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Review Article

Association between Chronic Liver Disease and Atherosclerosis: An Inflammation as Common Pathway

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ABSTRACT

Atherosclerosis status as an inflammatory disease has been suggested and anti-inflammatory therapy with canakinumab for atherosclerotic disease has been recently reported. The author previously described the relationship between APRI (aspartate aminotransferase to platelet ratio index) and endothelial function assessed by Flow-Mediated Vasodilation (FMD), thereby suggesting that APRI may reflect systemic atherosclerosis condition in elderly patients without hepatic-related causes. Some reports of the relationship between NAFLD (Non Alcoholic Fatty Liver Disease)/NASH (Non alcoholic Steato Hepatitis)and atherosclerosis status and between chronic Hepatitis C Virus (HCV) infection and atherosclerotic state have been described. As both chronic liver disease and atherosclerosis involve severe inflammatory processes, at least common pathway may be present for the development and treatment of these inflammatory diseases. The current knowledge of the relationship between chronic liver diseases (NAFLD/NASH and HCV infection) and atherosclerosis and a novel therapeutic strategy is reviewed. Based on the several evidences, the author suggests that an association between chronic liver disease and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway. It is plausible that direct acting antivirus therapy is a potential strategy for not only liver disease but also endothelial dysfunction and atherosclerosis in patient with HCV infection. It has been suggested that momelotinib as a novel treatment may play a potential therapeutic benefit to a high-risk patients with NAFLD/NASH.

Keywords: Liver fibrosis; Atherosclerosis; NAFLD/NASH; Hepatitis C virus infection; Inflammation

INTRODUCTION

Atherosclerosis status as an inflammatory disease has been suggested [1]. Recently, it has been reported that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab leads to a significantly lower rate of recurrent cardiovascular events, independent of lipid-level lowering [2]. The author previously described the relationship between APRI (aspartate aminotransferase to platelet ratio index) and endothelial function assessed by Flow-Mediated Vasodilation (FMD), thereby suggesting that APRI may reflect systemic atherosclerosis condition in elderly patients without hepatic-related causes [3,4]. FMD and Nitroglycerin-Mediated Vasodilation (NMD) in the brachial artery is a potential tool for estimating vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis [5]. The author has reported some studies on the diseases of migraine, Cardiovascular Disease (CVD), Chronic Kidney Disease (CKD), dyslipidemia, and aging liver [3,4,6-12] using FMD and NMD test. Some reports of the relationship between NAFLD/NASH and atherosclerosis status has been described [13,14], while relationship between chronic Hepatitis C Virus (HCV) infection and atherosclerotic state have been also reported [15,16]. As both chronic liver disease and atherosclerosis involve severe inflammatory processes, at least common pathway may be present for the development and treatment of these inflammatory diseases. With respect to the therapeutic strategy, a new Direct Acting Antivirus (DAA)-treatment reverses infectious status and enhances endothelial function in patients with HCV infection [16], while momelotinib as a targeting of the signaling controls of PNPLA3 to reduce transcription, expression, and function has been discovered in patients with NAFLD/NASH [17]. In this article, the current knowledge of the relationship between chronic liver diseases (NAFLD/NASH and HCV infection) and atherosclerosis will be reviewed. The author also describes a novel therapeutic strategy for Chronic Liver Diseases (CLD).

