MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Stephen A. Harrison, MD

Examining the Nomenclature Change From NAFLD and NASH to MASLD and MASH

Mary E. Rinella, MD
Professor of Medicine
Director of the Metabolic and Fatty Liver Program
University of Chicago Pritzker School of Medicine
Chicago, Illinois

G&H Why was the nomenclature for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis changed?

MR From a historical perspective, the terms nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) were not ideal, as they were exclusionary terms that required the elimination of all other diseases as the diagnostic criteria and thus were diagnoses of exclusion. Another issue was that some people felt that these terms were stigmatizing owing to the use of the words *fatty* and *nonalcoholic*. Furthermore, nonalcoholic does not specifically reflect the underpinnings of the disease. The catalyst for the nomenclature change, however, was the introduction of another term in a paper in 2020, metabolic dysfunction-associated fatty liver disease (MAFLD). Importantly, the definition of that term included a subset that was somewhat distinct from NAFLD owing to more restrictive metabolic criteria and the allowance of liberal alcohol use. Thus, this would have had a negative impact on biomarker development and our understanding of the natural history of the disease, which is based on decades of observational data. We are on the cusp of having a therapy for the disease and have made significant strides in biomarker development, and adopting MAFLD had the risk of altering biomarker development and response to therapeutics.

G&H Could you explain the Delphi process by which the new nomenclature was developed and finalized?

MR The Delphi process was felt to be the best way to reach consensus as objectively as possible on a topic that was controversial and contentious in some aspects. I, on behalf of the American Association for the Study of Liver Diseases (AASLD), and Professor Philip N. Newsome, on behalf of the European Association for the Study of the Liver (EASL), put together a global steering committee that included members from Asia, Africa, Latin America, and Europe. A total of 224 people representing 56 countries participated in the survey rounds, and there were 4 rounds of voting over a 2.5-year period. Representatives from patient organizations were also included as well as members of the pharmaceutical industry. Via the Delphi process, a list of statements was developed through literature- and expert-based consensus from working groups assembled to represent all of the aforementioned stakeholders. This was an iterative process in which statements were modified according to comments and the results of the preceding round of voting. Around 2700 comments were considered and used to shape the subsequent statements.

G&H Could you outline the new nomenclature that was chosen?

MR One of the important decisions that came out of this process was that there should be an umbrella term, *steatotic liver disease* (SLD), under which would sit different causes for the accumulation of steatosis in the liver. One category under SLD is *metabolic dysfunction-associated steatotic liver disease* (MASLD), which is what we previously referred to as NAFLD except that the presence of at least 1 cardiometabolic risk factor is required to make the diagnosis. MASLD includes *metabolic dysfunction-associated steatohepatitis* (MASH), which was previously known as NASH, and, although not specifically articulated in

the paper, *metabolic dysfunction-associated steatotic liver* (MASL) (previously nonalcoholic fatty liver [NAFL]) to identify those with MASLD who do not meet the criteria for MASH. Another category under SLD is MetALD, which includes people who drink above the alcohol limit allowed for MASLD, greater than 20 g/day for females and greater than 30 g/day for males, but less than 50 g/day for females and less than 60 g/day for males, beyond which would be considered alcohol-related liver disease, which is another disease that sits under the umbrella of SLD. Other subcategories of SLD include drug-induced liver injury and niche-specific causes of steatosis.

> … in most iterations, 95% of the people surveyed agreed that steatohepatitis should remain relevant for our understanding of disease, development of biomarkers, and assessment in clinical trials.

G&H What were some of the most important statements that were considered during the Delphi process?

MR Some of the most important statements were related to the definition of the disease, firstly, that steatohepatitis was a very important aspect of the disease and its main driver. This had been minimized and was considered not to be particularly relevant in the previously proposed nomenclature known as MAFLD. The consensus on steatohepatitis was extremely high; in fact, in most iterations, 95% of the people surveyed agreed that steatohepatitis should remain relevant for our understanding of disease, development of biomarkers, and assessment in clinical trials.

Another important statement involved alcohol. As mentioned, the MAFLD definition would have changed the understanding of the natural history of the disease, partly because there were no specific limits on alcohol consumption; this would have encompassed a population of patients with a more accelerated disease course. One of the most important outputs of this process was that alcohol use above the previously defined limits outlined by the definition of NAFLD needed to be considered a separate entity. Therefore, we developed the new disease subcategory known as MetALD, which was meant to encompass people who have what was known as NAFLD and who also drink alcohol beyond allowed limits for NAFLD/MASLD. This will now enable the studying of this population independently because these patients, in addition to having a different natural history, may respond differently to drugs and may have different cut-offs for biomarkers.

G&H What were the biggest challenges of this process?

