examination Survey, these proportions were 80%, 7.8% and 14.2%, respectively.[15] In both studies, patients who met the definition of NAFLD but not MAFLD had no or mild metabolic conditions and also milder liver fibrosis, whereas patients with MAFLD but not NAFLD were more likely to have significant liver disease. The latter finding is likely related to inclusion of patients who have metabolic risk factors and also drink excessively.[14,16]

Although we still need more data from different parts of the world, the prevalence of these discordant subgroups (that is, patients who meet the criteria for one but not the other term) may be different in different regions based on in the prevalence of lean NAFLD, hepatitis C, hepatitis B and alcohol related liver disease.[17]

The panel also proposed that patients with cirrhosis, even in the absence of typical features of steatosis or steatohepatitis, should be considered as having MAFLD-related cirrhosis if they

meet at least one of the following criteria: past or present evidence of metabolic dysregulation (according to MAFLD criteria), with either documentation of MAFLD in previous biopsy or steatosis by imaging techniques.

CONTROVERSIES

After the publication of the new MAFLD nomenclature and definition, a group of hepatologists from the US wrote a commentary in HEPATOLOGY opposing the proposal.[18] Subsequently, a group of hepatologists from Europe and the US wrote another commentary in the *Journal of Hepatology* highlighting issues surrounding the new nomenclature.[19] Meanwhile, the Asian Pacific Association for the Study of the Liver has published the first guidelines using the term MAFLD,[20] followed shortly afterwards by the Latin American Association for the Study of the Liver.[21]This has stimulated a heated debate in the scientific community. In this section, we highlight the main discussion points.

Disease awareness

Compared with other metabolic diseases such as diabetes and obesity, NAFLD is less recognized by the public, healthcare providers outside hepatology and policymakers.[21-24] Hepatologists and liver organizations are trying to engage the other disciplines by increasing representation at major meetings in internal medicine, cardiology and endocrinology. The

worry is that the name change may confuse the stakeholders, making it more difficult to get the message across.[18]

In response, representatives of patient advocacy groups from North America, Europe and the Asia-Pacific jointly wrote an article in support of the new nomenclature.[25] According to the patient groups, the name NAFLD may lead to stigmatization through including the word "alcoholic" in its name and implying that it is a self-inflicted disease. The name may cause more confusion as it emphasizes the exclusion of alcohol and ignores the actual cause of metabolic dysfunction. While it may be necessary to exclude excessive alcohol consumption in clinical studies for homogeneity, many patients in the real world have fatty liver disease from the effects of alcohol and metabolic dysfunction at the same time, and those with both risk factors tend to have disease that is more serious.[26]

Moreover, using the example of non-communicable diseases, the patient representatives argued that the "non-" prefix conveys a perception of the disease as unimportant.[27] Despite a much higher disease burden, non-communicable diseases have consistently received less funding than infectious diseases.

Drug development

In spite of the huge population of patients with NASH and the rapid rise of NASH as a leading cause of advanced liver disease and hepatocellular carcinoma in the Western world,[3] there is still no registered drug for the treatment of NASH.[28] Therefore, NASH drug development has become one of the hottest research areas in clinical medicine, with a number of agents now in phase 2b/3 development. Through a series of meetings with professional societies (American Association for the Study of Liver Diseases and European Association for the Study of the Liver) and clinical experts, the Food and Drug Administration and European Medicines Agency have provided guidance on NASH development, including the use of surrogate histologic endpoints (resolution of NASH without worsening of fibrosis or fibrosis improvement without worsening of NASH) for conditional approval of a therapeutic agent followed by long-term follow-up to confirm an impact on clinical outcomes. One unresolved issue of the MAFLD proposal is the decision to abandon the term NASH.[5] The rationale is that the dichotomous classification fails to capture the full spectrum of the disease and describe changes over time. Instead, Eslam and colleagues recommend describing the activity and fibrosis stage of MAFLD. However, abandoning the term NASH is incompatible with the current histologic endpoints of resolution or worsening of NASH. It is difficult to communicate the same concept using histologic scores, not to mention the prognostic significance of the NAFLD activity score beyond the correlation with fibrosis stage has not been firmly established.[29,30]

Ambiguity of metabolic dysfunction

Younossi and colleagues highlighted that there is a lack of consensus on the definition of "metabolic health".[18] They described alcohol-related liver disease, Wilson disease and total parenteral nutrition-associated fatty liver as other forms of metabolic liver disease to illustrate that the term MAFLD cannot resolve such ambiguity.

