Hepatitis B and concomitant hepatic steatosis

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Contributions: (I) Conception and design: R Kumar; (II) Administrative support: All authors; (III) Data analysis and interpretation: All authors; (IV) Manuscript writing: All authors; (V) Final approval of manuscript: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Hepatic steatosis is becoming more common in Asia with prevalence becoming as common as Western countries. Concomitant Hepatitis B and hepatic steatosis is increasingly encountered in clinical practice. The interaction between the two concomitant conditions at both molecular level and clinical outcome remains to be explored. The present review is aimed at summarizing the existing literature on the complex interaction of the two-concomitant disease.

Keywords: Hepatitis B; fatty liver; hepatic steatosis; NASH; steatohepatitis

Submitted Sep 05, 2016. Accepted for publication Oct 01, 2016.
doi: 10.21037/atm.2016.12.04
View this article at: http://dx.doi.org/10.21037/atm.2016.12.04

Introduction

Hepatitis B is estimated to have chronically infected 240 million people worldwide and is prevalent in the world affecting up to 10% in African countries (1). Hepatic steatosis is defined as fat deposition in the liver that exceeds 5% of the gross total weight of the liver or more than 5% of hepatic cells containing fat deposits based on microscopic examination (2) while in the common clinical practice physicians determine Hepatic steatosis based on ultrasound. Hepatic steatosis is a common histological feature of chronic hepatitis C and the association has been well described (3). The studies for hepatic steatosis and chronic hepatitis B are limited.

Prevalence

The prevalence of hepatic steatosis in HBV infected patients greatly varies from multiple studies around the world. In a meta-analysis done by Machado *et al*. (4). which included 17 studies worldwide showed that the overall prevalence of hepatic steatosis in HBV infected patients was 29.6%. However, consideration was made to exclude studies which included excessive alcohol consumption and prevalence was lower at 25.6%. Western countries do not seem to have higher prevalence of steatosis compare to Asian countries (5-9).

Molecular mechanisms

The molecular mechanism of hepatic steatosis induced by HBV infection has remained elusive.

Kang *et al*. (10) suggested that hepatic lipid accumulation may be due to the inhibition of secretion of apolipoprotein B by HBV X protein (HBx). Subsequently, another study by Kim *et al*. (11) showed that increased HBx expression mediated by sterol regulatory element binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor γ (PPAR γ) also increases hepatic lipid accumulation. In that study, they also observed frequent hepatic inflammation in HBx transgenic mice.

Wu *et al*. (12) in their study of expression of liver Fatty Acid Binding Protein 1 (FABP1) showed that HBx protein does indeed upregulate FABP1 production. The mechanism of this upregulation is via the interaction of HBx protein with liver-enriched transcription factors (HNF3β and

C/EBPα) and a lipid-sensor nuclear factor (PPARα) which in turn activates FABP1 promoter. Over expression of FABP1 is known to increase the rate of fatty acid uptake (13). Both Hensley *et al*. (14) and Oliveira *et al*. (15) showed that accumulation of lipids in rat liver increases oxidative stress in the hepatocytes. The presence of HBx protein is shown by Ren *et al*. (16) to increase oxidative stress and DNA damage on hepatocytes. Although still being studied in depth, the pathological course of Chronic Hepatitis B infection is likely contributed by the overall increase in oxidative stress by means of direct HBx protein and via the accumulation of lipids in hepatocytes.

Hepatitis B status and hepatic steatosis

Although the pathogenesis of hepatic steatosis caused by Hepatitis B infection can be explained on the molecular level, the association between Hepatitis B virus and hepatic steatosis is poor and remains controversial. The meta-analysis performed by Machado *et al*. (4) on 21 studies comprising of 4100 HBV infected patients showed no positive associations of HBV infection and hepatic steatosis. Moreover, seven studies from the meta analysis found strong negative effect of viral load on hepatic steatosis. In a more recent study by Enomoto *et al*. (17), they found a low frequency histological hepatic steatosis in patients with a high HBV-DNA level and concluded that there is unlikely an association between HBV infection and hepatic steatosis. In another large scale study in Taiwan by Cheng *et al*. (18) which recruited a total of 33,439 subjects, they showed an inverse relationship between prevalence of fatty liver and positive HBsAg status in subjects older than 50 years and no significant association between HBV infection and fatty liver in subjects younger than 50 years. Although fatty liver was diagnosed via ultrasound and no liver biopsy was performed, the overwhelming statistics on these recent study showed that association between HBV infection and hepatic steatosis is not as strong as what previously thought.

