Title: Progress is impossible without change – understanding the evolving nomenclature of steatotic liver disease and its impact on hepatology practice

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Contents

Abstract

The American, European and Latin American Liver societies have proposed a change in the nomenclature we use to describe alcohol related liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). Additionally, a term encompassing both is now advocated, termed; steatotic liver disease which includes metabolic-dysfunction associated steatotic liver disease (MASLD) and MASLD with greater alcohol consumption (MetALD). These classifications offer increased relevance for clinicians, researchers, and patients alike. In this viewpoint we discuss the basis for this nomenclature shift and how it was developed. We also explore the challenges that will be faced in the adoption of such change.

The proposed change seeks to banish stigma associated with phrasing such as “alcoholic” and “fatty”. However, this is culturally nuanced, and stigma reflects different entities depending on location. If such a change is to be internationally accepted, there will be wide-reaching impact to colleagues in primary care, metabolic medicine, and of course, patients. We discuss those impacts and the opportunities the nomenclature change could offer, in particularly, for a patient group previously ignored by clinical trials; those with alcohol and metabolic risk factors.

Rationale for change

The most common cause of liver disease worldwide is the presence of excess fat in hepatocytes in a condition that until recently has been called 'non-alcoholic fatty liver disease (NAFLD)' with global prevalence recently estimated at over 30%.[1] Consequently between 1990 and 2017, the number of patients with compensated cirrhosis due to NAFLD doubled, decompensated cirrhosis trebled and NAFLD is the most rapidly increasing indication for liver transplantation in the USA.[2] Major advances have been made in understanding epidemiology, pathogenesis, diagnostics and therapeutics but patients, researchers and clinicians alike have expressed dissatisfaction with the name of the condition. Sufficient knowledge of aetiology has been acquired to define the condition by what it is rather than what it is not. A negative can imply a disease of lesser importance and may be contributing to under-recognition. In some languages and cultures, there is perceived stigma associated with terms such as "fatty" and "alcoholic". Perhaps the most pressing need for revision was the clinical reality that patients can have more than one aetiology and that hepatic steatosis related to metabolic syndrome can, and due to its high prevalence is likely to, occur concomitantly with other liver conditions, such as alcohol-related liver disease. In the summer of 2023, a multinational, multi-society consensus was published proposing a nomenclature change describing a spectrum of steatotic liver diseases (SLD) that would include non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ALD) and rare conditions that cause steatosis.[3]

Evolution of a historical disease to steatotic liver disease

"Fatty liver hepatitis" appeared in German medical literature in 1962,[4] while the term "non-alcoholic steatohepatitis" (NASH) was proposed in 1980 by Ludwig as the "hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis".[5] Evidence of an association between the metabolic syndrome, in particular type 2 diabetes (T2D), and this state has emerged over time. The condition now termed metabolic dysfunction-associated steatotic liver disease (MASLD) has undergone several revisions, most recently the 2020 consensus statement suggesting NAFLD should be called metabolic associated fatty liver disease or "MAFLD".[6,7] The international consensus statement of 2023 has aimed to refine descriptions of disease pathogenesis and to reduce stigma to patients through removal of both "alcoholic" and "fatty" from the broader nomenclature of steatotic liver diseases.[3]

Disease phenotypes of steatotic liver diseases

The new nomenclature proposes a wider disease spectrum of “steatotic” diseases, which includes ALD, as well as inherited metabolic diseases e.g., Wilson disease and glycogen storage disorders. It also better recognises the existence of liver disease due to more than one aetiology, for example viral hepatitis and MASLD or those with metabolic risk factors and elevated alcohol consumption. This phenotype is termed ‘MASLD and increased alcohol intake’ (MetALD), and is a separate entity to ALD.

