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Editorial

Changing the nomenclature from nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease is more than a change in terminology

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In this issue of *Clinical and Molecular Hepatology*, Gofton et al.[1] reviewed the difference between metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD). Since 2020, MAFLD has been proposed as a term referring to fatty liver diseases associated with metabolic dysfunction, as a replacement for the term NAFLD, which is based on negative diagnostic criteria.[2] MAFLD has subsequently been endorsed by several societies specializing in the study of liver diseases.[3,4] However, a consensus has not yet been reached across a significant number of key national and pan-national societies, and a consensus with broader global multi-stakeholders is required.

The change of nomenclature from NAFLD to MAFLD has several advantages; it raises awareness of the disease in patients and primary care physicians, clarifies treatment strategies, and enables a holistic approach to treating patients with liver disease.[5] First, MAFLD allows better recognition of patients with a more advanced stage of hepatic fibrosis and greater risk of overall mortality.[6-8] Second, MAFLD enables improved management of patients with comorbid liver diseases other than NAFLD. In the era of NAFLD, patients with chronic hepatitis B were classified as such regardless of presence of hepatic steatosis. Thus, the importance of lifestyle modifications in these patients has been underestimated. However, there is growing evidence that comorbid hepatic steatosis worsens the prognosis in patients with chronic viral hepatitis.[9-11] In this regard, MAFLD enables multidisciplinary treatment for such patients. Non-alcoholic-, alcohol-associated-, and viral hepatitis-steatotic liver disease will be discussed in the planned consensus meeting. These novel terms not only acknowledge the dual etiology of fatty liver disease, but also increase awareness of the diesase.[12] Third, MAFLD emphasizes metabolic dysfunction as the basic mechanism of fatty liver disease, both through its name and the inclusive diagnostic criteria.[2] This change in name also would allow in-

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tuitive explanation of causes and treatment approaches to patients. Additionally, it could reduce the time from diagnosis to treatment by omitting the need to exclude other liver diseases during diagnosis.

The change of nomenclature from NAFLD to MAFLD is more than a simple change in terminology and will have an extensive impact on research, the pharmaceutical industry, insurance companies, and government policies. The change in nomenclature to "MAFLD" requires significant changes in ongoing NAFLD clinical trial designs, primary endpoints, clinical outcomes of final approval, and therapeutic targets of treatment due to the new inclusion criteria.

There are several reasons to wait for a robust consensus on the nomenclature change among the broader body of stakeholders, including pharmaceutical companies, authorities, and various patient alliances.[13,14] First, the heterogeneous aspect of NAFLD is overlooked in MAFLD. In early clinical trials, researchers focused on controlling insulin resistance or metabolic risk factors, as NAFLD was deemed a manifestation of metabolic syndrome in the liver. However, most clinical trials with insulin sensitizers, lipid-lowering agents, and anti-obesity treatments have not been successful in NAFLD treatment. The development of fatty liver disease is based on heterogeneous mechanisms and is more complex than originally believed.[15] Thus, an excessive focus on metabolic dysfunction could veil novel therapeutic targets and delay drug development. Genetic factors,[16] intestinal dysbiosis,[17] and sarcopenia,[18] which are not closely related to metabolic dysfunction as to NAFLD, are underestimated pathophysiologies in MAFLD.[19] Nonetheless, these factors contribute to the development of NAFLD and are possible starting points for drug development. Second, the new definition of MAFLD may increase the heterogeneity of the target population during phase III clinical trials, as it also includes individuals with viral hepatitis or alcoholic liver disease. Controlling the effects of viral hepatitis and alcohol consumption is a complex problem. Third, the use of MAFLD resolution as a primary endpoint in clinical trials may lead to ambiguity. Currently, nonalcoholic steatohepatitis resolution without exacerbation of liver fibrosis is used as an endpoint in clinical trials for NAFLD. However, the endpoint in MAFLD would be different from the endpoint currently used in NAFLD. Therefore, long-term data are needed to determine whether improvement in metabolic dysfunction or normalization of bodyweight could be viewed as MAFLD resolution when it is achieved without histological improvement. Fourth, it may be difficult to evaluate the efficacy of candidate drugs in clinical trials when these drugs target inflammation or fibrosis without ameliorating metabolic abnormalities. A considerable number of candidate drugs under development is unrelated to metabolic improvement or weight loss.

In conclusion, we propose a cautious and in-depth discussion to reach a consensus among all stakeholders before the terminology is changed from NAFLD to MAFLD.

Authors' contribution

YEL, first drafting and revision of the manuscript; JDW, organized and supervised the manuscript. All the authors approved the final manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

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