This odd association may be partly due to the relationship of serum Adiponectin with HBV infection as mentioned by Wong *et al*. (19). Their prospective cohort of 266 chronic hepatitis B patients showed that there is a positive correlation between HBV infection and serum Adiponectin. Adiponectin is known to suppress fatty acid synthesis in the liver and also opposes synthesis and release of TNF-α in adipose tissue (20). However, more data would be needed for confirmation between the association of HBV infection and Adiponectin and the lack of direct correlation between HBV infection and hepatic steatosis.

HBV seroconversion and hepatic steatosis

Hepatic steatosis is also noted to have a role in seroclearance of Hepatitis B surface Antigen (HBsAg) in chronic HBV infection by Chu *et al*. (21). In a study of 155 patients, they found an increased chance of HBsAg clearance compared to the patients without a fatty liver on ultrasound.

The proposed mechanism by the authors were either that of hepatic steatosis causing an alteration of HBsAg cytoplasmic distribution which leads to seroclearance or steatosis-induced apoptosis hepatocytes leading to loss of HBsAg. An increased in FAS receptors on the surface of hepatocytes with hepatic steatosis could explain the apoptosis of the cells (22) and this in turn could result in viral clearance in patient with hepatic steatosis. However, given that no histo-immunological study were performed on the selected patients, it is unlikely a conclusion of how the seroclearance of HBsAg occurred in hepatic steatosis can be obtained.

Their study is not without any limitations. Firstly, fatty liver is diagnosed via ultrasound and hepatic steatosis is only considered present only if moderate to severe hepatic steatosis is seen via ultrasound. Presence of mild hepatic steatosis is considered under 'no hepatic steatosis'. Secondly, no multivariate analysis was done to determine if hepatic steatosis is an independent factor for seroclearance or just a co-factor of other more important attributes.

Wang *et al*. (23) performed a study on 3,212 patients with Hepatitis B infection and found that patients with hepatic steatosis which amount to 17.3% had statistically significant decreased intrahepatic HBsAg and HBcAg staining. Although these may not translate to seroclearance of HBsAg in the serum, that study does show that further study on this subject is warranted to conclude this association.

Hepatic steatosis, hepatitis B and virologic response to treatment

The data on implication of hepatic steatosis on antiviral therapy for chronic hepatitis B has been conflicting.

Cindoruk *et al*. (24) retrospectively analysed 142 Turkish patients who underwent pegylated interferon alfa-2a (with or without addition of Lamivudine) found no difference in sustained virologic response between individuals with or without hepatic steatosis. Ateş *et al*. (25) also found no statistically significant difference in virologic response for

patients receiving Interferon. Although, it should be pointed out that their study observed a higher sustained virologic response in the non Hepatic Steatosis group. Another more recent study performed in Turkey by Ceylan *et al*. (26), they found that although serum HBV DNA levels were found to be lower in patients with hepatic steatosis, the presence of hepatic steatosis has no effect on virologic response to either tenofovir or entecavir at 6 or 12 months. Interestingly, they also found that the presence of steatohepatitis may predict a favourable response in the tenofovir arm at 6 months. But given that their study was not designed to investigate patients with steatohepatitis and that they had a limited number of patients with steatohepatitis, it is difficult to draw a convincing association from it.

On the contrary, Jin *et al*. (27) in a prospective study of 267 Chinese patients with Chronic Hepatitis B infection and started on entecavir treatment, found that Hepatic Steatosis is a significant independent factor associated with Entecavir treatment failure. The authors measured virologic response at week 24th, 48th and 96th and confirmed that Hepatic Steatosis is a risk for treatment failure in a multivariate analysis. They attributed this findings to the decreased bioavailability of Entecavir in hepatocytes due to lipid accumulation and reduced activity of cytochromes in Hepatic Steatosis on drug metabolism. The major shortcoming of this study is that liver biopsy was not performed to evaluate for Hepatic Steatosis and the relatively high exclusion rate for the study (54 out of 267 patients enrolled) means a reduced external validity of the data presented.

The conclusion we could gather from the presence of the current data suggests that there is unlikely any significant difference in efficacy between oral medications or interferon in patients with Hepatic Steatosis.

Hepatic steatosis, hepatitis B and liver necroinflammation/fibrosis

Although molecularly possible to explain the pathogenesis of how Hepatitis B leads to lipid accumulation and the possibility of steatohepatitis, data currently available does not suggest the positive association as expected. Peng *et al*. (28) assessed a total of 153 adult with Chronic Hepatitis B infection with liver biopsy performed and found no significant correlation between stage of liver fibrosis and severity of hepatic steatosis. On a large scale study by Shi *et al*. (5) which involves 1,915 patients with Chronic Hepatitis B infection who has undergone liver biopsy, they found in a multivariate analysis that inflammatory grade in these patients was associated significantly only with viral factor and fibrosis stage, while the fibrosis stage was significantly associated with age and inflammatory grade.

