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NAFLD/NASH-Related Hepatocellular Carcinoma: Along with the Role of Genetics

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is attributed to liver-related morbidity and mortality, there is also growing evidence that NAFLD is a multisystem disease. NAFLD has to be considered as a significant independent risk factor for subclinical and clinical cardiovascular disease (CVD). The author previously suggested that an association between chronic liver disease (NAFLD/NASH and chronic hepatitis C virus infection: HCV infection) and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway. The growing incidence of NAFLD/ NASH has led to an increase of non-alcoholic steatohepatitis (NASH)-related hepatocellular carcinoma (HCC). Non-cirrhotic NAFLD-HCC has been also reported and the characteristic findings of a large cohort of HCC cases estimated the outcomes of patients with non-cirrhotic NAFLD-HCC were studied. In this article, the current knowledges of NAFLD/NASH- related HCC along with the genetics role have been reviewed. As NAFLD can develop HCC without NASH or cirrhosis, it is important to increase the effective screening and preventative strategies in patient with NAFLD/NASH. As PNPLA3 rs738409 C>G variant may be considered as an indicator of liver complication and/or death in patients with NAFLD, the further studies for PNPLA3 variant based on gene susceptibility will be needed especially in patient with non-cirrhotic NAFLD.

Keywords: NAFLD/NASH-related HCC; Non-cirrhosis NAFLD-HCC; Genetics; PNPLA3 variant; Atherosclerosis

Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; CVD: Cardiovascular Disease; NASH: Non-Alcoholic Steatohepatitis; HCC: Hepatocellular Carcinoma; FMD: Flow-Mediated Vasodilation; PWV: Pulse Wave Velocity; IMT: Intima-Media Thickness; NMD: Nitroglycerin-Mediated Vasodilation; CKD: Chronic Kidney Disease; TE: Transient Elastography; CLD: Chronic Liver Disease; DM: Diabetes Mellitus; LSM: Liver Stiffness Measurement; APRI: Aspartate Aminotransferase to Platelet Ratio Index; TM6SF2: Transmembrane 6 Superfamily Member 2; MBOAT7: Membrane Bound O-Acyltransferase Domain-Containing 7; GWAS: Genome-Wide Association Studies.

Introduction

NAFLD is attributed to liver-related morbidity and mortality, there is also growing evidence that NAFLD is a multisystem disease [1]. The report suggested that NAFLD has to be considered as a significant independent risk factor for subclinical and clinical CVD [2]. The author previously suggested that an association between chronic liver disease (NAFLD/NASH and HCV infection) and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway [3]. As the prognosis of NAFLD depend on the severity of liver fibrosis, the

accurate diagnosis of liver fibrosis is important to prevent progression of liver fibrosis to cirrhosis and HCC at screening test in the general population [4]. The growing incidence of NAFLD/ NASH has led to an increase of NASH-related HCC [5]. Bengtsson et al. [6] characterized a large cohort of HCC cases estimated the outcomes of patients with non-cirrhotic NAFLD-HCC. They mentioned that patients with non-cirrhotic NAFLD-HCC differ from those with cirrhosis in age, tumor size, and allocated treatments. Current studies indicated that genetic susceptibility increases risks of NAFLD, NASH, and NASH-related cirrhosis [7]. The pharmacological therapeutic have not been approved in patients with NASH and liver transplantation is the only available therapy for liver cirrhosis. The raised overall and liver-specific mortality and increased risks of cirrhosis, liver failure and HCC were represented in patients with NASH. Genetic variations in five genes including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 have emerged as reproducibly and robustly predisposing individuals to development of NASH [8]. It has been reported the relationship between PNPLA3 rs738409 C>G variant and liver-related outcomes [9]. In this article, the author will review the current knowledges of NAFLD/NASH-related HCC along with the genetics role.

