Original Article

Effect modification of hepatitis B viral load on the association between metabolic risk factors and hepatic steatosis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: MY Shi, TP Lee; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: MY Shi, TP Lee; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: It is not clear if chronic hepatitis B (CHB) infection potentiates the severity of hepatic steatosis (HS) in patients with metabolic risk factors. We tested for the effect modification of hepatitis B viral load on the association between metabolic risk factors and HS.

Methods: In this retrospective cross-sectional study, we included adult subjects, who had non-cirrhotic nonalcoholic fatty liver disease and CHB infection with positive hepatitis B envelope antibody. We reported descriptive statistics, stratified by detectable and undetectable hepatitis B viral load, by Kruskal-Wallis Rank Sum Test and chi-square. We reported coefficients of two multivariate regression predicting odds of HS > stage 2, testing for interaction between metabolic risk factors and hepatitis B viral load.

Results: When controlled for age, sex, and hepatitis B treatment, the odds of HS > stage 2 increased significantly by 77% for each additional metabolic risk factor [odds ratio (OR) 1.77, 95% confidence interval (CI): 1.20–2.69, P=0.005]. The odds of HS > stage 2 was not associated with detectable hepatitis B viral load (OR 1.00, 95% CI: 0.83–1.19, P=0.986). The association between the odds of HS > stage 2 and metabolic risk factors did not significantly change as hepatitis B viral load increased [ratio of odds ratio (ROR) 1.01, 95% CI: 0.94–1.08, P=0.839].

Conclusions: Our study does not find evidence of effect modification of hepatitis B viral load on the association between metabolic risk factors and HS in non-cirrhotic and hepatitis B envelope antibody positive patients with CHB viral infection. It suggests that the odds of HS in CHB infected patients is affected by metabolic risk factors and not by hepatitis B viremia.

Keywords: Hepatic steatosis (HS); metabolic risk factors; hepatitis B DNA level; viremia; chronic hepatitis B infection

Received: 05 May 2022; Accepted: 17 August 2022; Published: 25 January 2023.

doi: 10.21037/tgh-22-44

View this article at: https://dx.doi.org/10.21037/tgh-22-44

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects about 25% of the general population in the United States and worldwide (1,2). Meanwhile, chronic hepatitis B (CHB) infection was a leading cause of liver-related morbidity and mortality affecting more than 296 million individuals worldwide in 2019 (3). The global prevalence of hepatic steatosis (HS) in CHB patients was estimated to be 34.94% [95% confidence internal (CI): 32.01–37.9%] (4).

Published literature did not support a positive correlation between CHB and HS (5-9), although co-existence of CHB reportedly increased the risk of developing advanced fibrosis, cirrhosis and hepatocellular carcinoma in patients

with NAFLD (10-12). This may lead to the assumption that the impact of CHB on the progression of chronic liver diseases is independent of the presence of HS. On the other hand, the strong correlation between metabolic risk factors (MetRFs) and NAFLD (13-16) has led to a new disease definition of metabolic associated fatty liver disease (MAFLD) (17). The presence of MetRFs in patients with NAFLD may pose threats to studies investigating the association between CHB and NAFLD. The impact of CHB on MetRFs or metabolic syndrome (MetS) remains controversial (18-20). Furthermore, in many instances, MetRFs were adjusted as confounding factors or used for subgroup stratification (7,21,22). Without a clear understanding of how HBV viral factors affect HS in the presence of MetRFs, the conclusions about the association between CHB and HS may be challenged.

In this retrospective observational study, we aimed to investigate the effect modification of hepatitis B viral load (HBV VL) on the association between MetRFs and severity of HS. We hypothesized that hepatitis B viremia would not affect the known association between MetRFs and HS. We present the following article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-44/rc).

Methods

Study design and setting

This is a single-center, retrospective cross-sectional study conducted at Sandra Atlas Bass Center for Liver Diseases, New York, United States. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Boards and Ethics Committees (Northwell IRB: #21-0663), and individual consent for this retrospective analysis was waived.

Participants

Subjects who were evaluated at our liver center from January 1st, 2012 to April 1st, 2019, aged 18 to 89 years, with a co-diagnosis of NAFLD and CHB by International Classification of Diseases, 9th or 10th version, clinical modification codes, were selected for the study. Subjects were excluded if they had significant current or past alcohol use (men ≥21 drinks per week, and women ≥14 drinks per week), or other co-existing chronic liver diseases, which included chronic hepatitis C virus infection, alcohol-associated liver disease, Wilson's disease, hemochromatosis, celiac disease, primary biliary cholangitis, primary sclerosing cholangitis, granulomatous liver diseases, other infiltrative liver diseases, drug induced liver injury, and primary or metastatic liver malignancies. Secondary screening was performed to select population of interest: (I) subjects with positive serum HBV surface antigen, total core antibody, and envelope antibody (HBeAb) with positive or negative envelope antigen; and (II) subjects who had underwent transient elastography (TE) for evaluation of HS severity, categorized by controlled attenuation parameter (CAP) (23,24). Subjects with fibrosis stage 4 (or cirrhosis) on TE were excluded from analysis.