MASLD is characterized by excess fat accumulation within hepatocytes and the diagnosis requires the co-existence of at least one cardiometabolic risk factor, which was not required for the previous definition of NAFLD. Such cardiometabolic risk factors will include those commonly encountered by clinicians: insulin resistance, T2D, obesity, hypertension, and hyperlipidemia. Patients diagnosed with MASLD should have secondary causes of steatosis excluded, such as substantial alcohol intake (as this may indicate a diagnosis of MetALD), medications or inherited metabolic conditions. Using this new definition, it should be acknowledged that there will be a cohort of patients previously labelled as NAFLD who are now termed cryptogenic SLD, owing to a lack of cardiometabolic risk factors or secondary causes of steatosis. A subset of individuals with MASLD will have steatosis associated with cellular injury and lobular inflammation — termed metabolic dysfunction-associated steatohepatitis (MASH).[8]

ALD continues to dominate morbidity and mortality from chronic liver disease in the Western world, particularly Europe.[9] The Global Burden of Disease study highlights that of the 1,256,900 deaths due to liver disease (2016), 27% were directly related to alcohol use. Similarly, the authors note that 245,000 liver cancer deaths were attributed to alcohol use disorders (30% of liver cancer deaths).

Mortality in those with ALD is proportionally greater for patients from lower socioeconomic groups;[10] these patients are often younger and this is reflected in significant economic losses, as two-thirds of potential years of life lost are working years.[10] In the UK, which has a high level of alcohol related morbidity[11], 4.4.% of the population are responsible for over one third of all the alcohol consumed.[12]

MASLD and increased alcohol intake (MetALD)

The major step forwards for patients is acceptance that MASLD can exist with other liver disease aetiologies; principally alcohol. Alcohol, MASLD and co-morbid type II diabetes, hypertension and other risk factors are believed to contribute synergistically to the progression of liver disease.[13,14] This new disease entity acknowledges that patients may have varying

components of metabolic dysfunction alongside a range of alcohol consumption patterns and it may not be clear which is the dominant risk factor in an individual. For example, the GALAXY consortium highlighted the major role of insulin resistance in predicting liver fibrosis amongst individuals with ARLD.[15] The nomenclature change will enable clinicians and researchers to focus on this currently under-served group who are excluded from observational and interventional studies of NAFLD/NASH, which further contributes to stigma around alcohol use disorder.

Developing the New Nomenclature

The development of the new nomenclature was driven by the American Association for Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL) and the Latin American Association for the Study of the Liver (ALEH). Representatives from these organizations chaired the steering committee which aimed to provide representation from key stakeholders across clinical practice, research, patient groups and geographical areas. The resulting Delphi Panel consisted of 225 members (297 invited across the process) who predominately worked in clinical research (54%) and within Hepatology (82%) across 54 countries, covering six continents. Patients and policy advocates played a prominent role in the process; comprising 9% or participants. Representation from primary care was not quantified, although these are presumed to be within the 'other' group (9%).

A modified Delphi method was utilised to generate a consensus answer. The Delphi process consisted of four rounds of online surveys and two in-person meetings (both in the USA) and utilised a Likert-like scale for responses to draft consensus statements. Consensus was defined *a priori* as a vote of 67% (supermajority).

Whilst the DELPHI method is a commonly practised methodology, it must be acknowledged there is, in the words of others, "*no consensus in consensus methodology*".[16,17] The DELPHI method has advantages. These include participant anonymity, removing bias and influence of individuals that could dominate discussion. It is iterative, accommodating multiple rounds of feedback. Flexibility of online surveys would allow participants to reflect on questions posed without significant time pressure. Criticism of this methodology includes the steering committee, who would be subject to their own inherent biases around the terminology. This could skew consensus, particularly following in-person meetings. A valuable outcome of the DELPHI process is contingent on the design and linguistic nuances of the questionnaire provided to participants. Finally with multiple rounds of surveys, the risk of participant burnout rises.

The authors used the following questions to shape and define the new nomenclature:

1. What are issues with current nomenclature, and can they be addressed?
2. What is the importance of steatohepatitis in disease definition and endpoints?
3. How should the role of alcohol be accounted for?
4. How might name change impact disease awareness, clinical trials and regulatory approval pathways?