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LIVER FIBROSIS

Liver Fibrosis (LF) is a manifestation of chronic liver injury leading to cirrhosis and Hepatocellular Carcinoma (HCC). Hepatic Fibrosis is the pathological basis of CLD. The genesis of liver fibrosis in the liver causes the accumulation of Extracellular Matrix (EXM) components [18,19]. LF is a key step in the development of various CLDs to cirrhosis and HCC [18,20]. Common diseases that cause liver fibrosis include chronic Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) infection, alcohol abuse, Nonalcoholic Steatohepatitis (NASH), and autoimmune liver disease, etc. It has been suggested that liver fibrosis is a reversible process, if it is not treated; it may lead to liver cirrhosis and HCC [18]. Zhangdi et al. [21] described that inflammation serves as a predominant role in liver fibrosis via communication and interaction between inflammatory cells, cytokines, and the related signaling pathways. It has been suggested that cross activation of HSCs, Kupffer cells, and other immune cells is a hallmark for the pathogenesis of liver fibrosis. In addition, cell signal pathway-related apoptosis, autophagy, collagen and inflammatory cytokine production are implicated in the development of liver fibrosis by crosstalk with immune cells. The activation of HSC serves as a main role in the development of liver fibrosis. Genetically, He et al. [22] have suggested that it is significant to analyze the changes in gene expression that accompany the HSC activation process. They have detected 146 upregulated and 18 downregulated genes in activated HSCs. These genes were suggested to be the key genes associated with HSC activation, leading to facilitate the progression of liver fibrosis in different liver diseases including HBV-, HCV-, and NAFLD- associated liver fibrosis. They detected that ARID5B, GATA6 [23], MITF, PBX1, PLAGL1, SOX4 [24] and SOX9 [25] were upregulated in activated HSCs as well as in liver fibrosis tissues.

CLD-RELATED ATHEROSCLEROSIS

Association between NAFLD/NASH and atherosclerosis

The report by Byrne et al. [26] described that NAFLD is not only attributed to liver-related morbidity and mortality, but there is growing evidence that NAFLD is a multisystem disease. It has been suggested that NAFLD increases risk of Type 2 Diabetes Mellitus (T2DM), CVD and cardiac diseases, and Chronic Kidney Disease (CKD) [9]. The liver pathology of NAFLD affects hepatic structure and function, leading to cause mortality and morbidity caused by cirrhosis, liver failure, and Hepatocellular Carcinoma (HCC). However, it has been suggested that the majority of deaths among patients with NAFLD contribute to CVD. Based on the increasing evidence, Byrne et al. described that the presence and severity of NAFLD is associated with an increased prevalence and incidence of CVD, independently of established CV risk factors [26]. They also suggested that NAFLD is associated with CKD, independently of cardio-renal risk factors on the basis of the some studies [26]. The major risk factors including age>50 years, obesity, insulin resistance, T2DM, increased ferritin levels, and patatin-like phospholipase domain-containing 3 (PNPLA3) I 148M polymorphism, for hepatic fat and fibrosis development in NAFLD have been established. Hepatic lipid accumulation (e.g., di-acyl glycerol) in NAFLD impairs insulin signaling (insulin resistance:RI). Francque et al. [27] also have described that NAFLD has to be regarded as a significant independent risk factor for subclinical and clinical CVD. They also mentioned that studies indicate CV mortality to be the most important cause of death in patients with NAFLD. Many evidences pointed out that NAFLD associates with endothelial dysfunction, increased Pulse Wave Velocity (PWV), increased coronary arterial calcifications, and increased Intima-Media Thickness (IMT) that are established CVD indicators [27]. It has been indicated that NAFLD is part of a complex multisystem disease with multiple bidirectional relationships. The several potential pathophysiological mechanisms that NAFLD may contribute to CVD have been suggested. Structural alterations, endothelial dysfunction, homocysteine and oxidative stress, altered lipid profiles, angiogenic factor, haemotosis inflammation and cytokines, hepatokines, adipokines, gut-liver connection, and genetic profiles have been considered as significant pathophysiologic mechanisms [27]. Persico et al. [28] have noted that IR-associated eNOS (endothelial nitric oxide synthase) dysfunction might represent a pathological linkage between NAFLD and CVD. They also described that eNOS dysfunction might be considered as an essential pathophysiological feature of the first hits of the chronic progressive process of NAFLD/NASH. Ozturk et al. have described that NAFLD itself may contribute to a risk of CVD and increased risk of CVD mortality, independent of classical CVD risk factors based on the evidences [13]. With respect to the underlying mechanisms linking NAFLD and atherosclerosis, recent researches indicate the associations with increased hepatic insulin resistance, dyslipidemia, oxidative stress, inflammation and decreased adiponectin concentrations. They concluded that NAFLD causes the increased risk of endothelial dysfunction and atherosclerosis in young adult men, independent of metabolic syndromes [13]. In a systematic review, Oni et al. [14] have reported that NAFLD is also associated with the severity of subclinical atherosclerosis, including increased carotid IMT, endothelial dysfunction, arterial stiffness, and coronary calcification. The regulation of the secretion of certain cytokines and molecules such as selenoprotein P, sex hormone-binding globulin, fibroblast growth factor 21, retinol –binding 4, and adropin have been regarded as the potential mechanisms [29].With regard to the reactive hyperemia peripheral artery tonometry (RH-PAT), according to the Long's report [30], the relationship with reduced PAT response assessed by digital vascular function suggests that NAFLD may contribute to microvascular dysfunction. Tuttolomondo et al. [31] mentioned the association between NAFLD and RH index assessed by PAT study reflecting atherosclerotic change at multivariate analysis. Recently, Chen et al. [32] have described that higher liver function scores such as APRI are associated with increased risk of all-cause and cardiovascular mortality among patients with CAD. Currently, Abdallah et al. [33] have reported that the growing proof of the association between NAFLD and subclinical CVD may suggest that NAFLD status is not only a marker but also may be involved in pathogenesis of CVD [34]. Santos et al. [34] described that specific therapy for NAFLD must be examined in an adequate trial to determine the potential evidence of reducing both liver disease and CVD and to clarify the link between NAFLD and atherosclerosis condition. Genetically, it has been reported that PNPLA3 I148M may be associated with a very small reduction in the risk of ischaemic heart diseases [35,36]. While, Unalp-Arida et al. [37] described that PNPLA3 I148M was associated with liver-related and all-cause mortality but not with CVD mortality in general population.

