Letter to editor

Metabolic Dysfunction-associated Steatotic Liver Disease

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**Abstract**

The American Association of Liver Medicine has introduced a new definition for metabolic fatty liver disease (MASLD) in June 2023: metabolic dysfunction-associated steatotic liver disease. It is the result of pertinent research and clinical procedures related to earlier definitions that are more suited for patient care. It is also a more accurate terminology, as it recognizes an increased risk of myocardial infarction, ischemic stroke, heart failure, and arrhythmias, that are associated with MASLD, a systemic disease that affects the brain and causes depression, sleeplessness, and dementia. Risk factors for the progression of MASLD include age, iron deposition, diabetes, metabolic syndrome, alcoholism, renin-angiotensin system inhibitors, and metabolic syndrome.

**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 (MASLD) in June 2023: metabolic dysfunction-associated steatotic liver disease. It is the result of pertinent research and clinical procedures related to earlier definitions that are more suited for patient care. It is also a more accurate terminology, as it recognizes an increased risk of myocardial infarction, ischemic stroke, heart failure, and arrhythmias, that are associated with MASLD, a systemic disease that affects the brain and causes depression, sleeplessness, and dementia. Risk factors for the progression of MASLD include age, iron deposition, diabetes, metabolic syndrome, alcoholism, renin-angiotensin system inhibitors, and metabolic syndrome. It is evident that there is a link between the onset of dyslipidemia, insulin resistance (IR) and metabolic dysfunction-associated steatotic liver disease (MASLD), since fatty liver disease affects over 75% of people with type 2 diabetes[1]. Additionally, there is a strong epidemiological correlation. The term "non-alcoholic fatty liver disease" should be changed to "MAFLD" according to several studies in 2020–2022. There is a relationship between the development of MASLD and IR as well as serum glucose concentrations and consequently increased endogenous production of triglycerides, all depending on the role of IR as a precipitating factor, even though MAFLD is thought to be of metabolic origin and involved many possible inducing factors. By preventing the process of lipolysis in adipose tissues in the insulin-resistant state, fatty acids into the liver can be increased to yield the same effect. Hepatic steatosis changes the production of adipokines, fatty acid metabolism, and insulin resistance (IR) in skeletal muscles, adipose tissues (AT), and liver, all of which can engage in complementary interactions. Since MASLD is more prevalent in T2DM patients, it may be concluded that MASLD increases the likelihood of developing T2DM[2]. Parts of metabolic syndrome (MetS) can be observed in 90% of MASLD patients. This fact justifies the change of MASLD nomenclature. Marchesini et al. discovered that, among individuals with hepatic steatosis, the odds ratios for developing liver fibrosis and dysmetabolic steatohepatitis were significantly higher when MetS was present (3.2 and 3.5, respectively). Furthermore, MetS is a helpful biomarker for estimating the possibility of fatty liver associated with obesity. The significance of IR in the pathogenesis of MASLD is supported by some reports. Given that 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, an increasing body of research indicates 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 like abnormal metabolic function or disorder can be used to generalize the etiology of MASLD. According to estimates, there is a 24% global prevalence of MASLD, usually seen in Asia, the US, Europe, and South America with the highest incidences, followed by the Middle East. The rise in serum insulin concentration may 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 free fatty acids in serum 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 disregarded this process in favor of focusing on the roles 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 persons will develop metabolic fatty liver disease and fatty liver, respectively. For obstructive sleep apnea (OSA) and the so-called metabolic syndrome, they are nearly identical to include traits like abnormal fasting glucose, obesity, hypertension, and hyperlipidemia, according to medical study conducted in the last ten years. This indicates that MASLD is becoming more common in Asian countries annually. In 2016, a meta-analysis study revealed that Asia had a greater prevalence (27.4%) than either North America (24%) or Europe (23.7%). Over the past 30 years, there has been a global increase in the prevalence of non-obese MASLD patients[5]. However, studies have shown that non-obese MASLD patients had lower rate of hypertension, hyperuricemia, and abnormal fasting glucose when compared to their obese counterparts. However, these patients do not reflect healthy individuals with normal metabolisms; rather, they simply do not appear to be obese. Lean MASLD patients have a higher chance of undiagnosed visceral fat buildup, dyslipidemia, and hypertension when compared to the control group. APRI (Aminotransferase-to-Platelet Ratio Index) and the NAFLD fibrosis score (NFS), FIB-4 index, and current liver stiffness measurement (LSM) are among the non-invasive assessment techniques for liver fibrosis that are currently widely utilized in clinical practice. In order to determine whether a patient has liver fibrosis, APRI applies a formula based on the patient's blood platelet count and GOT, as they will have a decrease in platelet value 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, MASLD patients' course and reaction to treatment differ significantly. According to epidemiological research, the incidence of MASLD could reach 21.9% in the US and up to 31% in Asia. However, the incidence of MASLD verified by biopsy exceeded to 61% in the US, but such test is rarely performed on Asian patients. The areas with the highest distribution of fat are visceral and subcutaneous adipose tissues, which have varying fat properties. Although the intrahepatic fat content of obese individuals is higher, 45% of them fall into the metabolically healthy category since they do not exhibit any metabolic disorder symptoms. It's uncertain if these individuals are superior to others who are metabolically healthy and of normal weight, as they are less likely to get cardiovascular issues[7,8]. However, 30% of individuals who are normal weight have metabolic syndrome, which increases their risk of cardiovascular disease. This is due to the fact that visceral fat, as opposed to subcutaneous fat, is linked to a higher risk of metabolic abnormalities, and thus, the distribution and properties of fat, as well as their location like peripheral fat, are more significant factors in predicting metabolic risk than fat quantity. 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 association fatty liver disease (MAFLD). These publications stated that the presence of hepatic steatosis (determined by imaging, histological examination, or blood biomarker) plus at least one of the following metabolic criteria can be used to diagnose MAFLD: 1. Being overweight; 2. Given a diabetes diagnosis; and 3. Metabolic syndrome showing higher 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 commonly regarded as the sole indicators of MAFLD. The histology has minimal predictive value but can forecast the course of fibrosis. It is therefore best to take individuals with advanced fibrosis (F3 and F4) into consideration when making a diagnosis. Compared to healthy groups, this stage is predictive with rising hepatic and extrahepatic morbidity and mortality. 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), overall mortality (HR: 1.29, 95% CI: 1.04-1.59), and liver 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.

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