Hepatitis B and TM6SF2 variant

A recent look into the gene of Transmembrane 6 Superfamily Member 2 (TM6SF2) rs58542926 variant could provide some answers needed to the issues surrounding Chronic Hepatitis B and Hepatic Steatosis. Although TM6SF2 is a gene of unknown function in chromosome 19, it was shown by Kozlitina *et al*. (29) that a non-synonymous single-nucleotide polymorphism (SNP) where a substitution of adenine for guanine encoding the nucleotide 499 leads to an increased in hepatic triglyceride content and a decrease in plasma levels of triglyceride and low density lipoprotein-cholesterol. The detection of this variant gene led to more studies on the relation of it with viral hepatitis.

A recent study by Eslam *et al*. (30) with the help of the International Liver Disease Genetics Consortium database on 507 Chronic Hepatitis B Chinese patients found that the presence of rs58542926 T allele was associated with presence of steatosis in patients with CHB. However, there was no association seen between the grade of severity of steatosis and the allele. Interestingly, this variant is associated with presence of higher HBV DNA. The authors postulated that promotion of hepatic steatosis by this gene variant may lead to HBV replication because of the role of HBx protein plays in lipid accumulation thus, signifying the importance of lipid synthesis and accumulation in the pathways of HBV infection. Although all the CHB patients studied were of Chinese origin, there is no difference in the minor allele frequency (MAF) of this variant as both the Chinese and the Caucasian ancestry documents a MAF of 0.07 (31). A study on the relationship between HBx protein and TM6SF2 rs58542926 variant, however, is lacking currently. It is important to note that the authors also did not find any significant association between the rs58542926 variant with fibrosis stage or cirrhosis.

Hepatocellular carcinoma and concomitant hepatitis B and hepatic steatosis

A Recent study from Hong Kong by Chan *et al*. (32) demonstrates increased risk of developing hepatocellular carcinoma (HCC) among patients with Chronic Hepatitis B and concomitant Hepatic Steatosis. They found in their

study of 270 HBV infected patients that there is a hazard ratio of 7.27 in developing hepatocellular carcinoma if they have liver biopsy proven hepatic steatosis as well. In their study, they also found an increased risk of HCC development if patient have APOC3 gene polymorphism. However more data is required in assessing increased risk of developing hepatocellular carcinoma.

Conclusions

The association of hepatic steatosis and chronic hepatitis B infection is still under study and possible pathogenesis of Hepatitis B virus causing steatosis is being explored molecularly. Although seroclearance of hepatitis B is observed in patients with hepatic steatosis, there is a gap of knowledge of how this happen. The outcome of treatment with oral antiviral or interferon does not seem to be affected by the presence of hepatic steatosis. However, viral factors seems to be the factor which is affecting liver necroinflammation and fibrosis rather than hepatic steatosis per se. The recent findings of TM6SF2 rs58542926 variant and the association with hepatitis B virus means there is much more to study especially the relationship between the HBx protein and this variant.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ott JJ, Stevens GA, Groeger J, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212-9.
2. Schiff E, Sorell M, Maddrey W. Diseases of the Liver. 11th ed. Philadelphia: Lippincott-Williams and Wilkins; 2012. Available online: http://www.wiley.com/WileyCDA/WileyTitle/productCd-0470654686.html
3. Lonardo A, Adinolfi LE, Loria P, et al. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. Gastroenterology 2004;126:586-97.
4. 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;26:1361-7.
5. Shi JP, Fan JG, Wu R, et al. Prevalence and risk factors of hepatic steatosis and its impact on liver injury in Chinese patients with chronic hepatitis B infection. J Gastroenterol Hepatol 2008;23:1419-25.
6. Poortahmasebi V, Alavian SM, Keyvani H, et al. Hepatic steatosis: prevalence and host/viral risk factors in Iranian patients with chronic hepatitis B infection. Asian Pac J Cancer Prev 2014;15:3879-84.
7. Lesmana LA, Lesmana CR, Pakasi LS, et al. Prevalence of hepatic steatosis in chronic hepatitis B patients and its association with disease severity. Acta Med Indones 2012;44:35-9.
8. Thomopoulos KC, Arvaniti V, Tsamantas AC, et al. Prevalence of liver steatosis in patients with chronic hepatitis B: a study of associated factors and of relationship with fibrosis. Eur J Gastroenterol Hepatol 2006;18:233-7.
9. Petta S, Cammà C, Di Marco V, et al. Hepatic steatosis and insulin resistance are associated with severe fibrosis in patients with chronic hepatitis caused by HBV or HCV infection. Liver Int 2011;31:507-15.
10. Kang SK, Chung TW, Lee JY, et al. The hepatitis B virus X protein inhibits secretion of apolipoprotein B by enhancing the expression of N-acetylglucosaminyltransferase III. J Biol Chem 2004;279:28106-12.
11. Kim KH, Shin HJ, Kim K, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology 2007;132:1955-67.
12. Wu YL, Peng XE, Zhu YB, et al. Hepatitis B Virus X Protein Induces Hepatic Steatosis by Enhancing the Expression of Liver Fatty Acid Binding Protein. J Virol 2015;90:1729-40.
13. Wolfrum C, Buhlmann C, Rolf B, et al. Variation of liver-type fatty acid binding protein content in the human hepatoma cell line HepG2 by peroxisome proliferators and antisense RNA affects the rate of fatty acid uptake. Biochim Biophys Acta 1999;1437:194-201.
14. Hensley K, Kotake Y, Sang H, et al. Dietary choline restriction causes complex I dysfunction and increased H(2)O(2) generation in liver mitochondria. Carcinogenesis 2000;21:983-9.
15. Oliveira CP, da Costa Gayotto LC, et al. Oxidative stress in the pathogenesis of nonalcoholic fatty liver disease, in rats fed with a choline-deficient diet. J Cell Mol Med 2002;6:399-406.

