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LETTER

Metabolic dysfunction-associated steatotic liver disease of older people

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Abstract

An international panel of experts proposes clear and simple criteria for the diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD), moving it from a disease of exclusion to one of inclusion. An international panel of experts from 22 countries proposes a new definition for the diagnosis of MAFLD that is both comprehensive and simple, and independent of other liver diseases. The diagnosis is based on the recognition of underlying abnormalities in metabolic health, recognizing that MAFLD often coexists with other conditions. Future research will be useful in routine clinical practice. Further initiatives are now needed to subphenotype patients with MAFLD and fatty liver disease in general, to drive precision patient management and to create effective pathways between primary care and liver clinics. The criteria are in addition to one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. We propose a set of criteria to define cirrhosis associated with MAFLD and propose a conceptual framework to consider other causes of fatty liver disease. Finally, we clarify the distinction between diagnostic criteria and inclusion criteria for research studies and clinical trials. Based on the evidence of hepatic steatosis, achieving consensus on the criteria for MAFLD will help to unify terminology, enhance the legitimacy of clinical practice and clinical trials, improve clinical care, and advance the clinical and scientific field of liver research.

Keywords: Metabolic dysfunction, non-alcoholic fatty liver disease, liver cirrhosis

The American Association of Liver Medicine has introduced a new definition for metabolic fatty liver disease: metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is a type of steatosis caused by factors other than excessive alcohol consumption. The exact cause isn't fully understood, but it often occurs with other metabolic disorders such as high cholesterol, obesity, and diabetes. It is the result of MASLD, a systemic disease that affects the brain and causes depression and insomnia. Risk factors for the progression of MASLD include age, iron deposition, diabetes, metabolic syndrome, alcoholism, renin-angiotensin system inhibitors, and metabolic syndrome. It is apparent that there is an association between the onset of dyslipidemia, insulin resistance (IR) and MASLD, as fatty liver disease affects over 75% of people with type 2 diabetes [1]. There is a relationship between the development of MASLD and IR, as well as serum glucose concentrations and consequently increased endogenous triglyceride production, all dependent on the role of IR as a precipitating factor, although MAFLD is thought to be of metabolic origin and involves many possible inducing factors. Hepatic steatosis alters adipokine production, fatty acid metabolism, and IR in skeletal muscle, adipose tissue (AT), and liver, all of which may interact in a complementary manner. Since MASLD is more prevalent in type 2 diabetes mellitus (T2DM) patients, it can be concluded that MASLD increases the likelihood of developing T2DM [2]. Parts of the metabolic syndrome (MetS) can be observed in 90% of MASLD patients. This fact justifies a change in the nomenclature of MASLD. Marchesini *et al*. found that among individuals with hepatic steatosis, the odds ratios for developing liver fibrosis and dysmetabolic steatohepatitis were significantly

