EDITORIAL

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The New Nomenclature for Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD) and its more severe subtype non-alcoholic steatohepatitis (NASH), is the most common chronic liver disease (CLD) worldwide and represents an increasing burden of morbidity and mortality, and comes with a substantial individual patient suffering and a considerable societal cost [1]. In the past two decades, intensive research has been conducted to understand disease pathophysiology and clinical course better and develop diagnostic and therapeutic tools for disease management. Changing the name and the definition of the disease is, hence, something that could potentially have a huge impact and needs careful consideration of the pros and cons.

CONSENSUS PROCESS

Recently, a new framework for naming and defining diseases hallmarked by liver steatosis has been endorsed by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), the Asociación Latinoamericana para el Estudio del Hígado (ALEH) and a large group of other stakeholders implying that this is currently the standard to use in research as well as in the clinics [2].

This new nomenclature results from a thorough consensus process using a stringent Delphi methodology, with 236 people of different expertise and widespread geographical distribution going through 4 Delphi rounds and two meetings to achieve a solid consensus.

RATIONALE FOR THE NOMENCLATURE CHANGE

The process was initiated because the term NAFLD, although widely adopted since its introduction in 1980, came with several limitations. First, the term "fatty" comes with a stigma for many patients. Although there are regional and cultural differences, this was felt to be addressed. Secondly, the disease is characterized by what it is not; specifically, it is not caused by alcohol consumption, which was the most recognized and common cause of liver steatosis when the term was introduced by Ludwig et al. [3]. Typically, disease names highlight a specific feature or the cause, such as autoimmune hepatitis or drug-induced liver injury (DILI). In contrast, NAFLD denotes what it is not. Third, the consequence of this, reflected in the definition that requires alcohol consumption above the 20/30 g/d threshold to be excluded, precludes the co-existence of NAFLD with moderate to severe alcohol consumption. In clinical practice, however, many patients with liver steatosis have both cardiometabolic risk factors and consume > 20/30g of alcohol per day. Before the new nomenclature, there was no way to accurately name this clinical reality, impacting research and clinical management. Fourth, the diagnosis of NAFLD also required another disease to be ruled out, making it difficult to accurately diagnose, study, and treat patients who combined multiple risk factors for steatosis and chronic liver disease.

The process included a diverse group of participants, such as expert hepatologists with special interests and expertise in NAFLD, specialists in alcohol-related liver disease, and professionals from non-hepatology fields connected with the condition (including endocrinologists, diabetologists, obesity physicians, and pediatricians). General practitioners and active patient involvement were essential. The Delphi rounds and two meetings facilitated discussions, clarified statements, and ensured a comprehensive consensus process.

STEATOTIC LIVER DISEASE: AN UMBRELLA TERM

In renaming and redefining NAFLD, it became evident that an umbrella term, steatotic liver disease (SLD), was necessary. This term, chosen to avoid stigma, covers various single etiologies of steatosis, from common (metabolic, alcohol) to less frequent causes. SLD emphasizes the need for a thorough investigation when steatosis is identified. Importantly, diseases under the umbrella are not redefined; instead, it acknowledges that steatosis can be a prominent feature. For instance, Wilson's disease retains its definition, but if a patient develops steatohepatitis, a comprehensive examination for other causes becomes essential for proper management and prevention of progression.

Besides this list of single etiologies, the concept of the umbrella term also allows all potential combinations. A patient living with obesity, drinking 50 g of alcohol daily, and taking methotrexate can, if diagnosed with steatosis, now be accurately labeled as having three causes of steatosis combined. While diligent physicians undoubtedly identified this combined etiology and ideally addressed it by simultaneously addressing various causes, there were no effective means of appropriately labeling it. This lack of clarity made explaining to patients confusing and led to their exclusion from clinical trials and the majority of research, rendering them an underserved group in various aspects.

The replacement term for NAFLD is metabolic dysfunction associated steatotic liver disease (MASLD), a term reflecting our current understanding that NAFLD is mainly caused by overweight/obesity and adipose tissue dysfunction, insulin resistance, and the more comprehensive cluster of cardiometabolic risk factors referred to as metabolic syndrome. The fact that this name indicates the root cause of the disease eases communication with patients about their disease. Also, the definition is straightforward and can be easily applied based on clear criteria. Of note, the framework of steatohepatitis and fibrosis has not changed, so concepts about disease severity are as before, just replacing the term non-alcoholic steatohepatitis (NASH) with metabolic dysfunction associated steatohepatitis (MASH).

Another consequence of this approach is that a small group of patients with steatosis, but for whom no cause can currently be identified and whom we previously named NAFLD, end up being classified as a new category of cryptogenic SLD. This is important, as these patients can now more easily be informed that we cannot explain why they have steatosis. It reduces the heterogeneity in the former NAFLD population and allows us to study this specific group better, hoping to find aetiological clues that will allow for a precise diagnosis (and hopefully accompanying treatment).

