Hypertension Research (2023) 46:539–541
https://doi.org/10.1038/s41440-022-01117-6

COMMENT

Mechanisms underlying the bidirectional association between nonalcoholic fatty liver disease and hypertension

Hironori Nakagami[1]

Keywords NAFLD · Hypertension · Insulin resistance

Received: 30 September 2022 / Accepted: 7 October 2022 / Published online: 6 December 2022

Hypertension and nonalcoholic fatty liver disease (NAFLD) are common cardiovascular risk factors and are closely related to obesity and metabolic syndrome. In clinical evidence, hypertension is an independent predictor of NAFLD, and NAFLD is associated with an increased risk of incident hypertension [1–3]. In prospective clinical studies, the chance of hypertension in individuals with NAFLD was higher than that in individuals without fatty liver disease [4]. Additionally, the adjusted hazard ratios for prehypertension and hypertension were high in the mild NAFLD group (1.18 and 1.07, respectively) and higher in the moderate-to-severe group (1.62 and 1.14, respectively) [5, 6]. As their association is bidirectional, hypertension may promote the onset of NAFLD [7, 8]. In a prospective clinical study, the development and persistence of hypertension predicted the onset of NAFLD (1.45 and 1.61, respectively) [9].

Siafi et al. demonstrated that the fatty liver index (FLI), which is a validated marker of NAFLD and a screening tool for hepatic steatosis, has independent prognostic value for the incidence of cardiovascular events in newly diagnosed, never-treated hypertensive patients [10]. Of importance, the FLI high-risk pattern (more than 60 units) for underlying NAFLD was associated with a 7.5-fold higher outcome rate than the lower-risk FLI pattern. These results suggest the synergistic or additional effect of NAFLD and hypertension on the incidence of cardiovascular events. Siafi et al. also demonstrated that in patients with diabetes mellitus, the rate of cardiovascular events was more than threefold greater; however, the presence of metabolic syndrome was not associated with a differential propensity of the FLI to predict cardiovascular outcomes. These results also suggest that NAFLD plus hypertension increases the risk of cardiovascular events more than NAFLD plus diabetes or metabolic syndrome. What is the mechanism underlying the association of NAFLD and hypertension?

One of the potential mechanisms is insulin resistance (IR). The liver is a major target organ for insulin, and insulin resistance is known to be related to hypertension as well as diabetes [11]. Experimental evidence has highlighted a causal relationship between NAFLD and IR that is independent of obesity. Mechanistically, the reduced hepatic insulin action leads to impaired suppression of glucose and lipid production, which further induces systemic IR. Hepatokines, such as fetuin-A and fibroblast growth factor 21, are liver-derived proteins that are released from the injured liver [12]. The altered hepatokine profiles in NAFLD also drive the development of systemic IR by directly impairing insulin signaling and indirectly regulating lipid and glucose metabolism. For example, IR contributes to fatty liver disease development by enhancing ectopic fat accumulation. Lipid accumulation in the liver leads to chronic hepatic inflammation and endoplasmic reticulum stress, which may cause insulin resistance. Insulin activates phosphatidylinositol 3-kinase and the Akt pathway, which causes vasodilation by inducing endothelial nitric oxide production. Thus, IR may induce vasoconstriction in target organs. For example, IR in renal vasculature and tubules contributes to water retention and sodium reabsorption, leading to hypertension. Adipose tissue is also a target organ for insulin, and adipocytokines (i.e., adiponectin or leptin) may affect both NAFLD and hypertension. The vicious cycle of insulin resistance and lipid accumulation in NAFLD may contribute to the incidence of hypertension.

