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COMMENT

Metabolic dysfunction-associated fatty liver disease reflects a significantly higher risk of hypertension than non-alcoholic fatty liver disease

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Fatty liver is one of the most frequently diagnosed diseases, being found in about 30% of the patients undergoing health checkups. It has become a global problem, with an increasing trend due to lifestyle changes under the coronavirus disease pandemic impact [1]. Fatty liver is a risk factor for cirrhosis and hepatocellular carcinoma, and various diagnostic criteria have been considered for early diagnosis and treatment. Since 1998, non-alcoholic fatty liver disease (NAFLD), which is defined by the presence of fatty liver and exclusion of conditions that may cause fatty liver such as viral liver disease and alcohol consumption, has been widely used. The leading causes of NAFLD are overeating, picky eating, and reduced activity, and many patients have concomitant metabolic abnormalities, such as obesity and glucose intolerance [2, 3]. However, the diagnosis of NAFLD has been problematic because it does not incorporate assessment of metabolic abnormalities. These metabolic abnormalities have also been implicated in the development of liver fibrosis, atherosclerotic cardiovascular disease (ASCVD), and patient prognosis [4, 5]. In 2020, a definition of the fatty liver associated with metabolic dysfunction was proposed as metabolic dysfunction associated fatty liver disease (MAFLD) based on the recent accumulation of evidence regarding the importance of metabolic dysfunction in the treatment of patients with fatty liver [6, 7]. MAFLD is diagnosed when the fatty liver is combined with either (1) overweight/obesity, (2) type 2 diabetes mellitus, or (3) two or more metabolic abnormalities (hypertension, visceral fat accumulation, impaired glucose tolerance, dyslipidemia) in a thin/normal weight patient. Thus, MAFLD is a criterion that can positively capture high-risk fatty liver patients regarding metabolic abnormalities. It is expected to contribute to the early diagnosis and risk prediction of chronic kidney disease and cardiovascular disease. Its association with cardiovascular risk and life expectancy has been reported [8, 9]. Regarding the association between blood pressure and fatty liver, it has been shown that a relationship exists in NAFLD independent of traditional cardiometabolic risk factors [10]. On the other hand, no reports exist on MAFLD. This may be because blood pressure is included as part of the definition of MAFLD, making it difficult to predict the association.

In the current issue of Hypertension Research, Mori et al. demonstrated the relationship between MAFLD and blood pressure using linear mixed-effects model analyses (Fig. 1) [11]. This study analyzed the association between hypertension and MAFLD after adjusting for age, gender, systolic blood pressure, uric acid level, eGFR, antihypertensive medication use, family history of hypertension, and smoking and drinking habits, using ten years of data from health screening visits at a single institution. Comparison of blood pressure and MAFLD was difficult because blood pressure is included in the diagnostic criteria, but linear mixed-effects model analyses were used to perform the analysis. The results showed that patients with MAFLD had a higher rate of increase in systolic blood pressure over time than those without MAFLD. They also showed that MAFLD is more strongly correlated with blood pressure than NAFLD. This method is superior in that it can evaluate values that have been measured repeatedly over a long period of time, and it can also evaluate the presence of missing values.

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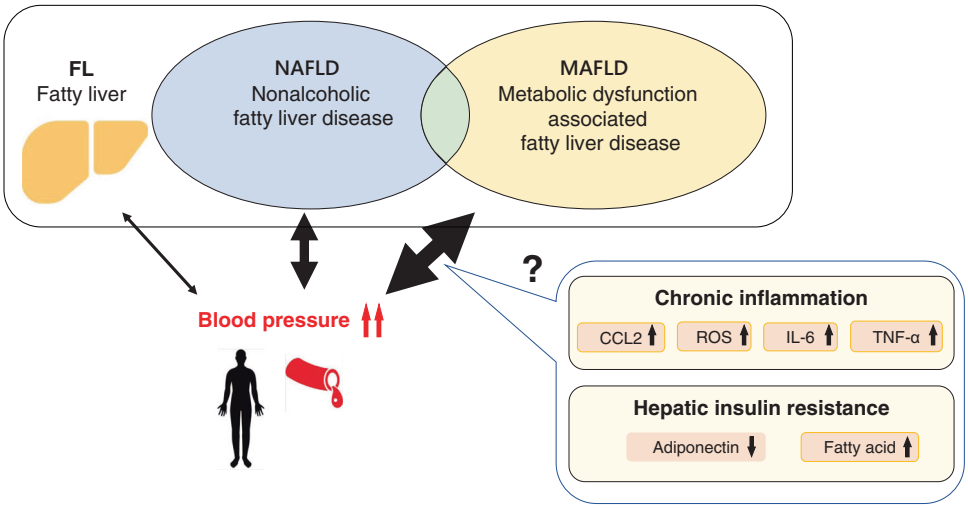

Fig. 1 The association between diagnosis of metabolic dysfunction associated fatty liver disease (MAFLD) with hypertension was greater than the associations with diagnoses of fatty liver (FL) and non-alcoholic fatty liver disease (NAFLD). CCL2 Chemokine C-C motif ligand 2; IL-6 interleukin-6; ROS reactive oxygen species; TNF-α tumor necrosis factor-α

On the other hand, the mechanisms involved in the elevation of blood pressure in MAFLD are unclear. Two hypothesized mechanisms by which fatty liver may contribute to elevated blood pressure are chronic inflammation and hepatic insulin resistance. Concerning chronic inflammation, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and Monocyte chemotactic protein 1(MCP-1) are known to be elevated in NAFLD. Fat accumulation in the liver promotes leukocyte infiltration through enhanced expression of these cytokines, which exacerbates the pathogenesis from simple fat deposition in the liver to liver injury [12, 13]. In addition, Chronic inflammation stimulates sympathetic nerves via Chemokine C-C motif ligand 2 (CCL2) and reactive oxygen species (ROS) upregulation, which induces further vascular inflammation through noradrenaline-mediated T cell regulation, contributing to the pathogenesis of hypertension [14, 15]. Furthermore, Cytokines such as TNF-α and IL-6 have also been shown to regulate the expression of components of the renin-angiotensin system, particularly angiotensinogen production in the liver and kidney, leading to angiotensin II-dependent hypertension [16].

Hepatic insulin resistance may also contribute to elevated blood pressure. Anderson E et al. reported that in fatty liver, the activation of the fatty acid synthesis system inhibits insulin action, resulting in insulin resistance and hyperinsulinemia, which activates the sympathetic nervous system [17]. Watt M et al. demonstrated decreased insulin sensitivity due to decreased adiponectin and elevated TNFα associated with chronic inflammation in patients with MAFLD [18].

Thus, the relationship between MAFLD and blood pressure is significant, and it is assumed that various factors are involved in the mechanism. It is desirable to fully elucidate the mechanism through basic animal studies and clinical research and to apply the findings to clinical practice. In addition, since this study was a single-center study, a larger scale data set is needed.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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