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Review Article

Link between Non-Alcoholic Fatty Liver Disease and Hypertension: Non-Alcoholic Fatty Liver Disease as a Multisystem Disease

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Abstract

The prevalence and incidence of non-alcoholic fatty liver disease (NAFLD) is increasing due to the epidemics of obesity and type 2 diabetes mellitus (T2DM). Many studies provided the evidence of the decreased flow-mediated vasodilation (FMD), increased carotid intima-media thickness (IMT), and increased brachial ankle pulse wave velocity (baPWV) in patients with NAFLD. Recently, a link between NAFLD and hypertension along with new genetic expression, ADIPOQ C11377G and AGTR1 has been shown. It is putative that NAFLD may induce systemic inflammation, insulin resistance, oxidative stress, and increased vasoconstriction and decreased vasodilation, subsequently leading to hypertension. Under the systemic inflammation, it has been suggested that NAFLD may promote sympathetic nervous system (SNS) and renin-angiotensin system (RAS) activation, and local vasculature and renal inflammation, subsequently leading to hypertension. The author has reviewed the current knowledge of the link between NAFLD and hypertension along with new genetic expression in this article. It is plausible that NAFLD is a multisystem disease and is associated with hepatic and extrahepatic disease.

Keywords: NAFLD, hypertension, ADIPOQ C11377G and AGTR1, multisystem disease, atherosclerosis

Introduction

Due to the increasing rates in parallel to obesity and type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) is the common liver disease worldwide [1]. Recently, a link between NAFLD and hypertension along with new genetic expression has been shown [2]. NAFLD is a multisystem disease and is associated with hepatic and extrahepatic manifestations [3, 4]. The author described the current knowledge of a link between NAFLD and hypertension along with the new genetic expression in this review article.

NAFLD as a Multisystem Disease:

Due to the epidemics of obesity and type 2 diabetes mellitus (T2DM), the prevalence and incidence of NAFLD continue to increase [1]. Whereas a close link between NAFLD and hypertension associated with the new gene expression has been reported [2]. It is known that NAFLD is a multisystem disease and is associated with hepatic (hepatocellular carcinoma: HCC) and extrahepatic (cardiovascular disease: CVD, coronary artery disease: CAD, and chronic kidney disease: CKD) manifestations [3, 4]. Many studies showed that NAFLD is associated with endothelial dysfunction estimated by flow-mediated vasodilation (FMD) study, increased intima-media thickness (IMT) by assessed common carotid artery, and increased pulse wave velocity (PWV) that are established as CVD and atherosclerosis indicators [3]. A recent clinical report by Narayan et al. also described that endothelial dysfunction is independent of metabolic syndrome (MS) in patients with NAFLD [5].

Link between NAFLD and Atherosclerosis

The author previously described that an association between chronic liver disease (NAFLD/Non-Alcoholic Steatohepatitis: NASH and chronic C virus hepatitis infection) and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway [6]. The clinical practice guidelines stated that CVD should be identified in NAFLD irrelevant of the presence of traditional risk factors [4]. Flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) examinations in the brachial artery are the promising procedures for assessing vascular endothelial and vascular smooth muscle cell (VSMC) function in atherosclerosis [7]. Previous studies on the diseases of migraine, CVD, chronic kidney disease (CKD), dyslipidemia, aging liver, and COVID-19 using FMD and NMD examinations have been provided [8-19].

