pISSN 2287-2728
eISSN 2287-285X

CMH

https://doi.org/10.3350/cmh.2018.0101
Clinical and Molecular Hepatology 2019;25:40-41

Editorial

Can hepatic steatosis really promote hepatitis B viral hepatocarcinogenesis? The jury is out on.

Won Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

Keywords: Fatty liver; Hepatitis B virus; Insulin resistance; Liver cancer; Metabolic syndrome

See Article on Page 52

There is accumulating evidence that metabolic risk factors such as high body mass index, insulin resistance, and concurrent fatty liver can boost the risk of hepatocelluar carcinoma (HCC) in patients infected with hepatitis B virus (HBV).[1-3] The exact mechanism by which hepatic steatosis can promote HBV-related hepatocarcinogenesis is still unknown; however, fatty liver represents a proinflammatory state and a condition of profound insulin resistance. Thus, insulin and insulin-like growth factors may partly promote the development of HCC through their proliferative and anti-apoptotic effects.[4]

HBV is not likely steatogenic unlike hepatitis C virus; rather, HBV infection seems to decrease the risk of nonalcoholic fatty liver disease (NAFLD) according to recent epidemiological studies.[5,6] In a similar manner, hepatic steatosis seems to affect HBV replication adversely with a higher chance of HBV seroclearance in an immunocompetent mouse model of HBV replication, although HBV X protein (HBx) is shown to favor lipid accumulation in cell culture systems.[7,8] Eventually, the humanized mouse model of HBV would be required to solve the HBV-steatosis conundrum.

It has been suggested that hepatic steatosis can result in either cytoplasmic hepatitis B surface antigen distribution or hepatocellular death, thereby leading to HBV seroclearance.[9] It is already well established that steatosis is related to alterations in gut microbiota, dysbiosis, and hepatic inflammation. Gut microbiota can also activate innate immunity leading to HBV seroclearance.[10] Thus, gut dysbiosis caused by hepatic steatosis may play a role in viral clearance, which still needs to be validated. Paradoxically, hepatic steatosis limits the replication of HBV, while steatosis offers contributory environment for pathogenic liver conditions that can culminate in HCC.

In the current issue, the authors demonstrated that histologically confirmed NAFLD significantly increased the risk of HCC development in patients with chronic hepatitis B, although propensity score matching showed no significant association between fatty liver and HCC development.[11] Based on these results, they finally concluded that NAFLD as a hepatic manifestation of metabolic syndrome but not hepatic steatosis per se, may be a harbinger of

Abbreviations:

HBV, hepatitis B virus; HBx, hepatitis B virus X protein; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease

Corresponding author : Won Kim
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea
Tel: +82-2-870-2233, Fax: +82-2-831-2826
E-mail: drwon1@snu.ac.kr
https://orcid.org/0000-0002-2926-1007

Received : Nov. 28, 2018 / **Accepted :** Dec. 5, 2018

HCC that portends worse clinical outcomes in patients with HBV infection. Nonetheless, several points merit further scrutiny.

First, due to the retrospective design, it was unclear whether HBV-related hepatocarcinogenesis predated hepatic steatosis or hepatic steatosis increased the risk of HCC in patients with HBV infection. Indeed, HBx-induced lipogenesis is mediated by liver X receptor during HBV-related hepatocarcinogenesis.[12] Second, we are not sure of what is the main culprit of HBV-related hepatocarcinogenesis, since insulin resistance might confound or mediate the effect of hepatic steatosis on hepatocarcinogenesis. Finally, it might be overlooked that nonalcoholic steatohepatitis or severe fibrosis could precipitate de novo oncogenesis from HBV infection, since they did not provide detailed information on the histological severity of NAFLD. In future, further research regarding the effect of HBV-steatosis concurrence on the minichromosome (covalently closed circular DNA) formation is strongly warranted to reveal the molecular pathways of steatosis-induced, HBV-related hepatocarcinogenesis.

Conflicts of Interest

The author have no conflicts to disclose.

REFERENCES

1. Kim K, Choi S, Park SM. Association of high body mass index and hepatocellular carcinoma in patients with chronic hepatitis B virus infection: a Korean population-based cohort study. JAMA Oncol 2018;4:737-739.
2. Kim JH, Sinn DH, Gwak GY, Kang W, Paik YH, Choi MS, et al. Insulin resistance and the risk of hepatocellular carcinoma in chronic hepatitis B patients. J Gastroenterol Hepatol 2017;32:1100-1106.
3. Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017;32:667-676.
4. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002;94:972-980.
5. Joo EJ, Chang Y, Yeom JS, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. Hepatology 2017;65:828-835.
6. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 2011;26:1361-1367.
7. Hu D, Wang H, Wang H, Wang Y, Wan X, Yan W, et al. Non-alcoholic hepatic steatosis attenuates hepatitis B virus replication in an HBV-immunocompetent mouse model. Hepatol Int 2018;12:438-446.
8. Kim KH, Shin HJ, Kim K, Choi HM, Rhee SH, Moon HB, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology 2007;132:1955-1967.
9. Zhang Z, Pan Q, Duan XY, Liu Q, Mo GY, Rao GR, et al. Fatty liver reduces hepatitis B virus replication in a genotype B hepatitis B virus transgenic mice model. J Gastroenterol Hepatol 2012;27:1858-1864.
10. Chou HH, Chien WH, Wu LL, Cheng CH, Chung CH, Horng JH, et al. Age-related immune clearance of hepatitis B virus infection requires the establishment of gut microbiota. Proc Natl Acad Sci U S A 2015;112:2175-2180.
11. Lee YB, Ha YJ, Chon YE, Kim MN, Lee JH, Park HN, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019;25:52-64.
12. Na TY, Shin YK, Roh KJ, Kang SA, Hong I, Oh SJ, et al. Liver X receptor mediates hepatitis B virus X protein-induced lipogenesis in hepatitis B virus-associated hepatocellular carcinoma. Hepatology 2009;49:1122-1131.