5. Can an alternative name reduce heterogeneity and allow for future advances?

Key findings from the process were that ‘non-alcoholic’, and ‘fatty’ were stigmatizing although a consensus was not achieved (61% and 66%, respectively), and that the incorporation of ‘metabolic disease/disorder’ would improve communication of understanding of the disease for patients (72%) and healthcare professionals (80%). To better incorporate alcohol and other conditions associated with hepatic steatosis, an overarching ‘umbrella’ term was preferred (78%), designated as ‘steatotic liver disease’ (95% of first and second choice votes). ‘Steatohepatitis’ was felt to have significant prognostic relevance (95%) with the ‘resolution of steatohepatitis’ an appropriate treatment goal and trial endpoint (93%).

Alcohol consumption in patients with NAFLD was addressed with a consensus reached that 30g-60g (3.75 – 7.5 units) of daily alcohol or greater was likely to change the natural history of liver disease and should be studied independently (95% and 90% respectively). Defining the term for this cohort of co-pathology was more challenging, MetALD proving the preferred term, and incorporates current alcohol use with thresholds at 140-350g/week (17.5-44 units/week) for women and 210-420g/week (26–52 units/week) for men. This allows for a spectrum to define dominance of MASLD, or ALD. This definition does not include past alcohol use which may have an impact on clinical trajectory.

Whilst the authors made substantial effort to provide geographical representation during this multistep DELPHI process, there remained a dearth of representation across African and east Asian nations, where a large proportion of the world population (>3 billion) are situated.

Challenges & opportunities

Adoption of a new definition

An important step towards achieving the aims of the new nomenclature will be its adoption by clinicians and patients. Internationally, credibility for SLD terminology will require universal liver society adoption. At the time of writing only EASL, AASLD and ALEH have publicly adopted the nomenclature, with societies across Africa, the Middle East and Asia yet do so. Furthermore, NAFLD was not just a term used by hepatologists; this nomenclature change will need time to percolate through to healthcare professionals across multiple specialties. This will include gastroenterology, general medicine, primary care, diabetes and endocrinology. Medical school curricula will evolve to incorporate its use, and of course, patient acceptability and understanding remain pivotal.

Impact for patients

An aim of the process was to de-stigmatise the language around two major causes of liver disease, namely their components "*alcoholic*" and "*fatty*". In Northern Europe and North America, the term "*fatty*" can be used in a demeaning or shaming way. In a global survey of almost 2000 patients with NAFLD, almost half of patients surveyed from South Asia and the USA said the term "*fatty liver*" made them feel uncomfortable.[18] A third of patients from the same regions reported similar feelings towards the term "NAFLD". However, this this is not true of all languages and cultures; the same survey found over 90% of patients from the Middle East or North Africa had either never experienced stigma related to a NAFLD diagnosis or were not concerned by it.[18] Related to this, prominent patient groups have challenged the notion that the term "*fatty liver*" is stigmatising[19]. It is interesting that in many languages, unlike English, the words used to describe an overabundance of lipids differ from those used to describe a person with overweight or obesity.

This process has removed "alcoholic liver disease", perceived as pejorative, and adopted "alcohol-related liver disease" instead. By acknowledging explicitly that MetALD exists, the hepatology community can now address a disease that probably accounts for a significant proportion of SLD encountered in clinical practice in many parts of the world, for example in Europe where both obesity and alcohol use disorder are prevalent and likely overlap.[20,21] It is intended that the nomenclature will provide clarity for patients in understanding their disease and accessing accurate guidance, whilst also minimising stigma. The MetALD nomenclature also encourages clinicians to enquire more closely about alcohol history in a way that could previously have been glossed over, particularly for those working outside hepatology. It could support greater collaboration between Metabolic Medicine and Alcohol services. In the UK,

Cancer Research UK publicised greater cancer rates amongst individuals with obesity in a national campaign. Similar campaigns highlighting greater alcohol consumption and obesity being deleterious in consort would be impactful. Clinician adoption and patient acceptance going forward will be essential, and as will efforts to objectively assess the impact of the new nomenclature, the effects of the changes and any unintended consequences.