NAFLD/NASH-Related Atherosclerosis

Byrne et al. [1] described that NAFLD is attributed to liver-related morbidity and mortality, there is also growing evidence that NAFLD is a multisystem disease. The liver pathology of NAFLD affects hepatic structure and function and cause mortality and morbidity due to the cirrhosis, liver failure, and HCC. Mechanisms contributing to the pathogenesis of HCC also occur with obesity and insulin resistance. The report by Francque et al. [2] have suggested that NAFLD has to be considered as a significant independent risk factor for subclinical and clinical CVD. Many evidences indicated that NAFLD associates with endothelial dysfunction assessed by flow-mediated vasodilation (FMD) study, increased pulse wave velocity (PWV), increased coronary arterial calcifications, and increased intima-media thickness (IMT) by evaluated common carotid artery that are established CVD indicators [2]. It has been indicated that NAFLD is part of a complex multisystem disease with multiple bidirectional relationships [2]. The author previously suggested that an association between chronic liver disease and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway [3]. Flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) tests in the brachial artery is a potent procedure for assessing vascular endothelial and vascular smooth muscle cell (VSMC) function in atherosclerosis [10]. The author has described some reports on the diseases of migraine, CVD, chronic kidney disease (CKD), dyslipidemia, and aging liver [11-19] using FMD and NMD examinations.

Studies of Liver Fibrosis in General Population

The study by You et al. [4] have indicated that the prevalence of significant liver fibrosis using transient elastography (TE) was 6.9% in healthy subjects, suggesting that the prevalence of significant liver fibrosis was fairly high. They mentioned that BMI, ALT level, carotid IMT, and the number of calcified carotid plaques were independently associated with the presence of significant liver fibrosis [4]. As the prognosis of chronic liver disease (CLD) such as HCV infection and NAFLD, depends on the severity of liver fibrosis, the accurate diagnosis of liver fibrosis is important to prevent progression of liver fibrosis to cirrhosis and HCC at screening test in the general population [4]. The report by Koehler et al. [20] has indicated that higher age, presence of diabetes mellitus (DM) and/or steatosis, higher ALT level, greater spleen size, current or former smoking, and positive viral serology for hepatitis B and/or C are factors associated with clinically relevant fibrosis in a general population from the Rotterdam Study. They described that the suggestive of clinically relevant fibrosis representing liver stiffness measurement (LSM) ≥8.0 kPa on TE, was present in 5.6% in a large population-based study of older adults. Well, concerning the aging liver, our previous study indicated that the relation between aspartate aminotransferase to platelet ratio index (APRI) and endothelial function assessed by FMD study were recognized, thereby indicating that APRI may reflect systemic atherosclerosis condition in elderly patients without hepatic-related causes. The result indicated that aging liver and systemic atherosclerosis may concomitantly occur [18,19]. The author also suggested that 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 [18,19].

NAFLD/NASH-Related HCC

The growing incidence of NAFLD/NASH has led to an increase of NASH-related HCC [5]. Several reports have identified that NASH can lead to advanced fibrosis and cirrhosis. In result, the risk of HCC developments have raised [21]. The report by White et al. showed that the cumulative annual incidence rate for the occurrence of HCC in patients with NASH-related cirrhosis is approximately 2.4%-12.8% [22]. It has been suggested that HCC development has been also identified in patients with NAFLD without NASH or cirrhosis. These patients usually less likely to diagnose by surveillance compared to HCC with viral hepatitis [23]. A similar increasing tendency has been reported in HCC without cirrhotic NAFLD/NASH [24]. Bengtsson et al. [6]

reported that patients with non-cirrhotic NAFLD-HCC were observed in 37% of NAFLD-HCC. They mentioned that patients with non-cirrhotic NAFLD-HCC, compared with patients with cirrhotic NAFLD-HCC, were older, a lower prevalence of type 2 diabetes mellitus, larger tumors, and allocated treatments [6]. With respect to the therapeutic, it has been reported that NASH-related HCC is the growing indication for liver transplantation. Cholankeril et al. [5] indicated that increased efforts of effective screening and preventative strategies especially in patient with non-cirrhotic NASH based on genetic susceptibility are needed to decrease the occurrence of NASH-related HCC [5].

