From NAFLD to MAFLD: a "redefining" moment for fatty liver disease

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The term non-alcoholic fatty liver disease (NAFLD) was coined in 1980 to characterize a disease similar to alcoholic fatty liver disease that developed in patients without a history of excessive alcohol intake.[1] Morphologically, NAFLD is characterized by excess fatty infiltration of the liver in the absence of known causes of liver disease (eg, alcohol, autoimmune liver disease, viral hepatitis, etc). The clinical manifestations of NAFLD (both hepatic and extrahepatic) depend on the outcome of complex interactions between its primary drivers including poor lifestyle habits and diet, a dysfunctional microbiota, genetic predisposition, and environmental cues that result in metabolic dysfunction and liver disease. However, bringing all patients with their markedly different clinical courses under the NAFLD umbrella belies its complexity and implies a homogeneous disease state that then negatively impacts clinical management and a deeper understanding of pathogenesis. With advances in current knowledge on the spectrum of fatty liver diseases, it is apparent that the four-decade-old outdated term NAFLD can no longer serve to usefully describe a highly heterogeneous disease. The disease as we understand it today not only impacts patients who consume alcohol and those who do not, but also potentially impacts all patients with any form of liver disease, by acting as a disease modifier.[2]

NAFLD is inherently a disease defined first and foremost by the exclusion of excess alcohol intake. However, even this exclusion is problematic as what defines "excess alcohol" intake is uncertain and to date has been defined by expert opinion rather than hard data.[3] Indeed, more recent information suggests that there are no safe limits for alcohol nor is there a data-driven threshold of consumption that does not over the long term, increase the risk of liver disease.[4] Moreover, a recent study suggests that some gut microbiota produce alcohol and can contribute to liver damage.[5] The explicit requirement to rule out competing etiologies such as viral hepatitis or immune-mediated liver diseases, complicates the diagnostic process at the coalface, and subliminally implies that metabolic dysfunction does not contribute to the natural history or progression of disease such as viral hepatitis once they have been labeled as such. This is manifestly untrue when there is a significant body of literature suggesting that alcohol-associated liver disease progresses more rapidly in the context of metabolic dysfunction and obesity, as also those with hepatitis C or B.[6,7] In addition, for the clinician, the varied diagnostic thresholds for alcohol ingestion in published reports blurs the line between non-alcoholic fatty liver (NAFL) and alcoholic fatty liver. Apart from these cogent scientific reasons for the lack of validity of the term NAFLD, it must be recognized that the term "alcoholic" in the name, bring with it stigmatizing social constructs and societal norms.

To address these issues, a consensus was recently reached by an international expert panel for a name change from NAFLD to metabolic associated fatty liver disease or "MAFLD."[2] Subsequently, a new set of diagnostic criteria for MAFLD was proposed to better reflect current knowledge of the disease.[8] These criteria are based on the presence of hepatic steatosis in the presence of one or

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more of overweight/obesity, type 2 diabetes mellitus, or evidence of metabolic dysregulation. The new definition is a landmark in hepatology bringing a new way of thinking about diseases of the liver that are associated with fat deposition and metabolic dysfunction. Importantly, MAFLD brings the liver disease into closer alignment with our current understanding of obesity, metabolic syndrome, and systems biology. Moreover, for clinicians, the definition simplifies the diagnostic process by using "positive" criteria rather than exclusionary ones and establishes a conceptual framework grounded in science for considering other etiologies that might contribute to fatty liver diseases. In doing so, it is now possible to embrace the heterogeneity of MAFLD not only in patients where metabolic dysfunction is the only driver, but also patients with other liver diseases where the same dysfunction can alter the outcome of the diseases. Clearly, within the corpus of the term "metabolic dysfunction", we can also now move towards greater disease subtyping that can ultimately lead to precision medicines based on a systems narrative. Another important difference is that NAFLD, the old term comprises only simple steatosis and non-alcoholic steatohepatitis. With the new terminology, MAFLD is viewed as a disease process where simple steatosis (MAFLD with no inflammation and fibrosis) merges into MAFLD with for example grade 1 inflammation and stage 2 fibrosis, to MAFLD with grade 0 inflammation and stage 4 fibrosis. In other words, it captures the full spectrum of the disease. Moreover, "cryptogenic cirrhosis" and lean MAFLD can now be diagnosed by physiological and metabolic criteria rather than being viewed as completely separate entities. Not to be forgotten, the new nomenclature circumvents the stigmatization associated with "alcoholic" by reducing etiological competition between purely alcoholic and metabolic dysfunction related liver disease.

Today, MAFLD is recognized as a highly prevalent disease affecting one in four people globally and is the leading cause of chronic liver disease in the United States and Europe.[9] The prevalence of MAFLD is following a similar trajectory in the Middle East and Asia, with China having the highest incidence and projected future burden of 314 million cases by 2030.[10,11] Unchallenged and un-tackled, MAFLD has the potential to become the most common cause of liver cancer, liver failure and liver transplantation in China, creating a potentially enormous cost to society and patients and their families. Consistently, outside China, the direct annual medical costs of MAFLD was estimated to exceed $100 billion in the United States and €35 billion in Europe (The United Kingdom, France, Germany, and Italy).[12]

While there is an obvious need to reduce disease burden, public health responses to MAFLD are sub-optimal. For instance, a cross-sectional survey conducted in 2019 of 29 European countries (Norway, Switzerland, and all European Union countries except for Malta) revealed that none had written strategies or action plans for this disease.[13] This lack of response can, we believe, be partially attributed to differences in perception of the disease due to an outdated nomenclature and definition. In Europe for instance, alcohol is regarded as the primary cause of chronic liver disease.[14] Similarly, while deaths due to non-communicable diseases are 30 times more than human immunodeficiency virus, it receives 17 times less funding.[15] Therefore, public strategies are understandably focused on this rather than MAFLD and it is not helped by the overlapping disease features. Indeed, it could be argued that eliminating or effectively managing MAFLD will go a long way to reduce the health burden and societal costs of alcohol-associated liver disease as the two frequently co-exist and synergistically contribute to both hepatic and extrahepatic adverse outcomes.

Undoubtedly, the renaming of NAFLD to MAFLD is a defining moment and serves as a catalytic call to action that will result in turbocharging systematic improvements in disease awareness, advocacy, research, and through this, clinical management. Given the potential for greater good most importantly for patients affected by liver diseases, widespread adoption of the new definition will first be required by patients, practitioners, medical organizations, the pharmaceutical industry, and regulatory agencies. Already, such momentum is seen in the various editorials published on these two landmark reports,[16-19] and moves by national and regional societies the world to develop guidelines based on this terminology and definition and new ways of conceptualizing and managing this disease. While global endorsement of MAFLD is expected to take time, it is nevertheless a necessary step toward ensuring success in tackling the disease.

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Conflicts of interest

None.

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