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COMMENT

The causal relationship between non-alcoholic fatty liver disease, hypertension, and cardiovascular diseases: implications for future research

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Keywords Non-alcoholic fatty liver disease · Metabolic syndrome · Hypertension · Cardiovascular disease

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Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic fat accumulation associated with insulin resistance and is defined as the histological presence of steatosis in >5% of hepatocytes [1]. NAFLD encompasses the spectrum of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) and is closely related to not only the progression of liver disease, such as cirrhosis and hepatocellular carcinoma, but also metabolic syndrome [1, 2]. Recently, NAFLD has also been referred to as metabolic dysfunction associated with steatotic liver disease (MASLD) to emphasize its strong relationship with metabolic dysfunction [3]. The metabolic abnormalities include glucose intolerance (type 2 diabetes, impaired glucose tolerance, or impaired fasting glycemia), insulin resistance, central obesity, dyslipidemia, and hypertension, which are established risk factors for cardiovascular disease (CVD) [4]. NAFLD is prevalent and appears to be increasing worldwide [5]. This trend has been found in Japan, with an estimated prevalence rate of 25.5–29.7% [6, 7]. This prevalence is predicted to increase and subsequently may affect approximately half of the population by 2040 in Japan [7]. People with NAFLD frequently have comorbid hypertension (HT). The prevalence of NAFLD was reported to be approximately 50% in patients with HT. Additionally, the percentage of cases with HT is almost 20% higher in patients with NAFLD than in those without NAFLD [8]. Moreover, HT is an independent predictor of NAFLD, and NAFLD is associated with an increased risk of incident HT [9]. Therefore, there may be a bidirectional association between elevated blood pressure (BP) and NAFLD, but a clear relationship has still not been proven.

In the present study, Hu et al. examined a large-scale cohort (China Multi-Ethnic Cohort and UK Biobank) to investigate the temporal relationship between hepatic steatoses and BP using cross-lagged panel models [10]. Cross-lagged panel analysis is a widely used method for identifying temporal relationships and enables assessing bidirectional effects [11]. They showed that hepatic steatosis more strongly contributed to elevated BP than the pathway from elevated BP to hepatic steatosis. These authors used a surrogate score of the fatty liver index that was calculated from the body mass index, gamma-glutamyl transferase, triglycerides, and waist circumference for the main analysis. They also conducted validation analysis using a magnetic resonance imaging-derived proton density fat fraction instead of the fatty liver index, and consistent results were obtained. Subsequently, once they identified BP as a potential mediator in the development of CVD, they also used a causal mediation model to assess the mediation effect in the development of CVD. Causal mediation analysis was used to identify intermediate variables (or mediators) in the causal pathway between the treatment and the outcome [12]. They found that the mediation proportion for systolic BP and diastolic BP in the hepatic steatosis–CVD association was 12.2% and 5.2%, respectively, and the natural indirect effect of systolic BP was statistically significant. Moreover, although the elevation in BP positively mediated the hepatic steatosis–CVD association, the mediation proportion of BP in the hepatic steatosis–CVD association was low. Additionally, the mediation effect on the hepatic steatosis–stroke association was relatively stronger in stroke than in ischemic heart disease.

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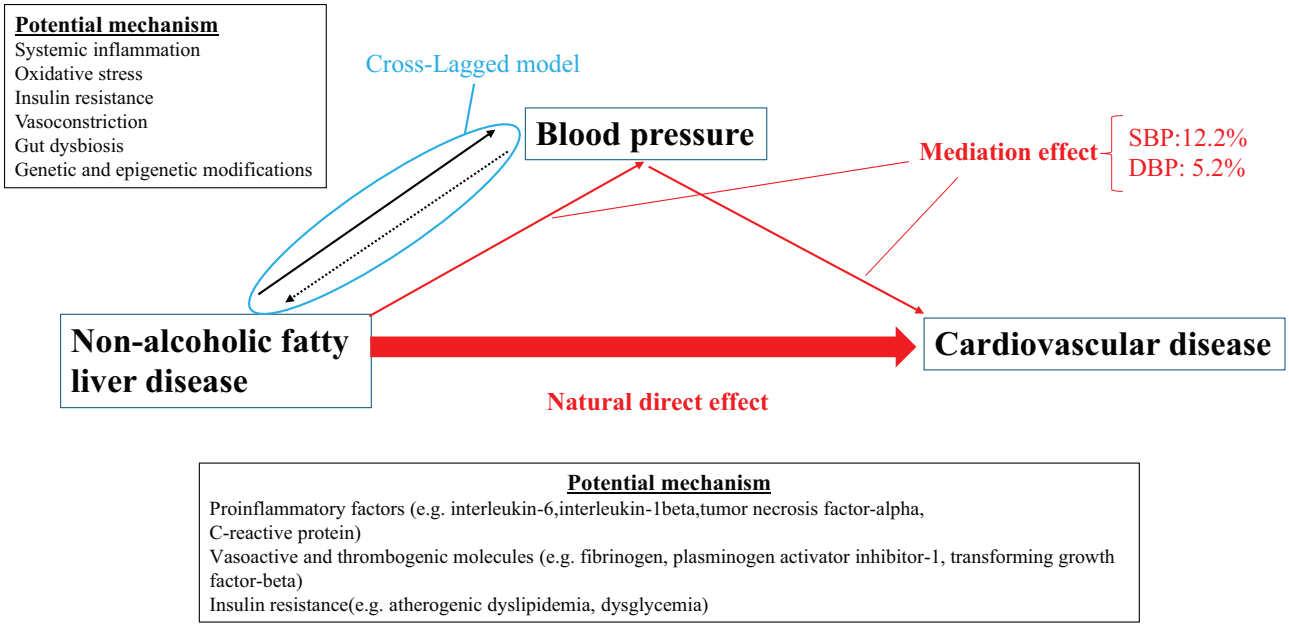
Graphical Opinion