Systemic inflammation is also a putative mechanism linking NAFLD and hypertension. NAFLD has been reported to be associated with a systemic inflammatory response that is characterized by the elevation of inflammatory factors, such

✉ Hironori Nakagami
nakagami@gts.med.osaka-u.ac.jp

[1] Department of Health Development and Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamada-oka, Suita, Osaka, Japan

as interleukin-6 and CC-chemokine ligand 2 [13]. Under NAFLD conditions, hepatocellular lipotoxicity and hepatocyte injury trigger an innate immune response and promote the production of proinflammatory factors. These factors are further released into the blood to accelerate chronic inflammation. Moreover, inflammation is involved in the activation of the sympathetic nervous system (SNS), leading to the development of hypertension. Indeed, patients with NAFLD had impaired cardiac and autonomic function with elevated inflammatory factors, such as interleukin-18 and tumor necrosis factor-α. Inflammation is also involved in the activation of the renin-angiotensin system (RAS), which essentially contributes to blood pressure regulation [13]. The RAS is well known to play an important role in the treatment of hypertension. Angiotensin II has been shown to enhance insulin resistance by interacting with liver insulin receptor and its signaling pathway. The activation of the local RAS in chronic liver disease contributes to liver injury and fibrosis through angiotensin II-mediated stimulation of fibroblast proliferation and the release of inflammatory cytokines. Interestingly, a single nucleotide polymorphism of angiotensin II type 1 receptor was associated with the occurrence of NAFLD [14]. These results suggest that the RAS can be involved in the development of both hypertension and NAFLD.

Siafi et al. also found that patients with an FLI low-risk pattern have better blood pressure control, which suggests that NAFLD may affect the development of hypertension. Similarly, Kasper et al. reported the findings of their pilot study to evaluate the status of hypertension management in NAFLD patients using 24-hour-ambulatory blood pressure monitoring (24-h-ABPM) [15]. A total of 101 datasets were evaluated, and the median age of the study population was 52 years. The study population included females (46.5%), smokers (25.7%), and individuals with type 2 diabetes (25.7%). Forty-nine patients (48.5%) with NAFLD had a medical history of hypertension; however, controlled hypertension was confirmed in only 10 patients (21.3%) with NAFLD with treated hypertension. Sustained uncontrolled hypertension despite treatment was observed in 20 patients (42.6%) with NAFLD. Masked hypertension (normal office blood pressure with elevated out-of-office blood pressure) was identified in 22 patients (21.8%), 12 of whom were receiving antihypertensive treatment (masked uncontrolled hypertension). In this study, approximately two-thirds (60.4%) of NAFLD patients suffered from uncontrolled hypertension, which is significantly higher than the reported rates of ~40–50% in the general population. These results suggest that we should pay more attention to uncontrolled hypertension in individuals with NAFLD in the management of hypertension. Therapeutic treatment approaches are still under development because of the complexity and heterogeneity of the pathogenesis of NAFLD. Thus, whether improvement in NAFLD status can modify blood pressure should be evaluated, and the results may confirm the hypothesis that NAFLD drives the development of hypertension.

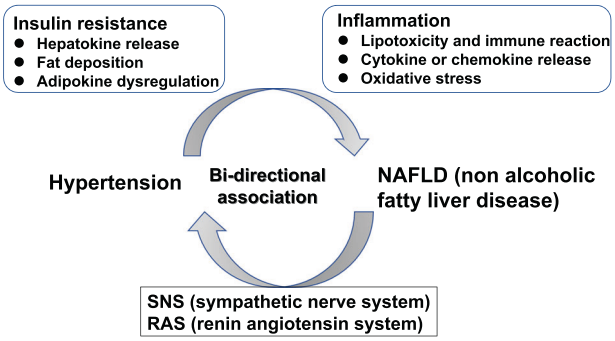

Fig. 1 The vicious cycle in the bidirectional association between hypertension and NAFLD. Hypertension is an independent predictor of NAFLD, and NAFLD is associated with the development of hypertension. The mechanism underlying this interaction might be insulin resistance or inflammation with the activation of the SNS and RAS

Overall, NAFLD contributes independently to the development of hypertension and vice versa. The mechanism underlying this interaction might be insulin resistance or inflammation with the activation of the SNS and RAS (Fig. 1). In the future, new therapies that are effective for both NAFLD and hypertension will be explored to reduce the risk of cardiovascular diseases.