Association between HCV infection and atherosclerosis

Several studies of APRI have focused on patients with HCV, HCV/Human Immunodeficiency Virus (HIV) co-infection, alcoholic liver disease [38], and HBV [39]. Barone et al. [15] have indicated that an

inverse correlation between FMD study and liver elastography was recognized in patients with chronic HCV infection, suggesting that HCV advanced liver fibrosis promotes atherosclerosis by inducing endothelial dysfunction independently of common CV risk factors [15]. While, the studies indicated that chronic infections and chronic inflammatory autoimmune disease [15,40,41] also cause atherosclerosis due to systemic inflammation. Munoz-Hernandez et al. [42] noted that HCV promoted steatosis in the liver, leading to an upregulation of inflammatory biomarker that generate oxidative stress, insulin resistance and liver damage, and an accumulation of fatty acids deposits. In result, the thickening of the artery wall and athromatous plaques was represented. Tomiyama et al. [43] reported that hepatitis C virus seropositivity associated with increased pulse wave velocity. With respect to the therapeutic strategy, Schmidt et al. [16] described that new Direct Acting Antivirus (DAA) treatment reverses and enhances endothelial function in patients with HCV infection. Munoz-Hernandez et al. [42] suggested that hepatitis C virus clearance by DAA agents improves endothelial dysfunction and subclinical atherosclerosis. While, Butt et al. [44] mentioned that DAA therapy for HCV infection is associated with a reduced risk of CVD events. Given these evidences of endothelial dysfunction and treatment effects in patients with HCV infection, the author emphasizes that the hepatic virus infectious disease can contribute to not only liver damage but also systemic atherosclerosis condition.

NON-CLD-RELATED ATHEROSCLEROSIS

Association between aging liver and atherosclerosis

It has been demonstrated that in the cellular and molecular biology, aging is associated with chronic and low-grade inflammatory state characterized by increases in circulating acute phase proteins and pro-inflammatory cytokines [45]. In our previous study, the relationship between APRI and endothelial function were recognized, thereby indicating that APRI may reflect systemic atherosclerosis condition in elderly patients without hepatic-related causes. Because aging liver may be considered as one of the causal factors of liver fibrosis, the author suggested that systemic atherosclerosis condition and liver fibrosis may concomitantly occur at the higher APRI of Upper Limit of Normal (ULN). It might be useful to investigate the higher APRI for the early detection and prevention of clinical and/or subclinical diseases in elderly patients without hepatic-related causes as previously mentioned [3,4].