However, these terms have been used for almost two centuries; Thomas Addison described fatty liver associated with alcohol and tuberculosis in 1836.[22]

Research

To date, patients with MetALD have been excluded from NASH clinical trials, and clinical researchers have a genuine opportunity to better understand this significant cohort of patients who can now be actively recruited as a subgroup of interest or population in their own right. This will widen access to treatments that prevent or reverse significant liver disease. [14] Treatment options to manage metabolic risk and abstinence could be considered. Murine models have already suggested Semaglutide could have abstinence aiding properties.[23,24] As a starting point, glucagon like peptides-1 (GLP-1) analogues and emerging GLP-1/glucose-dependent insulinotropic polypeptide agonists e.g. Tirzapetide, could be trialled to observe impact on MASLD, MASH and MetALD.

There may be a sliding scale of interaction between the number and severity of cardiometabolic risk factors and different levels of alcohol consumption. Understanding these synergistic risks, and which is dominant, is important to tackle the multimorbidity clinicians face within the spectrum of SLDs. There are pertinent questions that have yet to be answered; how long the MetALD phenotype may persist after alcohol cessation and for how long a history of alcohol excess remains relevant.

A straight swap?

Pragmatically, many will view MASLD and NAFLD as a straight swap in nomenclature, as a large proportion of patients with NAFLD are likely to have at least 1 element of metabolic syndrome. The DELPHI panel considered that the change in nomenclature would have no impact on the interpretation of existing and new clinical trials as the core definition of NAFLD/MASLD did not substantially change.[3] Two recent letters in *Journal of Hepatology* describing data from cohorts in Hong Kong[25] and Sweden[26] reported 97.7% and 99.7% of patients with NAFLD met criteria for MASLD respectively. In both, geographically distinct, patient populations, elevated BMI was the commonest cardiometabolic risk factor. Ciardullo

et al recently demonstrated MASLD appears to be highly concordant with criteria for MAFLD using the National Health and Nutritional Examination Survey in the US .[27]

It is expected that multiple studies will extend this work in the coming years, but it remains to be seen whether the community and publishers will retrospectively apply the new nomenclature to data derived from historic studies, especially with regards epidemiology and natural history. To facilitate future research, the World Health Organization and International Classification of Disease will need updates. SLD, MASLD, MetALD and ALD will enter the coding lexicon and training will be needed for clinicians and administrators to use these terms.

To support the adoption of SLD nomenclature, future research exploring if a MASLD definition enhances the identification of fibrosis, liver related outcomes and mortality outcomes greater than that of a NAFLD or MAFLD diagnosis would be valuable.

Multistakeholder Involvement: Primary Care | Metabolic Medicine| Patients

Primary Care

The outlined nomenclature changes give opportunity for liver disease detection and management to be simplified and normalised in primary care. The umbrella term of SLD should allow for early diagnosis and coding, whilst the distinct categories of MASLD, MetALD and ALD should guide primary care clinicians to characterise and discuss the relative contributions of risk factors contributing to a patient's liver and wider cardiometabolic health in a more personalised and holistic way. The inclusion of at least one metabolic risk factor in the MASLD definition helps frame MASLD as 'belonging' within a group of conditions already routinely managed in primary care. This has been shown in qualitative research with primary care clinicians to add to the sense embedding liver health into routine chronic disease work[28] which is likely to improve routine early detection and allowing opportunity for lifestyle interventions.

However, it remains the responsibility of liver champions to create and educate multistakeholder groups involving hepatology, primary care, obesity medicine, endocrinology, addiction medicine, cardiology and public health.[29] The hope is that that the new nomenclature will facilitate policy-level social and public health interventions, and development of care pathways that optimise liver health as part of an envelope of metabolic risk reduction measures.

Metabolic Medicine

The benefits of holistic, patient-centred multidisciplinary care for patients with SLD and diabetes seem clear and are now increasingly adopted.[30] The formalised defining of MASLD highlights the multi-system components that drive the disease, which principally relates to insulin resistance and de-novo lipogenesis. However, to be impactful it must lead to a renewed emphasis on the combined management across specialties to optimise metabolic health and improve long-term liver-related, and cardiovascular outcomes. Challenges will remain as to how, and where this is best delivered to ensure optimal multidisciplinary management, but also smooth and effective linkage between primary and secondary care.

Patients

From a patient perspective, it is important to emphasise the necessity for the involvement of a diverse group of patients, support organisations and relevant charities in future discussions about the nomenclature changes.