Compliance with ethical standards

Conflict of interest The Department of Health Development and Medicine is an endowed department supported by Anges, Daicel, and FunPep.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ng CH, Wong ZY, Chew NWS, Chan KE, Xiao J, Sayed N, et al. Hypertension is prevalent in non-alcoholic fatty liver disease and increases all-cause and cardiovascular mortality. Front Cardiovasc Med. 2022;9:942753.
2. 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.
3. López-Suárez A, Guerrero JM, Elvira-González J, Beltrán-Robles M, Cañas-Hormigo F, Bascuñana-Quirell A. Nonalcoholic fatty liver disease is associated with blood pressure in hypertensive and non-hypertensive individuals from the general population with normal levels of alanine aminotransferase. Eur J Gastroenterol Hepatol. 2011;23:1011–7.
4. Lau K, Lorbeer R, Haring R, Schmidt CO, Wallaschofski H, Nauck M, et al. The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. J Hypertens. 2010;28:1829–35.

5. Ryoo JH, Ham WT, Choi JM, Kang MA, An SH, Lee JK, et al. Clinical significance of non-alcoholic fatty liver disease as a risk factor for prehypertension. J Korean Med Sci. 2014;29:973–9.
6. Ryoo JH, Suh YJ, Shin HC, Cho YK, Choi JM, Park SK. Clinical association between non-alcoholic fatty liver disease and the development of hypertension. J Gastroenterol Hepatol. 2014;29:1926–31.
7. Sorrentino P, Terracciano L, D'Angelo S, Ferbo U, Bracigliano A, Vecchione R. Predicting fibrosis worsening in obese patients with NASH through parenchymal fibronectin, HOMA-IR, and hypertension. Am J Gastroenterol. 2010;105:336–44.
8. Zhang T, Zhang C, Zhang Y, Tang F, Li H, Zhang Q, et al. Metabolic syndrome and its components as predictors of nonalcoholic fatty liver disease in a northern urban Han Chinese population: a prospective cohort study. Atherosclerosis. 2015;240:144–8.
9. Liu P, Tang Y, Guo X, Zhu X, He M, Yuan J, et al. Bidirectional association between nonalcoholic fatty liver disease and hypertension from the Dongfeng-Tongji cohort study. J Am Soc Hypertens. 2018;12:660–70.
10. Saifi E, Andrikou L, Thomopoulos C, Konstantinidis D, Kakouri N, Takakis F et al. Fatty liver index and cardiovascular outcomes in never-treated hypertensive patients: a prospective cohort. Hypertension Res. 2022 https://doi.org/10.1038/s41440-022-01015-x
11. Saad MF, Rewers M, Selby J, Howard G, Jinagouda S, Fahmi S, et al. Insulin resistance and hypertension: the Insulin Resistance Atherosclerosis study. Hypertension. 2004;43:1324–31.
12. Yoo HJ, Choi KM. Hepatokines as a link between obesity and cardiovascular diseases. Diabetes Metab J. 2015;39:10–15.
13. Watt MJ, Miotto PM, De Nardo W, Montgomery MK. The liver as an endocrine organ-linking NAFLD and insulin resistance. Endocr Rev. 2019;40:1367–93.
14. Kasper P, Martin A, Lang S, Demir M, Steffen HM. Hypertension in NAFLD: an uncontrolled burden. J Hepatol. 2021;74:1258–60.
15. Yoneda M, Hotta K, Nozaki Y, Endo H, Uchiyama T, Mawatari H, et al. Association between angiotensin II type 1 receptor polymorphisms and the occurrence of nonalcoholic fatty liver disease. Liver Int. 2009;29:1078–85.