LIVER FIBROSIS IN GENERAL POPULATION

The current noninvasive estimation including biomarker and imaging have been developed in NAFLD/NASH [46] With respect to the biomarker for NASH, the procollagen of type III collagen (PIIINP), precursor C3-protein (PRO-C3), Hyaluronic Acid (HA), and TIMP1 are regarded as the proprietary biomarkers of fibrosis. The nonproprietary biomarkers of fibrosis or biomarker panels include APRI, NAFLD Fibrosis Score (NFS), and BARD score. Serum DNA methylation such as the plasma DNA methylation of PPARy promotor has been reported as a promising biomarker for estimating fibrosis. Though the gold standard for diagnosis and staging of liver fibrosis is liver biopsy, elastography including Vibration-Controlled Transient Elastography (VCTE), Magnetic Resonance Elastography (MRE), a new procedure, Shear Wave Elastography (SWE) was studied to distinguish NASH and simple steatosis. MRI technology was used to assess hepatic steatosis, iron accumulation and fibrosis by 1H-MRS. VCTE, SWE, and MRE procedures have been regarded as the useful tool for NASH-related fibrosis [46]. You et al. [47] have described that the prevalence of significant liver fibrosis using TE was 6.9% in healthy subjects, indicating that the prevalence of significant liver fibrosis was fairly high. BMI, ALT carotid IMT, and the number of calcified carotid plaques were independently associated with the presence of significant liver fibrosis. They suggested that the prognosis of CLD such as chronic viral hepatitis and NAFLD, depend on the severity of liver fibrosis, thereby suggesting that the accurate diagnosis of liver fibrosis is important to prevent progression of liver fibrosis to cirrhosis and HCC in patients with CLD at screening test. In the general population, Unalp-Arida et al. [48] have described that higher liver fibrosis scores including APRI were attributed to a higher risk for overall and CVD mortality. Koehler et al. [49] have mentioned that higher age, presence of DM and/or steatosis, higher ALT, greater spleen size, current or former smoking, and positive viral serology for hepatitis B and/or C are factors associated with clinically relevant fibrosis. They described that the suggestive of clinically relevant fibrosis representing liver stiffness measurement (LSM) ≥ 8.0 kPa, was present in 5.6% in a large population-based study of older adults. LSM ≥ 8.0 kPa was strongly associated with steatosis and DM. Elastic properties of the normal liver changes as a result of aging. Age-related changes show the increased liver stiffness, reduced collagenolytic activity. In addition, cellular senescence, increased mitochondorial damage and oxidative stress may reduce the capacity of the liver to regenerate.

THERAPEUTIC STRATEGY FOR CHRONIC LIVER DISEASE

Keane et al. [50] described that a growing body of evidence associates vitamin D with hepatic disease, while Rai et al. [51] also mentioned that Vitamin D deficiency may serve as a novel marker and predictor of severity of CVD. For lipogenesis stage, 1,25(OH) D acts on adipocytes and inhibits NF-κB transcription and inhibits the expression of the inflammatory cytokines IL-6, TNFα, and IL-1β. With respect to the inflammation stage, 1,25 (OH)D down regulates the expression of Toll-like receptor (TLR)-2, TLR-4, and TLR-9 in these cells, ameliorating inflammation status. Concerning fibrosis stage, 1,25(OH)D acts on hepatic stellate cells by binding to Vitamin D Receptor (VDR), leading to induce fibrosis state [52]. Recent studies have suggested that vitamin D levels are decreased in advanced fibrotic stages in patients with HCV infection [53]. Dadabhal et al. [54] suggested that low vitamin D level is common in patients with chronic hepatitis C and is associated with advanced liver fibrosis from a systematic review and meta-analysis of the pooled clinical trials data. While, Sabei et al. [52] concluded that vitamin D levels do not predict the stage of hepatic fibrosis in NAFLD from a PRISMA compliant systematic review and meta-analysis of pooled data.