These changes will not completely remove the perceived stigma which is attached to liver disease but patients may welcome removing “fatty” and “alcoholic” from the description of their illness. However, the recommended changes are expected to cause some unease and confusion both for patients and healthcare professionals. This could be addressed at a national level by engaging diverse patient groups to co-produce clear, plain language information. This will help everyone understand the rationale for the changes and reassure them there will be no adverse impact on their care. Patients will be hopeful that the new definitions allow more people to access timely treatment, be included in clinical trials, and benefit from the development of new treatments.

Conclusions

Overall, the community has broadly welcomed the advent of the new SLD nomenclature as a comprehensive entity, with defined sub-categories, though some have expressed reservations.[31] An international consensus has been sought, and the advent of MetALD is a positive development that has the potential to advance practice. However, the extent to which the nomenclature is adopted and how it impacts care delivery, research and patients remains to be seen.

In order for the nomenclature to achieve the goals of the DELPHI panel, stakeholders must engage in developing programmes that deliver change across the entire SLD spectrum; improved tools for disease stratification, drug discovery and wider public health approaches to decouple the determinants of the disease.[32,33] Even the discussion around the name change will re-invigorate debate around public health and fiscal policy strategies to tackle obesity, particularly in younger people and alcohol harm reduction strategies.

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PNB – conceptualization, data curation, writing – original draft, review & editing; **ODT**: writing – original draft, review & editing; **WL**: writing – original draft, review & editing; **TM**: writing – original draft, review & editing; **LC**: writing –review & editing; **JAF**: writing –review & editing; **HJ**: writing – original draft, review & editing; **DM**: : writing –review & editing; **SM**: : writing –review & editing; **WR**: writing –review & editing; **KR**: writing – original draft, review & editing; **JT**: writing – original draft, review & editing; **AY**: writing –review & editing; **EAT**: writing –review & editing; **JDF**: writing –review & editing; **WA**: writing – review & editing**; KWMA**: conceptualization, data curation, writing – original draft, review & editing.

Contributors Statement

PNB & KWMA conceptualised, wrote the original and revised manuscripts. **PNB, KWMA, ODT, WL, TM** were responsible for data curation and writing the original manuscript. **HJ** provided primary care focused edits. **KR** provided patient focused edits. **JT** provided metabolic medicine focused edits. **WA, LC, JAF, DM, SM, WR, AY, EAT** and **JDF** reviewed and edited original and revised drafts.

Conflicts of Interest statement.

PNB has received consultation fees from Resolution Therapeutics and honoraria from Takeda; **LC** has received consulting fees from NovoNordisk and honoraria from Intercept Pharma. Elected committee member for British Society of Gastroenterology Liver Section, National Specialty Lead for Hepatology NIHR Clinical Research Network; **HJ** has received honoraria from NovoNordisk; **DM** has received consulted fees from Falk Pharma; **SM** has received grant funding from Gilead, consulting fees from Gilead, Abbvie, Intercept Pharma, NovoNordisk, and honoraria from Gilead; **WR** has received royalties and honoraria from Siemens Healthineers; **JT** has received payment for participation in Novartis Data Safety Monitoring Board; **EAT** has received consulting fees from Pfizer, NovoNordisk, Boehringer, Siemens Healthineers and honoraria from Echosens, Dr Falk and NovoNordisk; **JFD** has received grant funding from MSD, AbbVie and Gielad. He has received honoraria from MSD, AbbVie and Gilead; **WA** has received grant funding from GlaxoSmithKline, MSD and Gilead Sciences. He has received consulting fees from Metadeq Inc. He has received honoraria from GlaxoSmithKline, Gilead Sciences, UCB Biopharma and Conclusio**; KWMA** has received honoraria from Advanz Pharma.

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Search strategy and selection criteria

We searched Medline for full-length publications from 1 January 2000 to 1 September 2023 with the search term “stigma” combined with the terms “cirrhosis”, “alcohol”, “NAFLD”, “fatty liver”, without language restrictions. We selected further relevant publications from the reference lists of articles identified by this search strategy. We largely selected publications from the past 10 years but did not exclude highly relevant older publications.