There are potential mechanisms by which NAFLD promotes elevated BP, although the mechanism is not fully understood. One potential mechanism is systemic inflammation. In the condition of NAFLD, hepatocellular lipotoxicity and hepatocyte injury trigger an innate immune response and promote the production of proinflammatory factors, such as interleukin-6, tumor necrosis factor-α, and CC-chemokine ligand 2 [13]. These proinflammatory factors may accelerate chronic inflammation by being released into the circulation [12]. Inflammation is also related to the activation of the sympathetic nervous system (SNS), which can lead to elevated BP. Moreover, inflammation can activate the renin-angiotensin system, which plays a key role in the development of hypertension [13]. Insulin resistance (IR) is another main mechanism promoting the elevation of BP. In IR, excess free fatty acids released by adipose tissue deposit ectopic fat on perivascular fat and renal sinus fat. Proinflammatory cytokines are released by perivascular fat, which directly promote vascular IR and endothelial dysfunction [13]. Vascular IR impairs the phosphatidylinositol 3-kinase pathway, which can lead to vasoconstriction and, subsequently, to a reduction in endothelial nitric oxide production [13]. Renal sinus fat may affect renin–angiotensin system components through its paracrine function and kidney compression-related mechanical stress, contributing to renal sodium reabsorption [13]. Therefore, IR increases vasoconstriction and water–sodium retention, contributing to elevated BP. Other potential mechanisms are oxidative stress, gut dysbiosis, and genetic and epigenetic modifications [13].

The present study showed that NAFLD may be directly related to CVD, and BP partially mediated the association between NAFLD and CVD [10]. Although the mechanism of how NAFLD facilitates CVD is incompletely understood, there are multiple possible mechanisms through which NAFLD can directly increase CVD. One putative mechanism is that steatotic hepatocytes release extracellular vesicles, which increase vascular endothelial inflammation and promote atherogenesis through miR-1 delivery, reduced Kruppel-like factor 4, and nuclear factor-κB activation [14]. Other possible mechanisms are that steatosis in the liver releases proinflammatory, proatherogenic, and procoagulant mediators, contributing to CVD [14, 15].

The causes of chronic disease are diverse and the causal path is highly complicated. Therefore, cross-lagged panel analysis and causal mediation analysis could be promising analytical tools for identifying causal relationships. We once reported that eating before bed was related to a future risk of developing hypertension in Hypertension Research. We believed that eating before bed causes nocturnal hyperinsulinemia, which increases BP through activation of SNS activity, proliferation of vascular smooth muscle cells, and sodium retention. Additionally, low-quality sleep derived from a short time between dinner and bedtime may increase sympathetic nerve activity, which may induce HT. However, eating before bed may also be related to obesity or metabolic syndrome, which may indirectly affect HT. Therefore, further studies using causal mediation analysis are warranted to clarify whether eating before bed directly affects HT or mediates metabolic syndrome, subsequently

leading to HT. Considering causal relationships are indispensable for future HT research to understand complicated and intertwined causal relationships between exposure and progression of HT and to understand the pathogenesis of HT.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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References

1. Han SK, Baik SK, Kim MY. Non-alcoholic fatty liver disease: definition and subtypes. Clin Mol Hepatol Korean Assoc Study Liver. 2023;29:S5–16.
2. Diehl AM, Day C. Cause, pathogenesis, and treatment of non-alcoholic steatohepatitis. N Engl J Med. 2017;377:2063–72.
3. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79:1542–56.
4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. In: Lancet. Elsevier Limited; 2005:1415–28.
5. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77:1335–47.
6. Eguchi Y, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: A multicenter large retrospective study. J Gastroenterol. 2012;47:586–95.
7. Ito T, Ishigami M, Zou B, Tanaka T, Takahashi H, Kurosaki M, et al. The epidemiology of NAFLD and lean NAFLD in Japan: a meta-analysis with individual and forecasting analysis, 1995–2040. Hepatol Int. 2021;15:366–79.
8. López-Suárez A, Guerrero JMR, Elvira-González J, Beltrán-Robles M, Cañas-Hormigo F, Bascuñana-Quirell A. Nonalcoholic fatty liver disease is associated with blood pressure in hypertensive and nonhypertensive individuals from the general population with normal levels of alanine aminotransferase. Eur J Gastroenterol Hepatol. 2011;23:1011–7.
9. Ma J, Hwang SJ, Pedley A, Massaro JM, Hoffmann U, Chung RT, et al. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. J Hepatol. 2017;66:390–7.
10. Hu Y, Tang W, Liu Y, Zhang N, Zhu X, Tang D, et al. Temporal relationship between hepatic steatosis and blood pressure elevation and the mediation effect in the development of cardiovascular disease. Hypertens Res https://doi.org/10.1038/s41440-024-01708-5.
11. Han T, Lan L, Qu R, Xu Q, Jiang R, Na L, et al. Temporal relationship between hyperuricemia and insulin resistance and its impact on future risk of hypertension. Hypertension. 2017;70:703–11.
12. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods. 2010;15:309–34.
13. Zhao YC, Zhao GJ, Chen Z, She ZG, Cai J, Li H. Nonalcoholic fatty liver disease: an emerging driver of hypertension. Hypertension. 2020;75:275–84.
14. Targher G, Corey KE, Byrne CD. NAFLD, and cardiovascular and cardiac diseases: Factors influencing risk, prediction and treatment. Vol. 47, Diabetes and Metabolism. Elsevier Masson s.r.l.; 2021.
15. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: Clinical associations, pathophysiological mechanisms and pharmacological implications. Gut. 2020;69:1691–705.