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Editorial

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Metabolic Syndrome: A Warning Sign of Liver Fibrosis

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. The prevalence of NAFLD ranges from 20% to 40% in the general adult population and has been increasing rapidly.[1] NAFLD has a diverse histopathological spectrum ranging from simple steatosis to steatohepatitis with varying stages of fibrosis and, ultimately, cirrhosis that can predispose the patients to hepatocellular carcinoma. Cirrhosis is the eleventh most common cause of death, and liver cancer is the sixteenth leading cause of death globally.[2] Importantly, fibrosis stage in patients with NAFLD is associated not only with liver-related mortality, but also with all-cause mortality and morbidity.[3] Therefore, the importance of early identification and staging of fibrosis in patients with NAFLD is emphasized in the updated guidelines.[4,5]

Suggested major pathogenic risk factors for NAFLD are insulin resistance, dysregulated lipid metabolism, low-grade inflammation, increased oxidative and endoplasmic reticulum stresses, sarcopenia, and intestinal dysbiosis.[6] Because insulin resistance is the key component of metabolic syndrome (MetS; often referred to as insulin resistance syndrome) and hyperinsulinemia and insulin resistance play a major role in the pathogenesis of NAFLD, MetS and NAFLD are closely associated. In fact, approximately 90% of the patients with NAFLD have more than one feature of MetS.[7] Increased flux of adipose tissue-derived free fatty acids into the liver under insulin resistance has the potential to increase hepatic triglyceride accumulation, leading to NAFLD. However, whether hepatic insulin resistance is a cause or a consequence of hepatic steatosis remains unresolved. Reciprocal causality between NAFLD and MetS was reported in some longitudinal cohort studies, suggesting that the effect of MetS on NAFLD is greater than that of NAFLD on MetS.[8]

In this issue of *Journal of Obesity & Metabolic Syndrome*, Gangireddy et al.[9] investigated the relationships between MetS and its components with hepatic fibrosis and steatosis in a cross-sectional study using National Health and Nutrition Examination Survey data. As expected, they showed that subjects with MetS had a greater than three-fold increased risk of hepatic steatosis and fibrosis than subjects without MetS. More interestingly, MetS was an independent risk factor for hepatic fibrosis even in the absence of steatosis.[3] The steatosis-free fibrosis shown in this study might be NAFLD at a more severe stage or liver diseases other than NAFLD that cause fibrosis. Whatever the cause, the goals of treatment for chronic liver disease are to slow the progression of scar tissue in the liver, to prevent or treat symptoms and complications of cirrhosis, and to re-

duce the risk of hepatocellular carcinoma. Since chronic liver disease progresses to cirrhosis very slowly and asymptomatically, the disease is rarely diagnosed in the early stage. MetS is a significant warning signal for liver fibrosis, a precursor to cirrhosis that increases liver-related mortality.

It is unknown whether people with MetS should undergo screening tests for liver fibrosis. At present, routine screening for hepatic steatosis and fibrosis in the general population is not recommended because of the unclear cost-effectiveness, the lack of effective drug treatment, and unclear long-term benefits to screening.[4,10] However, some guidelines and consensus reports state that screening of hepatic steatosis and fibrosis can be considered with a multistep approach in at-risk groups (i.e., patients with MetS or type 2 diabetes mellitus and/or high-risk alcohol consumption) who have much higher prevalence of liver fibrosis than the general population.[5,11,12] For example, regarding the evaluation of patients with type 2 diabetes mellitus and NAFLD, ultrasonography-based stepwise approaches using noninvasive biomarker models such as fibrosis-4 or NAFLD fibrosis score as well as imaging studies such as vibration-controlled transient elastography with controlled attenuation parameter or magnetic resonance imaging proton density fat fraction are recommended, and the stage of fibrosis must be assessed appropriately.[5] Older age, obesity, diabetes mellitus, and aspartate transaminase to alanine transaminase ratio greater than one are significant predictors of severe liver fibrosis.[13] Advanced liver fibrosis is associated with an increasing number of metabolic comorbidities.[14] Notably, in a study with Korean health checkup examinees, the prevalence rate of significant liver fibrosis (estimated using magnetic resonance elastography) was higher in subjects with MetS (15.3%) than in those with fatty liver diagnosed by ultrasonography (11.3%).[15]

Recently, a consensus of international experts proposed changing the name of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). The proposed criteria for a positive diagnosis of MAFLD are based on hepatic steatosis in addition to one of the following three criteria, namely overweight or obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. The latter is defined by the presence of at least two metabolic risk abnormalities including the components of MetS.[16] Although controversies remain, the paradigm shift to MAFLD would reflect the underlying pathogenesis and help clinicians consider metabolic fatty liver disease. MAFLD not only increases the risk of liver-related complications (cirrhosis or hepatocellular carcinoma), but also affects the risk of cardiovascular disease, type 2 diabetes mellitus, and other extrahepatic diseases.[17] The definition of MAFLD does not clearly identify the risk of liver fibrosis or other histological features.[16] However, in a population based, cross-sectional study, MAFLD criteria were superior to the old NAFLD criteria for identifying patients with high liver stiffness measured by transient elastography.[18] Further studies are needed on clarification and subclassification of MAFLD related to prognosis compared to NAFLD.[16]

Although fibrosis was previously thought to be an irreversible process, the mild (F1) and moderate fibrosis (F2) stages for liver fibrosis can be reversible when the cause of injury is removed.[19] Several anti-fibrotic pharmacologic agents are being developed to attenuate hepatocellular injury, suppress inflammation in the fibrotic liver, or facilitate fibrosis resolution.[20] However, there are no approved drugs to treat liver fibrosis. Early detection of fibrosis and prevention of progression to cirrhosis by eliminating the cause are clinically important. There are several ongoing projects evaluating the implementation of different methods of screening for liver fibrosis in populations in different areas of the world.[12] If these are proven effective, diagnosing liver fibrosis in asymptomatic subjects will provide an opportunity to prevent disease progression.[12]

Gangireddy et al.[9] have contributed to awareness of the increased risk of liver fibrosis in MetS regardless of the presence or absence of steatosis. Larger, prospective studies are needed to confirm any independent contribution of MetS itself to the risk of hepatic fibrosis without steatosis. Furthermore, potential factors other than NAFLD that induce a close association between MetS and liver fibrosis, such as inter-organ communication, should be explored.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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