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Metabolic Dysfunction-Associated Steatotic Liver Disease: The Role of Hepatic Steatosis in Insulin Resistance and Metabolic Health

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Multinational liver societies have recently introduced the term metabolic dysfunction-associated steatotic liver disease (MASLD) to replace non-alcoholic fatty liver disease. This terminological change reflects a deeper understanding of the intrinsic link between fatty liver and metabolic disorders, as highlighted in the diagnostic criteria for MASLD [1]. Insulin resistance, a key factor in this association, plays a significant role in the development and progression of both hepatic steatosis and metabolic disease [2]. Hepatic steatosis is defined by the excessive accumulation of lipids within hepatocytes. In conditions such as diabetes and obesity, increased lipolysis in adipose tissue drives a greater influx of free fatty acids into the liver, while upregulated hepatic *de novo* lipogenesis further contributes to lipid accumulation [3]. Conversely, excessive lipid accumulation in the liver exacerbates both hepatic and peripheral insulin resistance through complex mechanisms involving lipid toxicity, oxidative stress, inflammation, and hepatokines [2].

Hepatic steatosis is not simply a consequence of insulin resistance; it also actively drives its progression [2]. Consequently, as an independent pathological entity, hepatic steatosis significantly influences the development and progression of metabolic disorders, such as diabetes, while also exerting detrimental effects on cardiovascular health [2,4]. Notably, the risk associated with fatty liver disease correlates with its severity and tends to diminish as the condition improves or resolves [5,6]. Meta-analyses further support this association, demonstrating that both the severity of hepatic steatosis and the extent of fibrosis are positively correlated with an increased risk of developing diabetes and cardiovascular diseases (CVD) [4,7]. Moreover, as hepatic steatosis worsens, it is linked to higher levels of fibrosis, further exacerbating its systemic impact [8].

To examine the relationship between the degree of hepatic steatosis and insulin resistance, we conducted a cross-sectional analysis using data from the 2017 to 2018 National Health and Nutrition Examination Survey (NHANES). Out of 5,145 adults who underwent liver ultrasound transient elastography (FibroScan 502 Touch, Echosens, Paris, France), 2,153 individuals with available insulin level measurements were included in the analysis. Hepatic steatosis was quantified using the controlled attenuation parameter (CAP), expressed in dB/m, while insulin resistance was defined by a homeostatic model assessment for insulin resistance greater than 3.0. Our analysis revealed a significant association between the degree of hepatic steatosis and insulin resistance. Using a restricted cubic spline regression model, we observed a J-shaped relationship between CAP scores and the risk of insulin resistance (Fig. 1). These findings suggest a dose-dependent rela-

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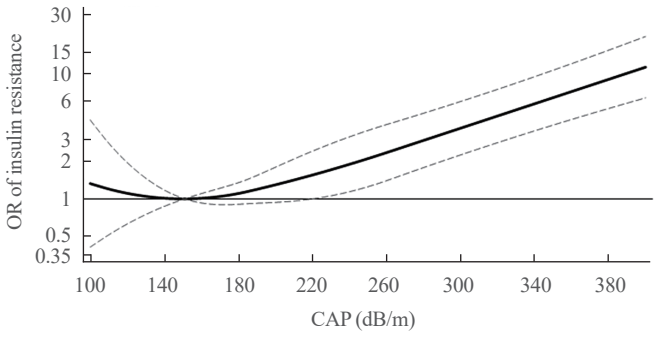

Fig. 1. Relationship between liver steatosis and insulin resistance. A restricted cubic spline model displays odds ratios (ORs) of insulin resistance according to the controlled attenuation parameter (CAP) score. The associations were adjusted for age, sex, body mass index, race/ethnicity, alcohol use, lipid-lowering medication, and diabetes status.

tionship between hepatic steatosis and insulin resistance, underscoring the importance of quantitative evaluation of hepatic steatosis in understanding its role in metabolic disease.

The prevalence of fatty liver disease in adults in Korea is estimated at approximately 20% to 40% [9]. Although fatty liver disease is strongly associated with an increased risk of developing diabetes or CVD, this risk varies among individuals [4,7]. Similarly, not all cases of simple steatosis progress to advanced liver disease, such as liver cirrhosis [10]. As our findings indicate, the risk of insulin resistance varies according to the severity of hepatic steatosis. Liver fibrosis is a key risk factor for the progression to advanced liver disease, and the activation of hepatic stellate cells is critical in the development and progression of fibrosis. In this process, hyperinsulinemia and hyperglycemia resulting from insulin resistance directly activate hepatic stellate cell, thereby contributing to the progression from fatty liver to steatohepatitis and liver fibrosis [10,11]. Therefore, hepatic steatosis is expected to affect these risks differently based on its severity.

The bidirectional relationship between hepatic steatosis and insulin resistance suggests that hepatic steatosis may be a modifiable factor in managing other metabolic diseases, such as diabetes and dyslipidemia. Recent results from a phase 3 study on resmetirom, a newly approved treatment for non-alcoholic steatohepatitis (NASH), support this view [12]. In that study, resmetirom reduced hepatic fat by over 40% from baseline—as measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF) or CAP—and significantly improved the lipid profile by reducing low-density lipoprotein, triglycerides, and apolipoprotein B levels. Furthermore, a marked reduction in MRI-PDFF with resmetirom was associated with a significant improvement in fibrosis. Treatment with resmetirom not only improved hepatic steatosis and NASH but also led to improvements in dyslipidemia. Additionally, greater improvements in hepatic steatosis correlated with more significant resolution of NASH, reductions in fibrosis, and more favorable lipid profiles.

Several therapeutic candidates targeting different mechanisms for the treatment of hepatic steatosis and steatohepatitis are currently under development or investigation. Future studies should determine whether improvements in hepatic steatosis, as measured by quantitative imaging techniques, are associated with a reduced risk of metabolic diseases, including diabetes and CVD. Moreover, prospective clinical trials evaluating the impact of hepatic steatosis reduction on long-term metabolic and cardiovascular outcomes are necessary to establish whether reducing liver fat can serve as a therapeutic target in managing metabolic diseases. Given the strong dose-dependent association between hepatic steatosis and insulin resistance, as well as its role in the progression or resolution of metabolic dysfunction, interventions aimed at reducing liver fat could enhance both hepatic and cardiometabolic health.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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