Emerging data suggest that genetic susceptibility increases risks of NAFLD, NASH, and NASH-related cirrhosis [55]. Liver fat accumulation, inflammation and fibrosis are characteristic appearances of NASH. The pharmacological treatment has not been approved in patients with NASH and liver transplantation is the only available therapy for liver cirrhosis. Guideline recommendations involve reducing body weight, dietary restriction, and physical activity [56]. A few studies indicated the associations of PNPLA3 I 148M with reduced protective effects of statins on steatosis and NASH in clinical trials [57,58]. Carlsson et al. [55] described that very limited evidence indicates that PNPLA3 I148M may modulate the response to therapy in NASH patients. They

also mentioned that other genes such as HSD17B13 may provide targets for therapeutic strategy [55]. As NAFLD and NASH are emerging worldwide epidemic, the identification of novel targets and therapeutic modalities has been required. It has been suggested that the strongest genetic risk factor for NAFLD/NASH susceptibility and progression is a Single-Nucleotide Polymorphism (SNP) in the PNPLA3, rs738409, encoding the missense mutation I148M. NAFLD/NASH has been identified as a complex disease spectrum including the interaction of several cell types, signaling networks, and genetic profiles [17]. BasuRay et al. [59] mentioned that accumulation of PNPLA3 on lipid droplets is the basis of associated hepatic steatosis. It has been indicated that reducing PNPLA3 levels in individuals homozygous for 148M may be an effective therapy for the entire spectrum of NAFLD. PNPLA3 is expressed in Hepatic Stellate Cells (HSCs) in both humans and mice. Some studies indicated that the variant PNPLA3 148M has been shown to promote the production of pro-fibrogenic cytokines which stimulate HSC activation leading to promote inflammation and fibrosis in NAFLD/NASH [60-62]. HSCs serve as the secretion of collagen 1 during liver injury, as occurs in late stages of NASH. It has been demonstrated that the silencing of PNPLA3 in 148M knock-in mice with Antisense Oligos (ASOs) decreased the collagen of the liver [63]. It has been expected that reducing PNPLA3148M in HSC and hepatocyte provides a multi-faceted beneficial treatment in patients with NASH. Schwartz et al. [17] represent that momelotinib reduces the expression of the PNPLA3 gene through the inhibition of BMP signaling rather than the JAK/STAT pathway. They provided momelotinib as a potential treatment for NASH and revealed connections between signaling pathway and PNPLA3. They reveal new signal pathways that regulate PNPLA transcription and conclude that momelotinib serve as a potential therapeutic benefit to a high-risk patients with NAFLD/NASH. Concerning the treatment in patients with HCV infection, some studies have indicated DAA as a potential therapy in both liver disease and endothelial function. Finally, Ross R. [1] has previously described atherosclerosis status as an inflammatory disease. It has been reported that anti-inflammatory therapy targets the interleukin-1β innate immunity pathway with canakinumab lead to a significantly lower rate of recurrent cardiovascular events, independent of lipid-level lowering [2]. As NAFLD/NASH, HCV infection and atherosclerosis involve inflammatory elements, at least common pathway may be present. In future, the author highly expects a novel common treatment for chronic liver disease and atherosclerotic disease [63].

SUMMARY

As aging liver and systemic atherosclerosis concomitantly occurs, the author emphasizes that prevention and early detection of higher APRI of ULN may be significant in elderly subject without hepatic-related disease. The author suggests that chronic liver disease including NAFLD/NASH and HCV infection accompanied with severe activity and long period of the inflammatory status represents a systemic disease and an association between liver fibrosis and systemic atherosclerosis may be present. Several studies provided that NAFLD/NASH is independently associated with atherosclerosis, suggesting that inflammation of NAFLD/NASH itself may cause systemic atherosclerosis status. While, it has been also described that the relationship between chronic hepatitis C virus infection and atherosclerosis state, indicating that inflammation of virus infection itself affect atherosclerosis condition. With respect to the therapeutic strategy, a new DAA-treatment reverses infectious status and enhance endothelial function in patients with chronic hepatitis C, while momelotinib as a targeting of the signaling controls of PNPLA3 to reduce transcription, expression, and function has been discovered in patients with NAFLD/NASH.

CONCLUSION

Based on the several evidences, the author suggests that an association between chronic liver disease and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway. It is plausible that direct acting antivirus therapy is a potential strategy for not only liver disease but also endothelial dysfunction and atherosclerosis in patient with HCV infection. It has been suggested that momelotinib as a novel treatment may play a potential therapeutic benefit to a high-risk patients with NAFLD/NASH.

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CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

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