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Editorials

A call for unity: The path towards a more precise and patient-centric nomenclature for NAFLD

Since the original description in 1849 of visceral and subcutaneous adiposity in overfed children by von Rokitansky (reviewed in Ayonrinde [1]), the field has struggled to come up with an adequate nomenclature. In the absence of alternatives, nonalcoholic fatty liver disease (NAFLD) was adopted because it described the presence of fat inside the liver while excluding another common cause, namely excess alcohol. Unlike non-A non-B hepatitis (now known as hepatitis C), NAFLD has persisted largely because of a lack of agreement about a nomenclature that was sufficiently better and because of knowledge gaps in terms of understanding its pathophysiology.

However, large population-based studies clearly demonstrate that, despite considerable phenotypic heterogeneity, the vast majority of diseases currently designated as NAFLD are related to so-called "metabolic" factors including overweight, visceral obesity, insulin resistance, and dyslipidemia. Although NAFLD accurately captures the increase in fat inside the liver, it has several shortcomings. Firstly, it does not explain what the cause is; rather, it describes what is not the cause, and hence it does not adequately capture the aforementioned entity. Secondly, the term "fatty" is perceived by many patients as being stigmatizing and thus hinders disease awareness and patient desire to engage with healthcare services. Thirdly, it does not take account of the common clinical scenario in which patients often have both metabolic-and alcohol-related contributions to fat inside the liver. The latter comes with several issues: patients with more than minimal and, by definition, nonrisky alcohol consumption of > 20 g and > 30 g for women and men, respectively, combined with metabolic risk factors are currently often labeled as having alcohol-only liver disease, which is not only stigmatizing but also potentially underestimates the true driver of liver disease—metabolic syndrome—and thus has implications for insurance and health benefits; it also contributes to hampering a fair examination of relative contributions of each factor and their potential synergistic effects in individuals who combine risk factors for both diseases. Moreover, it is not only the combination with alcohol that struggles from the current nomenclature, as patients with other chronic liver diseases (e.g., viral or autoimmune) can also have coexisting "metabolic" risk factors for fatty liver disease that contribute to the overall amount of liver injury.

To address this, an alternative suggestion was put forward in 2019, namely metabolic dysfunction– associated fatty liver disease (MAFLD), which required the presence of steatosis in coexistence with stipulated metabolic criteria. This had the advantage of being both an affirmative name and diagnosis, although its use of fatty in the title retained stigmatizing terminology according to both patients and providers, and the term "metabolic" was not universally conceived as well defined and yielded different connotations, especially in the pediatric population. Moreover, its permissive approach to alcohol consumption rendered it a very different condition to that currently known as NAFLD and studied in clinical trials and biomarker discovery studies. This raised concerns and highlighted the need to consider the potential impact of a change in definition on the existing body of evidence on NAFLD as well as the developmental path for drugs and biomarkers.

In response to this, multinational liver societies, together with patient advocacy groups, convened and endorsed a global nomenclature group in 2020 to review naming and definition options for NAFLD. At its inception, the participating liver societies were the American Association for the Study of Liver Diseases (AASLD), Latin American Association for the Study of the Liver (ALEH), Asian Pacific Association for the Study of the Liver (APASL), and European Association for the Study of the Liver (EASL), with the patient bodies being the Global Liver Institute, European Liver Patients' Association (ELPA), Liver Patients International (LPI), Fatty Liver Foundation (FLF), and American Liver Foundation (ALF). Each society and patient group was asked to nominate experts from their membership who would add input and vote in this process. Additionally, endocrinologists and pediatricians were involved at every stage of the process.

To undertake a process to determine if consensus could be reached for an improved nomenclature, the well-established Delphi methodology was employed. The resultant diverse panel of leading experts and key stakeholders from around the world addressed a number of central topics, which ultimately resulted in a series of statements and questions that were voted on across four iterative rounds of data collection. Questions covered a wide range of topics including stigma, suitability of NAFLD as a name, and the role of alcohol. Representation in the Delphi panel of over 200 participants was based on contribution to the field, size of organization, and global geography. A final response rate of over 75% was quite strong, given the large sample size involved in 4 rounds of data collection, attesting to the rigor of the methodologic approach employed.

As a predefined part of the process, after the second round of voting, a face-to-face meeting of the group was convened in Chicago in July 2022, which included online participation as well. This allowed for sharing and in-depth discussion and opposition of views and

Abbreviations: AASLD, American association for the study of liver diseases; ALEH, Latin American association for the study of the liver; EASL, European association for the study of the liver; NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction–associated fatty liver disease

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Table 1
Guiding principles in the selection of new nomenclature.

Affirmative—nonstigmatizing and respectful of other branches of medicine
Accurate in its description of the condition
Adaptable—providing a platform that allows for inclusion of past, present, and future knowledge
Adoptable—simple, clear, and understandable as well as translatable
Applicable across all patients and full age spectrum (pediatric through adult)
Able to define contribution of alcohol when greater than previously permitted

opinions and led to consensus on the principles underpinning the choice of names and definition for NAFLD and related conditions (Table 1). Other recommendations included broadening geographical representation further, resulting in 30 additional members being added to the voting group.

Two further rounds of voting were undertaken that incorporated feedback from the discussions at the meeting in Chicago. The first (Round 3) informed a well-attended multisociety meeting at the AASLD Liver Meeting in 2022 (also broadcast live), and the final (fourth) round further narrowed the remaining nomenclature options. One of the limitations of the Delphi method is that it cannot guarantee that consensus will be met for every issue that it is applied to, particularly those for which extensive debate exists. Certainly, consideration of a new nomenclature for NAFLD is a complicated and challenging undertaking. Nonetheless, a large, diverse panel with consistently high response rates over four rounds of data collection resulted in majority support for a way forward and speaks to the strength of this methodology.

Currently, the process of final recommendations on naming and defining NAFLD is ongoing. The outcomes of this final consensus will be announced in 2023, and a detailed report on methodology and results will be published alongside simultaneous publication in society journals, with engagement with a broader range of stakeholder groups, which ultimately should benefit from a broadly endorsed consensus solution to the aforementioned issues that were at the origin of this process.

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Declaration of Competing Interest

Norah A. Terrault consults for Moderna. She received institutional grants from GSK, Genentech-Roche, Helio Health, Gilead, and Durect. She has other interests in CCO and Simply Speaking. Thomas Berg advises and is on the speakers' bureau for AbbVie, Alexion, Intercept, Gilead and GSK.

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Reference

[1] Ayonrinde OT. Historical narrative from fatty liver in the nineteenth century to contemporary NAFLD -Reconciling the present with the past. JHEP Rep. 2021;3:100261.

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