Association between NAFLD and Hypertension

The study suggested that the prevalence of hypertension is significantly increased in individuals with NAFLD than in the general population [2, 20, 21]. Clinical and experimental studies suggested that NAFLD may promote the development and progression of hypertension, T2DM, and cardiovascular disease (CVD) [22]. According to the previous report, it is

thought that the relationship between NAFLD and hypertension is independent of other metabolic components [23]. It is putative that NAFLD may induce systemic inflammation, insulin resistance, oxidative stress, and increased vasoconstriction and decreased vasodilation, subsequently leading to hypertension [2]. Due to impaired cardiac and autonomic function in patients with NAFLD [24], it has been suggested that the elevated circulating levels of TNF-α and cytokeratin 18 were independently associated with increased sympathetic activity and decreased parasympathetic activity [2]. Additionally, it has been indicated that pro-inflammatory cytokines regulate the renin-angiotensin system (RAS) and promote systemic and local Angiotensin II (Ang II) formation [25]. Regulation of angiotensinogen (AGT) in liver and kidney organs is proposed as a key mechanism of Ang II-dependent hypertension [25]. Meanwhile, it is suggested that the increased leptin level and decreased adiponectin value have been observed in patient with NAFLD [26, 27]. With respect to functional and structural vascular alteration, the evidence for the decreased FMD, increased carotid IMT, and raised baPWV in patient with NAFLD has been shown, indicating an association between NAFLD and atherosclerosis. Whereas, to evaluate plaque metabolism and predict vascular risk, fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of atherosclerosis has been investigated [28]. Recently, a few reports including association between NAFLD and carotid inflammation and relationship between NAFLD and vascular inflammation have been described [29, 30]. It is known that recent clinical report suggested that endothelial dysfunction is independent of metabolic syndrome in patients with NAFLD [5]. Furthermore, clinical study provided the association between NAFLD and chronic kidney disease [31, 32]. Under the systemic inflammation, it has been suggested that NAFLD may promote sympathetic nervous system (SNS) and renin-angiotensin system (RAS) activation, and local vasculature and renal inflammation, subsequently leading to hypertension [2]. There is limited evidence on the genetic relation between NAFLD and hypertension, though the close association between NAFLD and hypertension has been identified. It is plausible that the new gene expression such as ADIPOQ C11377G and AGTR1 may strongly contribute to a link between NAFLD and hypertension [2]. With respect to the recommendations, the clinical practice guidelines have stated that NASH patients with fibrosis associated with hypertension should receive a closer monitoring because of the progression of this entity with a higher risk [4].

NAFLD/NASH-associated Hepatocellular Carcinoma

The current studies indicated that genetic susceptibility increases risks of NAFLD/NASH and NASH-associated cirrhosis [33]. It has been previously reported that five genes including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 known to be associated with NASH are involved in glucose and fat homeostasis regulatory pathways [33, 34]. Polygenic risk score (PRS) using PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 in NAFLD/NASH-related HCC has been provided [35, 36]. Recently, the author has described the reports of NAFLD/NASH-associated HCC from the current genetic advances [37-39].

Future Perspective

Now, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Omicron variant as a novel strain has emerged in November 2021 and is still ongoing. The Working Group on Atherosclerosis and Vascular Biology, and the Council of Basic Cardiovascular Science of the European Society of Cardiology recommended that the endothelial biomarker and function such as FMD test should be assessed for their usefulness of the risk stratification in patients with Coronavirus Disease 2019 (COVID-19) [40]. The author has previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19, cutaneous manifestation and vasculitis of COVID-19 in dermatology, and clinical manifestation of endotheliitis in COVID-19 along with flow-mediated vasodilation study [16-18]. Ergul et al. have reported that COVID-19 disease independently predicted endothelial dysfunction assessed by FMD study and may deteriorate existing CVD process [41]. NAFLD is a multisystem disease and is associated with hepatic and extrahepatic manifestations. Based on the evidence, the author suggests that the reports of the association between NAFLD and COVID-19 may increase because of the preexistence of endothelial dysfunction and systemic chronic inflammation and/or damaged RAS in patients with NAFLD.

Conclusion

The current knowledge of the link between NAFLD and hypertension along with new genetic expression has been reviewed in this article. It is putative that NAFLD is a multisystem disease and is associated with hepatic and extrahepatic disease.

Conflict of interest

Author declares that I have no conflicts of interest.

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