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From NAFLD to MAFLD: navigating the future of fatty liver treatment

SMC Laboratories, Inc. (SMC) is a Japan-based contract research organization with a focus on preclinical development in inflammation, fibrosis and oncology.

At the moment, there is a lack of clinically relevant preclinical models for fatty liver disease. This problem has led to most drug candidates that were successful in preclinical development failing once they reach clinical trials. Starting in the 2010s, there has been a growing emphasis on the importance of quality preclinical models—that is to say, clinically relevant ones—when it comes to increasing the number of potential drug candidates that successfully complete clinical trials. At SMC, the mission is to increase the number of drug candidates that successfully complete clinical trials by offering quality models that have a high clinical correlation. Drawing on years of experience studying non-alcoholic steatohepatitis (NASH)/non-alcoholic fatty liver disease (NAFLD), SMC has created the world's first preclinical model with a type 2 diabetic background that progresses from steatosis to NASH, followed by fibrosis, and finally hepatocellular carcinoma (HCC).

In order to delve into these matters further, SMC recently sponsored a discussion about the new diagnostic category of metabolic-associated fatty liver disease (MAFLD) as a replacement for the currently used NAFLD, what it means for the clinical management and treatment of fatty liver, and the need for new MAFLD disease models. The conversation was led by Hirokazu Takahashi, a physician specializing in hepatology, with expert replies from Takumi Kawaguchi of Kurume University School of Medicine, Japan, who has helped define and promote MAFLD (see 'Participant biographies').

What is the health burden of liver diseases generally and NAFLD in particular?

Liver diseases are a growing global health problem, especially fatty liver diseases driven by excessive alcohol consumption, a diet high in fat and sugar, and a sedentary lifestyle. Fatty liver diseases come in two major forms: alcoholic liver disease, which is caused by excessive alcohol consumption defined as >30 g/day and affects around 1–2% of the global population; and the more common NAFLD, which affects roughly 25% of the global population, with the incidence being higher in Western countries and lower in Asian countries.

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How is NAFLD diagnosed?

A diagnosis of NAFLD is based on exclusion criteria to rule out fatty liver caused by excessive alcohol consumption, which has different pathological features, as well as other etiological causes. If a patient presents with hepatic steatosis (fatty liver) and consumes <30 g/day of alcohol, then a diagnosis of NAFLD requires the patient to meet two other exclusion criteria: no viral infection, and no autoimmune or other background condition that could cause fatty liver. As such, an NAFLD diagnosis applies to all patients who have fatty liver that is not attributable to alcohol, viral infection or other conditions. In other words, an NAFLD diagnosis can be given regardless of the specific etiology underlying the fatty liver, making the NAFLD patient population a very heterogeneous group.

In addition, NAFLD comes in two forms. Roughly 75% of patients presenting with hepatic steatosis have a mild form of NAFLD that is simply called non-alcoholic fatty liver (NAFL), while 25% have a more severe form of NAFLD called NASH, the diagnosis of which requires an invasive liver biopsy in a hospital setting and which comes with its own risks. In many patients, NAFLD takes a progressive course, moving from NAFL to NASH, then to the development of liver fibroses, followed by cirrhosis of the liver and, finally, HCC.

What are the major issues in the clinical management of NAFLD?

There are a number. A diagnosis of NAFLD entails ruling out excessive alcohol consumption, but the information we get about alcohol intake is typically based on self-reports, which can be