16. Ren JH, Chen X, Zhou L, et al. Protective Role of Sirtuin3 (SIRT3) in Oxidative Stress Mediated by Hepatitis B Virus X Protein Expression. PLoS One 2016;11:e0150961.
17. Enomoto H, Aizawa N, Nishikawa H, et al. Relationship Between Hepatic Steatosis and the Elevation of Aminotransferases in HBV-Infected Patients With HBe-Antigen Negativity and a Low Viral Load. Medicine (Baltimore) 2016;95:e3565.
18. Cheng YL, Wang YJ, Kao WY, et al. Inverse association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. PLoS One 2013;8:e72049.
19. Wong VW, Wong GL, Yu J, et al. Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Am J Gastroenterol 2010;105:132-8.
20. Masaki T, Chiba S, Tatsukawa H, et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. Hepatology 2004;40:177-84.
21. Chu CM, Lin DY, Liaw YF. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci 2013;58:275-81.
22. Feldstein AE, Canbay A, Angulo P, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology 2003;125:437-43.
23. Wang MM, Wang GS, Shen F, et al. Hepatic steatosis is highly prevalent in hepatitis B patients and negatively associated with virological factors. Dig Dis Sci 2014;59:2571-9.
24. Cindoruk M, Karakan T, Unal S. Hepatic steatosis has no impact on the outcome of treatment in patients with chronic hepatitis B infection. J Clin Gastroenterol 2007;41:513-7.
25. Ateş F, Yalnız M, Alan S. Impact of liver steatosis on response to pegylated interferon therapy in patients with chronic hepatitis B. World J Gastroenterol 2011;17:4517-22.
26. Ceylan B, Arslan F, Batırel A, et al. Impact of fatty liver on hepatitis B virus replication and virologic response to tenofovir and entecavir. Turk J Gastroenterol 2016;27:42-6.
27. Jin X, Chen YP, Yang YD, et al. Association between hepatic steatosis and entecavir treatment failure in Chinese patients with chronic hepatitis B. PLoS One 2012;7:e34198.
28. Peng D, Han Y, Ding H, et al. Hepatic steatosis in chronic hepatitis B patients is associated with metabolic factors more than viral factors. J Gastroenterol Hepatol 2008;23:1082-8.
29. Kozlitina J, Smagris E, Stender S, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014;46:352-6.
30. Eslam M, Mangia A, Berg T, et al. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. Hepatology 2016;64:34-46.
31. Wong VW, Wong GL, Tse CH, et al. Prevalence of the TM6SF2 variant and non-alcoholic fatty liver disease in Chinese. J Hepatol 2014;61:708-9.
32. Chan AW, Wong GL, Chan HY, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2016. [Epub ahead of print].

Cite this article as: Lim CT, Kumar R. Hepatitis B and concomitant hepatic steatosis. Ann Transl Med 2017;5(3):38. doi: 10.21037/atm.2016.12.04