The difficulty of finding a perfect name stems from the fact that NAFLD is a heterogeneous disease with complex pathophysiology. There is no doubt that each component of the metabolic syndrome increases the risk of NAFLD and liver-related complications in a dose-dependent manner.[31,32] Nonetheless, none of these components is essential. For example, although NAFLD is more common in obese people, around 40% of NAFLD patients are non-obese.[33,34] Likewise, advanced liver fibrosis and hepatocellular carcinoma are more common in diabetic patients, but not all NAFLD patients have type 2 diabetes mellitus.[35,36] As we discussed above, several studies demonstrated that patients who fulfill the MAFLD criteria have more severe metabolic and liver disease than those who fulfill the NAFLD criteria alone.[14-16] In our opinion, these are valid observations but are insufficient to prove that the MAFLD criteria are better. First, because the diagnosis of MAFLD requires the presence of

metabolic risk factors, it comes as no surprise that MAFLD patients would have more severe metabolic disease. Besides, it is a balance between identifying and missing significant disease. As an analogy, if we change the definition of diabetes mellitus by increasing the hemoglobin A_{1c} cutoff from 6.5% (47.5 mmol/mol) to 9.0% (74.9 mmol/mol) (and adjusting the other criteria accordingly), patients who fulfill the new definition would of course have a much higher incidence of diabetic complications, but we will also miss many patients at risk of the complications. Future studies should clarify if the MAFLD criteria would miss patients with significant liver disease.[14]

In addition, Younossi and colleagues stated that "a change in terminology for a disease entity is justified when more scientific, complete understanding of its pathogenesis, or/and risk stratification, or/and molecular phenotyping, or/and novel precision medicine-based therapeutic approaches are elucidated."[18] While we acknowledge the importance of molecular and multiomic approaches in enlightening clinicians and researchers on the pathogenesis and management of the disease, there has been accumulating knowledge in the past few decades, and it is unclear whether there is a point when the scientific community can claim complete understanding of this heterogeneous disease. Besides, primary care physicians and endocrinologists are seeing the majority of NAFLD patients. The demand for advanced

diagnostics to diagnose and classify fatty liver disease may be unrealistic and go against the original aim to increase disease awareness among the public and other medical disciplines.

THE ROAD AHEAD

In our opinion, there are compelling reasons to think of a better name for what we have called NAFLD for decades. For the most common disease in our field, it is appropriate to use a name that says what it is rather than what it is not. On the other hand, the sentiments surrounding the lack of engagement with different stakeholders are well taken. The views of patients, colleagues from other medical disciplines, policymakers and regulators should be considered and respected. We therefore agree with Younossi, Ratziu and colleagues that further discussion is necessary.[18,19] Evidence needed to inform the future direction includes:

1. The meaning of hepatic steatosis in patients with concomitant liver diseases.
2. The impact of the proposed metabolic criteria. In the current form, the metabolic criteria were borrowed from different criteria of the metabolic syndrome and cardiovascular risk assessment.[5] The relative importance of the individual metabolic factors as well as the number and definition of each metabolic risk factors for the diagnosis of MAFLD should be evaluated. Several medical disciplines are moving away from the term ‘metabolic syndrome’. For instance, the diagnosis of type 2 diabetes and hypertension does not require

the presence of other metabolic risk factors. This aspect will need to be considered in future deliberations.

3. The impact of the selected criteria in different populations, e.g. adults and children, men and women, and regions.
4. The impact of abandoning the term steatohepatitis.

Hopefully, constructive discussions on these issues will eventually translate into improved disease awareness and patient care.

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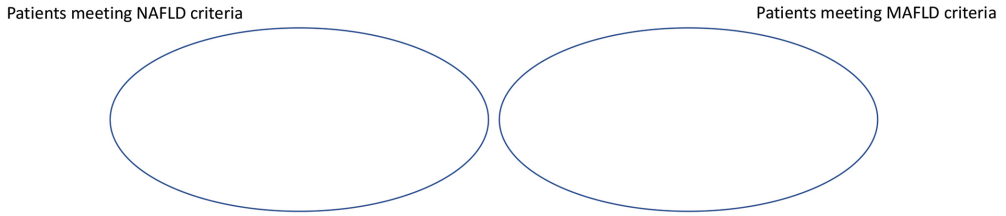
Table. Definitions of nonalcoholic fatty liver disease and metabolic-dysfunction associated fatty liver disease.

	MAFLD	NAFLD
Demonstration of fatty liver by imaging, histology or prediction scores	Required	Required
Exclusion of excessive alcohol consumption	Not required	Required
Exclusion of viral hepatitis and other liver diseases	Not required	Required
Exclusion of secondary causes of fatty liver (e.g. tamoxifen or methotrexate)	Not required	Required
Presence of overweight/obesity, type 2 diabetes or 2 other metabolic factors	Required	Not required

Figure. Overlap between patients classified as having nonalcoholic fatty liver disease and those with metabolic dysfunction associated fatty liver disease.



Overlap between NAFLD and MAFLD

≥80% of patients meeting criteria for one definition also meet the criteria for the second definition.