MR One of the biggest challenges was that the overall group was divided with respect to what name they wanted the disease to have, which is why we went to great lengths to have a legitimate and transparent process. Some people were very much in favor of using the MAFLD diagnosis and name. There was another group that was very interested in keeping NAFLD and not changing that definition at all.

A more minor point of contention involved the use of the term *metabolic* because it is difficult to define. That was something we went back and forth on primarily with endocrinologists and to some extent with the pediatric group within our consensus process. Ultimately, the supermajority supported the use of the word *metabolic* in the name of the disease because, even though the term is difficult to define, it gave people a sense of the cause and problem underlying the disease, which was felt to be useful.

G&H Might the new nomenclature have any impact on biomarker development, the regulatory process, clinical trials, and disease awareness?

MR Already several papers have been published looking at applying the new definition to, for example, the National Health and Nutrition Examination Survey; the NIMBLE (Non-Invasive Biomarkers of Metabolic Liver Disease) Consortium, which is a US National Institutes of Health (NIH)-based biomarker consortium; or the LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) Consortium, which is a European biomarker consortium. The population defined by the old and new definitions are essentially equivalent (97.5%-99%); that means biomarker development and the regulatory process should not be impacted at all by the nomenclature or definition change.

From a clinical trials perspective, the nomenclature

change should have no impact because the inclusion criteria largely involve liver biopsy, at least for now. Otherwise, as previously discussed, looking at clinical trial populations, the overlap between the previous and new terms should be close to 99%. With the new defining criteria for MASLD, it will be highly unlikely to miss people who have the disease, which is reassuring.

As far as the US Food and Drug Administration (FDA) goes, the impression that we have gotten is that the agency does not have any specific problem with changing the nomenclature. The only tricky part will be the time from now until billing codes are able to be modified.

Finally, there is a good deal of work to do initially in terms of disease awareness, but it is important to realize that right now only around 5% of people with the disease are actually diagnosed; thus, we were not doing a great job with disease awareness of NAFLD. We are optimistic and placing a lot of energy into disseminating the new nomenclature, and hopefully the more overt communication of the underlying cause of the disease will elevate the perceived importance of the disease and bring increased awareness over time. It will be an uphill battle initially, but I think we have the tools and the momentum to hopefully end up in a better place than we are today.

G&H How can awareness and education of the new nomenclature be spread?

MR One way is through its use in publications. In fact, only a few months after the online release of the joint publications announcing the new nomenclature, which is not in final print publication until December, the Delphi consensus statement has already been cited more than 184 times in the literature. The continued use of the nomenclature in national meetings across the globe and in publications will be very important. The largest liver societies, including AASLD, EASL, and the Latin American Association for the Study of the Liver, have formally adopted the new nomenclature, and the process and new nomenclature have already been endorsed by nearly 100 societies worldwide.

G&H What has been the reception to the new nomenclature from patients and the community?

MR The response has varied from patient groups; some have wholeheartedly embraced the nomenclature change, whereas others have had resistance to it. Even though we included as many patients as agreed to participate, we left participation completely open-ended and tried to work with several patient organizations to engage their members to participate in the process. We did not have much uptake from that despite our intentions.

We have not had any specific resistance from the community per se, but like anything else, the nomenclature is new and new things are always challenging. Even when the term primary biliary cirrhosis was changed to primary biliary cholangitis, there was resistance despite the acronym staying the same; it took many years for that change to completely sink in. Although there will be challenges because the nomenclature of MASLD and MASH is new and different, I think people will hopefully understand that the change moves the field forward and gives us a definition that is positive and not exclusionary and that eliminates stigma, which are all very important and good things. Getting used to the change will just take time.

G&H What are the next steps in the rollout of the new nomenclature?

MR An important next step is continuing to have conversations with the community, associations in other subspecialties, and other stakeholders such as the FDA, the NIH, and industry partners, of which there are many. In addition, we have plans to change International Classification of Diseases coding for the next iteration and are hopefully making progress with the Centers for Medicare and Medicaid Services to change billing and coding, which will help providers on the ground seeing these patients.

Disclosures

Dr Rinella has no relevant conflicts of interest to disclose.

Suggested Reading

Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158(7):1999-2014.e1.

Krag A, Buti M, Lazarus JV, et al. Uniting to defeat steatotic liver disease: a global mission to promote healthy livers and healthy lives [published online August 25, 2023]. *J Hepatol*. doi:10.1016/j.jhep.2023.07.029.

Rinella ME, Lazarus JV, Ratziu V, et al; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature [published online June 24, 2023]. *Hepatology*. doi:10.1097/HEP.0000000000000520.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797-1835.

Younossi Z, Yılmaz Y, Fan JG, et al. Stigma in NAFLD and NASH: a global survey of patients and providers. *J Hepatol*. 2023;78:S627-S628.