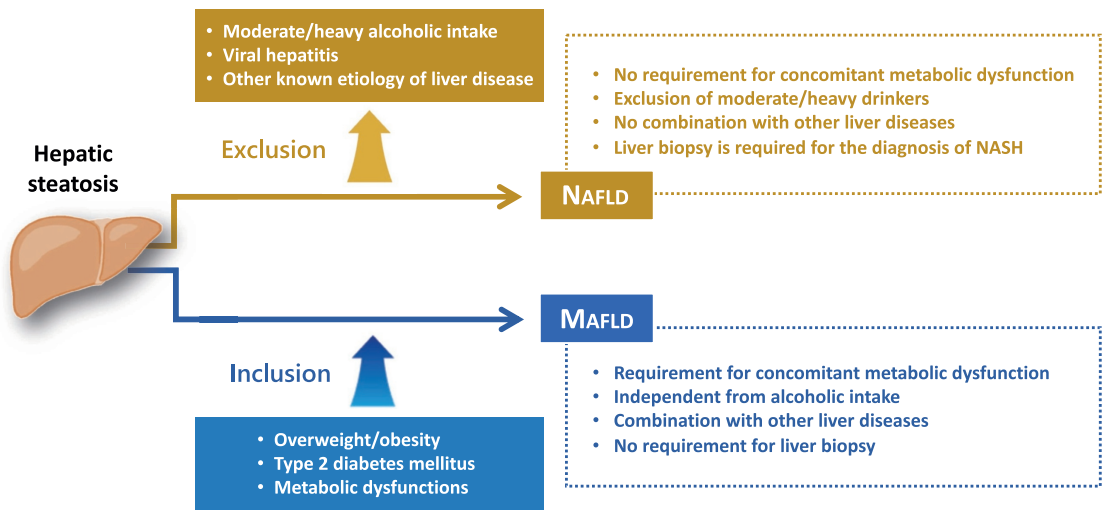

Fig. 1 | Diagnostic criteria for MAFLD and NAFLD. The difference in diagnosis between metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD). NASH, non-alcoholic steatohepatitis.

unreliable. And because NAFLD encompasses both the milder NAFL and the more serious NASH, an NAFLD diagnosis covers two very different pathological conditions. As mentioned earlier, finding out whether a patient has NASH requires an in-hospital liver biopsy. An NAFLD diagnosis also offers no insights into the etiology of the patient's disease, meaning that treatment cannot be matched to underlying pathological processes. Finally, and perhaps most importantly, NAFLD is diagnosed without reference to various metabolic dysfunctions—including obesity, diabetes mellitus and metabolic syndrome—that are now well-established risk factors for the progression of NAFLD, and which should be incorporated into clinical practice.

> **Although there are a number of drugs in phase 2 and 3 trials for NAFLD at the moment, none have been approved to date. The major challenge for developing pharmacological therapies for NAFLD has been the heterogeneity of the population captured by the diagnostic criteria**

Recently, many researchers and clinicians, including yourself, have proposed getting rid of the NAFLD diagnosis and replacing it with the new diagnostic entity MAFLD. What is the motivation for recommending this change?

There is very good evidence that the fatty livers observed in people who receive NAFLD diagnoses have a number of different causes, including genetic factors, obesity, a sedentary lifestyle, diabetes, side effects of drugs, and even rapid weight loss. The NAFLD category ignores this etiological diversity. The development of MAFLD as a diagnostic category to replace NAFLD is intended to bring these well-established metabolic factors into the diagnosis and management of fatty liver diseases.

How do the diagnostic criteria for MAFLD relate to those for NAFLD?

An NAFLD diagnosis is based on one inclusion criterion—the presence of hepatic steatosis—and three exclusion criteria: no excessive alcohol consumption, no viral infection and no underlying autoimmune or liver condition (Fig. 1). The MAFLD diagnosis, by contrast, is based entirely on inclusion criteria. If, in addition to hepatic steatosis, the patient is overweight or obese, or has type 2 diabetes, or is lean but shows signs of metabolic syndrome—which in turn is based on the presence of two of seven inclusion criteria—they can receive a diagnosis of MAFLD. As there is no need to eliminate viral infection or autoimmune/liver disorder, an MAFLD diagnosis is easier to perform than that for NAFLD.

Participant biographies

Hirokazu Takahashi is a professor and president of the Liver Center at Saga University Hospital, Saga City, Japan, and vice director of the Division of Metabolism, Diabetes and Endocrinology in the Faculty of Medicine at Saga University. Takahashi conducts basic research in hepatology as well as running clinical studies, and has published more than 190 articles and 10 book chapters. In 2019, Takahashi's work on biomarkers for NAFLD was included in The Best of the Liver Meeting collection produced by the American Association for the Study of Liver Diseases.