Emerging Role of Genetic in NAFLD/NASH

Current studies indicated that genetic susceptibility increases risks of NAFLD, NASH, and NASH-related cirrhosis [7]. Appearances of NASH are characterized by the liver fat accumulation, inflammation and fibrosis. The pharmacological therapeutic have not been approved in patients with NASH and liver transplantation is the only available therapy for liver cirrhosis. Increased overall and liver-specific mortality and raised risks of cirrhosis, liver failure and HCC were represented in patients with NASH [25,26]. Genetic variations in five genes including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 have emerged as reproducibly and robustly predisposing individuals to development of NASH [8]. It has been reported that these five genes known to be associated with NASH are involved in glucose and fat hemeostasis regulatory pathway. With respect to PNPLA3, a nonsynonymous SNP in PNPLA3 known as rs738409 c.444 C> G p.I148M is the first genetic variant found to be associated with NASH [7]. It is suggested that PNPLA3 I148M has allelic odds ratios of approximately two or three for risks of NAFLD, NASH, and HCC [9].Inactivating variants in the HSD17B13 gene have recently been liked with a reduced risk of chronic liver disease [27,28,29]. The studies demonstrated that the associations between the variant and reduced odds of HCC have been reported [30,31]. A SNP in TM6SF2 (transmembrane 6 superfamily member 2) is associated with increased liver fat content, NASH, advanced hepatic fibrosis and cirrhosis [32]. It has been reported that GCKR P446L is a loss-of-function variant. This valiant is associated with increased susceptibility to NAFLD, NASH, and NASH-derived HCC [33]. It has been reported that a SNP downstream of the gene encoding membrane bound O-acyltransferase domain-containing 7 (MBOAT7) may predispose to HCC [34]. Carlsson et al. [7] described that very limited evidence indicates that PNPLA3 I148M may modulate the response to therapy. They also mentioned that HSD17B13 may provide targets for treatment strategy in patients with NASH [7]. While, Schwartz et al. [35] suggested that the identification of novel targets and therapeutic modalities have been required for the emerging worldwide epidemic of NAFLD and NASH. They discovered that momelotinib reduces the expression of the PNPLA3 gene through the inhibition of BMP signaling rather than the JAK/STAT pathway. They reveal new signal pathways that regulate PNPLA3 transcription and conclude that momelotinib serve as a potential therapeutic benefit to a high-risk patients with NAFLD/NASH.

Relationship between PNPLA3 Rs738409 C>G Variant and Liver-Related Outcomes

A few studies including retrospective cohort studies and a meta-analysis report have identified that the severity of histological liver fibrosis is the strongest indicator not only of liver-related complications but also of death caused by extrahepatic diseases [36,37]. There is growing evidence that genetic factor can affect the severity of NAFLD. It has been demonstrated that the rs738409 C>G variant in PNPLA3 gene has been demonstrated by genome-wide association studies (GWAS) as an independent genetic risk factor in patients with NAFLD [38]. The variant has been associated with the severity of liver damage as well as with the presence of HCC [39,40]. Grimaudo et al. [9] suggested that patients with NAFLD carrying PNPLA3 rs738409 C>G variant are at higher risk of decompensation, liver cancer, and death. They mentioned that genotype analysis might be considered to identify the greatest risk for liver complications or death in patients with NAFLD.

Summary

It has been described that non-cirrhotic HCC can occur in patient with NAFLD, it is significant to increase the effective screening and preventative strategies in patient with NAFLD/NASH. It may be putative that the association between PNPLA3 rs738409 C>G variant and liver related outcomes including liver complications and death was identified. As PNPLA3 rs738409 C>G variant may be considered as an indicator of liver complication such as decompensation and liver cancer, and/or death in patients with NAFLD, the further studies for PNPLA3 variant based on gene susceptibility will be needed especially in patient with non-cirrhotic NAFLD.

Conclusion

- Non-cirrhotic HCC can occur in patient with NAFLD, therefore it is important to increase the effective screening and preventative strategies in patient with NAFLD/NASH.
- As PNPLA3 rs738409 C>G variant may be considered as an indicator of liver complication such as decompensation and liver cancer, and/or death in patients with NAFLD, the further studies for PNPLA3 variant will be needed particularly in patient with non-cirrhotic NAFLD.

Conflict of Interest

Author declares that I have no conflicts of interest.

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