Adding to the confusion in more than name

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The year 2020 witnessed a paradigm shift in the way we conceptualised and thought about the fatty liver disease which is responsible for a majority of the cases we see in routine clinical practice. For the preceding four decades, non-alcoholic fatty liver disease (NAFLD), a term coined to define a histological lesion, was used to describe a disease entity that clearly was common and rising in prevalence in parallel with that of diabetes and overweight/obesity. Despite decades of discomfort with the term, NAFLD told clinicians and patients what the disease is not and not what the disease is, and was associated with the stigma linked to the term alcohol. Inertia as is common in many areas of medicine persisted. All this changed with two landmark papers by an international panel that proposed a new term, metabolic (dysfunction) associated fatty liver disease or MAFLD, and a new definition (1, 2).

What is not as well appreciated by the field is that the papers were a proposal firstly of a term that reflected accumulated knowledge on disease pathogenesis and secondly and perhaps more importantly, it proposed a set of criteria on exactly what constituted the disease. The papers were published to wide acclaim (and some discontent) as a conceptual advance in the field and were there for all clinicians to examine for its clinical utility at the bedside and for clinical research. As fatty liver disease due to metabolic dysregulation impacts the life-course, paediatric criteria were also proposed (3). Subsequent years have seen more than 4000 citations for the two sentinel papers, over 7000 publications using the MAFLD terminology and definition, and widespread acceptance in clinical practice guidelines including the first by the Asian Pacific Association for the Study of Liver (APASL) (4), the middle east and north Africa (5), the Chinese Society of Hepatology (6) and many other national societies as well as patient organisations (7). From the perspective of clinical research, MAFLD and its definition demonstrated clinical utility, increased disease awareness, and importantly, identified
patients that are most at risk of hepatic and extrahepatic outcomes as compared to NAFLD (8-11). Another aspect that was not appreciated at inception was that MAFLD neatly stratified patients into three distinct groups (those with diabetes, those with overweight/obesity, and those with MAFLD but a healthy weight), each with its own distinct patient profile in cross-sectional studies, and different disease trajectories and outcomes (11). Such stratification has allowed clinicians to prognosticate, and will in future, enable tailored treatments based on phenotype.

In this issue, Kim and colleagues (12) undertake an appraisal of the terminology and definition of another term, metabolic dysfunction associated-steatotic liver disease (MASLD). Clearly, removal of any reference to alcohol in the proposed name is welcome and long overdue, as is acceptance of metabolic dysregulation as a core tenant and prerequisite for disease diagnosis. That the proposal has come after four decades highlights the inertia of societies and the importance of innovation and renewal from the grass roots in all scientific disciplines.

While the authors have undertaken an appraisal from both a hepatology and endocrinology perspective, as they imply, MASLD is a proposal with many unresolved questions. First and foremost, as suggested by others in the field and patient groups, the term “fatty-liver” when used to describe a liver with fat is not stigmatising (13,14). Further, as circulated on social media and from firsthand experience, clinicians know from everyday experience that when a patient is told they have MASLD, the first question asked is “what does steatotic liver disease mean” to which the answer invariably is that you have a “fatty liver”.

Be that as it may, Kim and colleagues highlight that there are concerns with the definition, and as well, several persisting misconceptions about the MAFLD definition. It is stated that MAFLD fails to incorporate alcohol consumption into its diagnostic criteria. The simple answer to this oft repeated statement as highlighted in the original papers, is that MAFLD defines a particular form of liver disease due to systemic metabolic dysregulation; the disease (MAFLD) has nothing to do with whether a patient drinks alcohol or not, or for that matter if the patient has concomitant viral hepatitis or not. As an example, if a patient has hepatitis C, it does not mean that the patient cannot also have a second liver disease such as hepatitis B. Only by defining what disease one is, can we decide if a patient also has disease two. MASLD fails to meet this basic tenant for disease diagnosis as it is proposed that you can have MASLD but if you have MASLD and “significant” alcohol consumption you have MetALD. MetALD is not a separate disease but the coexistence of 2 concomitant diseases in the same person. By their logic, if a patient has hepatitis B infection or Hepatitis C infection with MASLD, they should also be given a separate disease name, particularly as this is common in many parts of the world. MAFLD deftly avoids this issue by precisely defining what MAFLD is (just like we define what hepatitis C or B is) and stating that “patients who meet the criteria to diagnose MAFLD and who also have one of these concomitant conditions should be defined as having dual (or more) aetiology fatty liver disease” (2). In the example with a metabolic risk factor and hepatitis C, the SLD terminology reverts back to “combination aetiology”, exactly as proposed in the MAFLD definition. That alcohol is a “special case” does not meet scientific scrutiny; as Kim and colleagues suggest, “The distinction between MASLD, MetALD, and ALD is not always clear” and “the exact threshold for alcohol consumption that may lead to liver damage
remains unclear. Although some studies have proposed protective effects of mild alcohol consumption others have indicated no safe level of alcohol consumption especially among individuals with MASLD. Furthermore, the extent of metabolic dysfunction and the amount of alcohol consumption may vary over time among individuals” (12). With these very real caveats, would it not be more prudent and logical to define each liver disease a person has on its own merits rather than adding a new disease term with an arbitrary definition. Even in those with alcohol consumption >60 grams per day, it is a fallacy to consider that metabolic dysfunction will not contribute to their disease trajectory. In real life, liver disease outcomes are a combination of all the liver insults however minor or major, and arbitrary categorisation simply muddies the water, something that MAFLD cannot be accused off.

Another common misconception is that of “oversight” of steatohepatitis. To be clear, MAFLD is a set of criteria for clinical diagnosis, while steatohepatitis is a histological diagnosis. The histological features of the disease (steatosis, steatohepatitis, and fibrosis) are what they are and MAFLD in no way detracts from the histological disease activity (metabolic steatohepatitis) and/or fibrosis stage as reported in the original papers (1, 2).

The salient subcategories of SLD are illustrated in figure one (12); MASLD is diagnosed if one of the conditions are met. This would mean that a person with hypertension and hepatic steatosis has MASLD, or for that matter steatosis and a low HDL, with no clear evidence that these individuals have any adverse liver-related outcomes; for HDL and diastolic BP, the link to insulin resistance and steatosis is weak. A problem with the MASLD definition is that it tries to be “all things to all people” a problem inherent in consensus (rather than data-driven) approaches. MASLD is exactly as per the previous NAFLD definition, a heterogenous collection of diseases. Indeed, studies suggest that MASLD and NAFLD are almost identical. In contrast, for MAFLD, several population-based studies indicate that the three risk groups have differing initial presentations, different disease trajectories and different hepatic and extrahepatic outcomes and in all cases, outcomes worse than those with NAFD only, highlighting the clinical utility of the definition (8-11). As the critique suggests, over 90% of Koreans (and for that matter people in most affluent countries) with SLD have at least one cardiometabolic risk factor. This “may lead to potential over-classification of MASLD and MetALD but under-classification of pure ALD, cryptogenic SLD, and SLD with specific aetiology” (12). Unlike the MAFLD criteria which has a clear definition for MAFLD cirrhosis, the lack of a definition or a statement on MASLD-related cirrhosis also “continues to puzzle” (12).

Kim and colleagues (12) should be congratulated on their critique of MASLD. Given the many concerns, while MASLD is an advance on NAFLD, in many aspects it adds to confusion rather than representing a bold and rigorous attempt to redefine the field of fatty liver disease.

References