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higher in the presence of MetS (3.2 and 3.5, respectively). In addition, MetS is a useful biomarker for estimating the likelihood of fatty liver associated with obesity. The importance of IR in the pathogenesis of MASLD is supported by some reports. As MASLD is a very complicated and mixed disease, it is not reasonable to think of a single hypothesis to describe the pathogenic mechanism. Similar to diabetes and hypertension, MASLD is caused by both environmental and genetic factors. Indeed, a growing body of research suggests that a variety of environmental factors, such as tobacco exposure and air pollution, influence the development of fatty liver. Notwithstanding the fact that multiple factors contribute to MASLD, a particular concept such as abnormal metabolic function or disorder can be used to generalize the etiology of MASLD. It is estimated that the global prevalence of MASLD is 24%, with Asia, the USA, Europe and South America having the highest incidence, followed by the Middle East. The increase in serum insulin concentration can induce various physiological effects on different tissues [3, 4]. Despite the fact that fatty acid metabolism will exacerbate insulin resistance, Randle and colleagues first suggested in 1965 that the rise in serum free fatty acids was also a major factor in the decline in glucose oxidation and the development of IR. Over the past decade, a growing body of research has ignored this process in favor of focusing on the role that fatty acids and glucose play in the development of fatty liver disease. Over time, on an annual basis, 6.3% and 25% of healthy individuals will develop metabolic fatty liver disease and fatty liver, respectively. Obstructive sleep apnea (OSA) and the so-called metabolic syndrome are nearly identical in that they include features such as abnormal fasting glucose, obesity, hypertension and hyperlipidemia, according to medical studies conducted over the past decade. This suggests that MASLD is becoming more common in Asian countries every year. In 2016, a meta-analysis study showed that Asia had a higher prevalence (27.4%) than North America (24%) or Europe (23.7%). Over the past 30 years, there has been a global increase in the prevalence of non-obese patients with MASLD [5]. However, studies have shown that non-obese MASLD patients have lower rates of hypertension, hyperuricemia, and abnormal fasting glucose than their obese counterparts. However, these patients do not reflect healthy individuals with normal metabolism; rather, they simply do not appear to be obese. Lean MASLD patients are more likely than controls to have undiagnosed visceral fat accumulation, dyslipidemia, and hypertension. Aminotransferase-to-Platelet Ratio Index (APRI) and NAFLD Fibrosis Score (NFS), FIB-4 Index and Liver Stiffness Measurement (LSM) are among the non-invasive assessment techniques for liver fibrosis that are currently widely used in clinical practice. To determine whether a patient has liver fibrosis, APRI uses a formula based on the patient's blood platelet count and the quotient of the aspartate aminotransferase (GOT), as they will have a decrease in platelet count and an increase in GOT [6]. The abnormality of PNPLA3 gene, ethnic background, diet, alcohol consumption, genetic defect, intestinal flora and other factors are associated with the prevalence of MASLD. As a result, the course and response to treatment of MASLD patients vary widely. According to epidemiologic studies, the incidence of MASLD may be as high as 21.9% in the United States and up to 31% in Asia. However, the incidence of MASLD confirmed by biopsy exceeded to 61% in the USA, but such test is rarely performed in Asian patients. The areas with the highest fat distribution are visceral and subcutaneous adipose tissue, which have different fat characteristics. Although intrahepatic fat content is higher in obese individuals, 45% of them fall into the metabolically healthy category because they have no symptoms of metabolic disease. It's uncertain whether these individuals are superior to others who are metabolically healthy and normal weight because they are less likely to develop cardiovascular problems [7, 8]. However, 30% of normal weight individuals have metabolic syndrome, which increases their risk of cardiovascular disease. This is because visceral fat, as opposed to subctaneous fat, is associated with a higher risk of metabolic abnormalities, and therefore the distribution and characteristics of fat and its location, such as peripheral fat, are more important factors in predicting metabolic risk than the amount of fat. In 2020, there were two major statements that discussed updating and revising the definition of fatty liver disease, in addition to suggesting that NAFLD be renamed as metabolic associated fatty liver disease (MAFLD). These publications stated that the presence of hepatic steatosis (determined by imaging, histology, or blood biomarkers) plus at least one of the following metabolic criteria can be used to diagnose MAFLD: 1. Being overweight; 2. Having a diagnosis of diabetes; and 3. Metabolic syndrome with increased waist circumference, low HDL cholesterol, low HDL, hypertension, hypertriglyceridemia, insulin resistance: HOMA-IR > 2.5). High-sensitivity C-reactive protein (hs-CRP > 2 mg/L) or at least two risk variables are generally considered the sole indicators of MAFLD. Histology has minimal predictive value but may predict progression of fibrosis. Therefore, it is best to consider individuals with advanced fibrosis (F3 and F4) when making a diagnosis. This stage is predictive of increasing hepatic and extrahepatic morbidity and mortality compared to healthy groups. There is a significant increase in the risk of cardiovascular disease (HR: 1.55, 95% CI: 1.11-2.15), HCC (HR: 6.55, 95% CI: 2.14-20.03), all-cause mortality (HR: 1.29, 95% CI: 1.04-1.59), and cirrhosis (HR: 3.2, 95% CI: 1.05-9.81) [9]. Interventional treatment is not necessary for patients with early-stage F0-F2 MASLD since they do not appear to be liver disease. Reducing the risk of cardiovascular disease and addressing metabolic risk factors like diabetes are important for these individuals.

Declarations

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