Editorial

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# MASLD emerging from the fog of fatty liver

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The recent changes in the nomenclature of what has been defined for more than two decades as "non-alcoholic fatty liver disease" (NAFLD) derive from the lack of a clear pathophysiological framing and a longstanding uneasiness in using terms such as "alcoholic" and "fatty" for the hepatic manifestation of a systemic metabolic derangement mostly characterized by cardiovascular outcomes. Along these lines, the term "non-alcoholic" did not accurately capture the aetiology of the disease. For instance, individuals with risk factors for NAFLD, such as type 2 diabetes (T2DM), who consume more alcohol than the relatively strict thresholds used to define the non-alcoholic nature of the disease were not adequately recognised by the existing nomenclature.

The new nomenclature was the result of a modified Delphi process led by three large pan-national liver associations (EASL, AASLD, ALEH). Consensus was defined *a priori* as a supermajority (67%) vote. An independent committee of experts external to the nomenclature process made the final recommendations on the acronym and its diagnostic criteria.[1] It is important to stress that this process focussed on nomenclature and the definition of NAFLD rather than a determination of what constitutes hepatic steatosis or the assessment of disease severity.

The name chosen to replace NAFLD was metabolic dysfunction-associated steatotic liver disease (MASLD), under the overarching term steatotic liver disease (SLD). There was consensus to limit the new term to cases with at least one – and only one – of the five cardiometabolic risk factors, formerly identified as basic features of the metabolic syndrome. Those with no cardiometabolic risk factors and no other cause of hepatic steatosis would be classified as having cryptogenic SLD. A new category, outside pure MASLD, termed MetALD, was introduced to describe those with MASLD who consume greater amounts of alcohol per week (140 to 350 g/week and 210 to 420 g/week for females and males, respectively).

The term steatohepatitis was felt to be an important pathophysiological concept that should be retained. Metabolic dysfunction-associated steatohepatitis (MASH) was then proposed to replace the old term "non-alcoholic steatohepatitis" (NASH). The evaluation of hepatic fibrosis, either as part of screening strategies or individual clinical decisions, retains its full relevance and remains unchanged after this process.

The work of the panel was articulated to solve several issues (stigmatization with the old nomenclature, relevance of steatohepatitis in disease definition, positive impact of a new terminology on disease awareness and definition of therapeutic endpoints, *etc.*) but, in concrete terms, the process leading to the new nomenclature specifically addressed the role of alcohol intake. Alcohol *per se* causes both liver disease and metabolic alterations; it represents the main confounding factor affecting the clinical management and causing heterogeneity in patient populations recruited into clinical trials on agents proposed to cure NAFLD and its hepatic manifestations (*i.e.*, NASH and its evolution to cirrhosis), ultimately affecting regulatory approval pathways.

From the aetiopathogenetic point of view, SLD includes a wide spectrum of pathological situations which fall between pure metabolic steatohepatitis and pure alcoholic steatohepatitis. In terms of epidemiology, it is likely that a mixed form is the prevalent one at least in populations with diffuse habitual alcohol consumption. In other words, a significant percentage of individuals classified as having MASLD will have an alcohol intake just below the threshold leading to the classification of MetALD. From a clinical practice point of view, this implies that alcohol consumption needs to be more precisely assessed/monitored and different strategies for treatment and prevention should be employed. The question is how can it be done in routine clinical practice? Does the simple interview suffice?

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Considering the pathophysiology of SLD, there are several mechanistic overlaps between pure metabolic steatohepatitis and that due only to excess of alcohol once we exclude the obvious direct toxic effect of alcohol on the liver. In MASLD, the presence of insulin resistance and adipose tissue dysfunction (*e.g.*, "adiposopathy" with inflammation, fibrosis, and stem cell abnormalities) are strictly linked to the severity of liver disease and the development of the severe cardiovascular and metabolic complications of obesity.[2] Meanwhile, the function of adipose tissue is profoundly altered by excessive alcohol intake, with considerable detrimental effects on the liver contributing to the pathogenesis of MetALD.[3] These effects are exerted through alcohol-mediated alterations of the metabolic, endocrine, and immune functions of the adipose tissue.[4,5] Accordingly, a synergistic effect of alcohol abuse and obesity on the risk of progression towards T2DM and on liver-related morbidity and mortality has been well established.[6]