Takumi Kawaguchi is a professor and chairman of the Division of Gastroenterology in the Department of Medicine at Kurume University School of Medicine, Japan. Kawaguchi has published more than 250 papers, received numerous awards for his work, and served on many committees and panels focused on gastroenterology/hepatology. Recently, Kawaguchi was a member of the international panel that proposed the new definition of MAFLD, and he has been a leading advocate for promoting the concept in scientific and medical communities.

How does the shift from NAFLD to MAFLD change diagnosis in the clinical setting?

Take the case of a patient who is infected with hepatitis B virus (HBV) that is well controlled with medication but who also has fatty liver and type 2 diabetes. Based on current NAFLD criteria, this patient would be diagnosed as having chronic hepatitis B, but not with having NAFLD, because they failed to meet the no-virus exclusion criterion. As such, many of the well-established metabolic factors that drive NAFLD progression would be ignored. The same patient would, however, meet the criteria for MAFLD, and the fact that they have HBV would not exclude them, so in this case the metabolic dysfunctions of the patient would be part of the clinical picture.

Or take another case, in which a patient with fatty liver consumes >60 g of alcohol per day and has type 2 diabetes. Again, this patient could not receive a NAFLD diagnoses, but would be eligible for a MAFLD diagnosis, once again keeping the patient's metabolic dysfunction and its relation to their fatty liver in the clinical picture.

Pharmacological therapy for NAFLD has not been well-established. Why is that, and how might a shift to MAFLD aid in the development of new therapeutics for fatty liver disease?

Although there are a number of drugs in phase 2 and 3 trials for NAFLD at the moment, none have been approved to date. The major challenge for developing pharmacological therapies for NAFLD has been the heterogeneity of the population captured by the diagnostic criteria. A drug tested against a wide range of pathological processes, even if it works against some, will struggle to show any benefit overall. The redefinition of NAFLD as MAFLD, and the new diagnostic criteria, can help by stratifying clinical-trial populations according to their particular metabolic dysfunction. As described, the MAFLD criteria are based on the presence of at least one inclusion criterion out of three—obesity, diabetes and metabolic syndrome—which define at least three subtypes of MAFLD: overweight/obese MAFLD, diabetes MAFLD and lean/normal metabolic syndrome MAFLD. Recognition of these three subtypes of MAFLD should be factored into drug development and clinical-trial design in the future to test drugs in more homogenous patient populations in terms of pathological processes.

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How important will it be to create new animal models of MAFLD for developing drugs for fatty liver diseases?

This is very important, as it is crucial to test new drugs in models that reflect the biology of the conditions we wish to treat in humans. As MAFLD defines a new pathological condition, there is an urgent need to create new animal models that reflect MAFLD and its subtypes.

Today we have a good model for NASH in SMC's STAM mice, the first in which liver cancer is induced by NASH. STAM mice are produced by injection of low-dose streptozotocin, which induces a type-2 diabetic background, followed by a high-fat diet that leads to NASH and fibrosis/HCC in 100% of mice. Macroscopic and histological analysis of STAM mice has shown that steatosis develops by 6 weeks, steatohepatitis by 8 weeks, chronic fibrosis at week 12, and HCC after 16 weeks—a course of disease progression very similar to that of human NASH.

The STAM mouse model, which emerges against a diabetic background, is an established model for diabetes MAFLD. Yet that means there is still an unmet need for models that reflect the pathogenic processes operating in overweight/obese MAFLD and lean/normal MAFLD. It is also important to consider developing models that incorporate cardiovascular disease (the major cause of death in fatty liver disease) as well as extra-hepatic cancers into animal models to capture the clinical diversity of MAFLD-associated conditions that physicians have to manage.

SMC is currently exploring these models, as well as sedentary mouse models and others that will allow further exploration of the relationship between cytopenia and MAFLD—all of which will play a crucial role in developing new therapeutic approaches for the treatment of the new diagnostic entity MAFLD.

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