ADDRESSING ALCOHOL-RELATED LIVER DISEASE

The new framework will, by indeed inciting for a broad differential diagnosis, and consequently a combined treatment of all factors contributing to steatosis, improve the quality of patient care, as it should result in a more holistic approach. It should ease communication about the disease and reduce stigma. And it should boost research, especially on the additive and potentially synergistic role of both alcohol and metabolic risk factors. The patients combining these risk factors are underserved in research, and the role of metabolic risk factors in the case of severe alcohol-related liver disease is poorly characterized. This justifies alcohol-related liver disease (ALD) to be incorporated into this framework and the creation of the group MetALD, which comprises patients with metabolic risk factors who drink more than the "non-alcoholic" threshold but less than the 50/60 g/d threshold. Above this threshold, the panel considered alcohol to be the predominant cause and hence labeled this as ALD. Data suggest, however, that also in patients with excessive alcohol consumption, metabolic risk factors can contribute to disease evolution [4]. So, even in ALD, a thorough assessment of metabolic risk factors (as well as other competing risks for chronic liver disease) is mandatory. Addressing in detail all competing risks for SLD and CLD in our clinical research should be one of the logical consequences of adopting this new nomenclature. This research can only help improve our understanding of the interaction and potential synergism between all these contributing factors and ultimately help improve the care of our patients and foster preventive actions.

CONTINUITY WITH PREVIOUS RESEARCH

As most of the current data have been generated in the NAFLD era, a potential concern arises about the validity of these data when the new nomenclature is applied. As far as pre-clinical research is concerned, there is no issue, as the different NAFLD models try to mimic the pathophysiology related to lipid overload and metabolic stress, with several dietary models perhaps best resembling the human condition. In clinical research, the difference between the negative definition of NAFLD and the positive definition of MASLD lies in the category of patients with no cardiometabolic risk factor. This depends on how the cardiometabolic risk factors are defined and where the line is drawn to turn a mostly continuous parameter into a categorical classification. As discussed below, these definitions tend to evolve over time. The current definition separates a group of patients with steatosis and cardiometabolic risk factors from a group with steatosis in whom no cause for steatosis, including cardiometabolic risk factors, can be identified. Analyses of large datasets from the LITMUS (Liver Investigation: Testing Medical Utility in Steatohepatitis) [5] and NIMBLE (Non-Invasive BioMarkers of MetaBolic Liver DiseasE) [6] consortia investigating biomarkers and a recent study on the UK biobank show that the NAFLD and MASLD population largely overlap [7], with only a few percentages of patients with NAFLD not corresponding to the MASLD criteria. These observations, which are now rapidly supported by others, have several consequences. First, it demonstrates that the insights we acquired over the past decades on the root cause of NAFLD, namely the (dys)metabolic disease drivers, are correct, and hence, the choice of the new name aligns with the intention to designate a name that reflects the disease's cause. Secondly, it indicates that research findings on

disease pathophysiology, natural history, clinical outcomes, therapeutic interventions, and biomarker discovery remain essentially unchanged under the new framework. Third, it better delineates the group of patients whose metabolic drivers are not the presumable cause of steatosis or steatohepatitis. Under the old framework, "lean NAFLD" tried to capture and study these patients separately. Still, this purely Body Mass Index-defined group was not satisfactory, as it appeared that many of these patients had visceral adiposity, insulin resistance, and other metabolic abnormalities, still pointing towards metabolic drivers as the root cause in apparently susceptible people. The current group of cryptogenic SLDs reduces the heterogeneity of the former NAFLD population by avoiding including these patients without metabolic risk factors in the MASLD category. As mentioned, it should also allow us to study this particular group better to unravel the cause of their disease and develop treatments, as many of the current MASLD treatments (focusing on correction of cardiometabolic risk factors) make little sense in this group.

It is essential to recognize that the current proposal to change the NAFLD nomenclature is not the first [8]; however, previous proposals lacked the broad consensus process and rigorous methodology in the new SLD framework. The introduction of MAFLD addressed some NAFLD shortcomings but did not tackle stigma. While MAFLD criteria differ slightly, they aim to identify patients with likely cardiometabolic risk factors driving steatosis and steatohepatitis. One unintended consequence of MAFLD was its allowance for alcohol consumption, leading to studies that did not distinguish between MAFLD with and without significant alcohol intake. This blurred categories and confused the diagnosis, potentially minimizing the role of alcohol in liver disease management, especially for patients with metabolic syndrome. Although the impact on clinical care remains unclear, some researchers combined MAFLD patients with alcohol consumption, complicating analyses. Despite these challenges, MAFLD addressed some NAFLD issues and laid the groundwork for future initiatives. The SLD umbrella nomenclature, defining MetALD and cryptogenic SLD, represents an improvement, acknowledging single and combined etiologies while avoiding stigma.

ACKNOWLEDGMENT OF IMPERFECTION

Is the new framework perfect? Probably not. Any system categorizing diseases and patients is an imperfect oversimplification of a complex reality that mainly exists on continuums. The concept of harmful drinking is rightly contested, as any alcohol consumption may increase the risk for some diseases. Further study is required to understand the quantities necessary to induce steatosis or other liver lesions, especially when alcohol is not the sole cause. Results from these studies may lead to refinements or revisions of the current nomenclature. Another criticism is that a diagnosis based on just one cardiometabolic criterion might be too lax or that certain metabolic criteria need adjustment. Recent analysis from the UK biobank suggests that patient groups with MASLD or MAFLD, with alcohol consumption < 20/30g/d, were largely identical.

Thresholds of glycaemic control, lipid levels considered "healthy" and "normal" transaminases, and the thresholds for pulmonary hypertension… all were not carved in stone and have been adjusted as needed with evolving knowledge. That will also be the case for the new NAFLD nomenclature. But for the time being, it offers the reference framework for clinical care and research in the fields covered by the SLD umbrella and represents a significant step forward in the research and management of the patients concerned.

Conflicts of interest: None to declare.

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