The change in nomenclature has many positive aspects, some limitations, and some inherent consequences that will need to be managed. The first positive outcome is that MASLD has the dignity of a clinical entity that, by definition, requires a multidisciplinary approach involving at the same level specialists in different areas of internal medicine (*e.g.*, hepatology, T2D-endocrinology, cardiovascular). As extensively suggested in the past, MASLD will cease to be seen as an isolated hepatic manifestation referred to hepatologists, instead becoming the subject of a coordinated effort involving different specialists and, hopefully, primary care physicians. In this context, at the initial clinical assessment, a definition primarily based on cardiometabolic risk factors has potential limitations. Indeed, the key metabolic dysfunction underlying MASLD is insulin resistance, and the selected metabolic risk factors do not equally predict insulin resistance, as for example diastolic blood pressure and HDL-C are only weakly associated with insulin resistance. Indeed, insulin resistance and steatosis may be present in the absence of any cardiometabolic risk factors, especially in younger adults in the primary care setting. Consequently, patients with steatosis without overt cardiometabolic risk factors or other discernible cause are labelled as having cryptogenic SLD. This raises a question particularly for the prospective management of younger adults in which metabolic factors and cardiovascular risk are likely to increase with time. Another question is whether normoglycemic patients with SLD should all be tested by an oral glucose tolerance test, adding an insulin measurement for HOMA index or to determine oral glucose insulin sensitivity, before concluding that they have cryptogenic SLD. In the new nomenclature there is no mention of what was previously defined as lean NAFLD or lean NASH. The rationale for this change is based on a reclassification of most cases of lean NASH into the general MASLD category if metabolic risk factors are present. Risk factors for MAFLD in lean patients include high visceral fat (despite normal BMI) and insulin resistance, both conditions already included in the definition of the metabolic syndrome. Therefore, the term "lean" has been considered scientifically incorrect since multiple aetiologies can cause SLD and steatohepatitis in a lean individual.

Making a diagnosis of MASLD does not imply that other causes of SLD should not be considered. This is particularly relevant in the paediatric setting where it is imperative to exclude other causes of hepatic steatosis prior to applying the MASLD diagnostic criteria to ensure that dual pathology is not missed. In this line, the new nomenclature introduces the umbrella term SLD, highlighting diagnostic subgroups to be identified, *i.e.* drug-related and "monogenic" liver diseases, such as lysosomal acid lipase deficiency, Wilson disease, hypobetalipoproteinaemia, and inborn errors of metabolism.

As a second positive outcome, it is believed with large consensus that the new nomenclature will enhance disease awareness by aligning the diagnostic criteria for MASLD with widely recognized phenotypic traits in T2DM and cardiovascular medicine. Along these lines, positioning the presence of steatotic liver in the most appropriate pathophysiological context will reinforce the essential and central metabolic role of the liver and will somehow reduce the artificial compartmentalisation between adipose tissue, liver, glucose regulation/insulin function and cardiovascular manifestations. That said, hepatologists will need to adjust to this new framing and, while expecting a more effective multidisciplinary involvement by other specialists, should reject the idea that SLD is exclusively an area of hepatology, except when it concerns the management of patients with MASH that has evolved to cirrhosis and its complications. Hepatologists should expand their competence on the essential role of the liver in metabolism, while training and research should be strongly focused in this direction. Notably, following the pivotal joint publication of European clinical practice guidelines for NAFLD by the Liver, Diabetes and Obesity associations,[7] the cooperation is ongoing and is the basis for increasing disease awareness and improved management.[8,9]

In terms of clinical practice, the management of MASLD will require the implementation of multidisciplinary clinics in tertiary care with the establishment of appropriate referral pathways from primary care. This will ensure that once the diagnosis of MASLD and the presence or absence of a progressive chronic liver disease are established, the patient receives the best suited treatment and clinical follow-up. In this context, the use of non-invasive methods (*i.e.*, serum markers of liver fibrosis and elastography) to identify patients with potentially evolving MASH and need for referral to hepatology becomes even more essential. Accordingly, the use of non-invasive tests should become a pan-specialty screening and follow-up methodology and precise guidelines should be agreed upon and introduced in clinical practice.

A point regarding the new nomenclature that warrants attention is the definition of patients with MetALD, since this may lead to clinical consequences such as exclusion from pharmacological treatments developed for MASLD and other therapeutic options including liver transplantation.

In conclusion, the new nomenclature might help MASLD emerge from the fog of fatty liver. First, one of the main objectives of the new nomenclature is to increase MASLD awareness and obtain a positive social impact. However, it will not be easy to demonstrate the impact of the new nomenclature on awareness in the context of a general pressure to create integrated networks and easy biomarkers for screening, independent of acronyms. Beside obesity which has been always at

the centre of attention ("obesity epidemics" etc.), it is crucial to concentrate on the fact that more than 40% of patients with MASLD are non-obese (BMI 25-30). This is also very relevant because lifestyle interventions work in non-obese patients, and a less drastic weight loss may be sufficient to achieve disease regression. In addition, pharmacological therapy in non-obese patients may require special consideration and a different approach.

Second, the new nomenclature is expected to increase recruitment for therapeutic trials. Will it occur? Increasing awareness is expected to increase recruitment, but the generation of several subgroups of SLD may generate sub-trials with different endpoints. Regardless, the main limitation for recruitment remains liver biopsy and only a systematic use of efficient surrogate biomarkers might help to overcome this problem, including at the regulatory level.

Finally, an additional positive aspect of the new nomenclature is the preservation of existing data on natural history, biomarkers and clinical trials considering that 98% of the existing Registry cohorts of patients with NAFLD would fulfil the new criteria for MASLD. As reviewers for several journals, we are worried by the expected plethora of useless comparisons between old and new classifications that will be submitted to journals in the next few months. The game has started; we have a new nomenclature to exploit. Let's use it for a personalized treatment of our next patient without looking back to the fog of fatty liver.


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## Supplementary data

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