Variables

Reported variables included demographic information such as age, race, and sex; MetRFs such as median body mass index (BMI) (kg/m^2), hemoglobin A1c (HA1c) (%), triglycerides (TG) (mg/dL), high density lipoprotein cholesterol (HDL-c) (mg/dL), and low density lipoprotein cholesterol (LDL-c) (mg/dL) and proportion with history of hypertension (HTN); liver chemistry of median total bilirubin (mg/dL), alkaline phosphatase (ALP) (U/L), aspartate transaminase (AST) (U/L), and alanine transaminase (ALT) (U/L); and disease status of history of HBV treatment, hepatic fibrosis stage (F0-F3), as well as steatosis stage greater than two (HS >2) on TE, signifying for severe disease with >66% hepatocytes with fatty liver changes (25). The cut-off for steatosis stage 2 (S2) and 3 (S3), were defined as CAP >268 dB/m and >280 dB/m, respectively, by multi-etiology model. The variables in the regression analysis included number of MetRFs, HBV VL as represented by log of HBV deoxyribonucleic acid (DNA), as well as individual MetRF. MetRFs were defined as history of HTN/HTN medications use, HA1c >5.7%, TG >150 mg/dL, HDL-c <40 mg/dL for males or <50 mg/dL for females, and BMI >25 kg/m^2.

Objectives

The primary objective was to test for the effect modification of HBV VL on the association between number of MetRFs and HS. The secondary objective was to test for the effect modification of HBV VL on the association between each individual MetRF and HS.

Statistical analysis

Descriptive tabulations were reported for the study population overall and stratified by detected (D) and non-detected (ND) HBV VL. Continuous variables were summarized by median and interquartile range while categorical variables were summarized by percentage. We report results of statistical testing by Kruskal-Wallis Rank Sum Test and chi-square.

Multivariate regressions investigated the statistical significance of interaction between MetRFs and HBV VL. Age was included in years. HBV VL was included by adding one and then log transforming in order to include values equal to 0 while still reflecting the multiplicative growth of the virus and reducing the skew by outliers. The number of MetRFs for each subject was calculated. Two models were pre-specified. First, the log odds of HS >2 were regressed over age in years, sex, history of HBV treatment, HBV VL plus one and log transformed, the number of MetRFs, and an interaction variable between HBV VL and the number of MetRFs. In the second pre-specified model, we replaced the number of metabolic risk factors with the individual metabolic risk factors and included interaction variables between HBV VL and each of these risks. For each model, exponentiated coefficients, standard errors, 95% confidence intervals using standard error, and P values were reported for each covariate. The exponentiated coefficients were interpreted in results. P values were calculated from z-values arrived at by Wald test. Statistical significance was defined as α=0.05.

Results

Descriptive data (Table 1)

Participants

A total of 184 subjects who met the inclusion criteria were studied for the final analysis, and 67 subjects (36.4%) had a HS >2. Descriptive statistics showed that mean age was 51.7 years, 39.7% were female and 58.2% were Asian. There was no significant difference in age (P=0.160), sex (P=0.092) or race (P=0.222) across groups defined by detection of HBV VL.

Metabolic risk factors

There was no significant difference between BMI, history of HTN, HA1c, TG and LDL-c when comparing D *vs.* ND groups. Median HDL-c was significantly higher at 57.0 mg/dL (95% CI: 43.0–70.0) *vs.* 49.0 mg/dL (95% CI: 41.0–58.0) (P=0.004) in D *vs.* ND group (see *Table 1*).

Liver chemistry

Overall, medians of AST, ALT, ALP and total bilirubin were all within normal limits. While there was no significant difference in AST and ALT between two groups, median total bilirubin and ALP were significantly higher in ND group (see *Table 1*).

Clinical features

HBV treatment was significantly more common in ND *vs.* D group (89.0% *vs.* 17.1%, P<0.001). HS >2 was insignificantly more common in ND group (42.5% *vs.* 32.4%, P=0.220). Fibrosis stage equal or greater than two (≥F2) was more significantly seen in ND group (16.5% *vs.* 6.3%, P=0.034).

Main results

The two pre-specified models found no evidence of effect modification of HBV VL on the association between MetRFs and HS. In the first model, the exponentiated coefficient for the number of MetRFs was 1.77 (95% CI: 1.20–2.69, P=0.005). Interpreted in the setting of an insignificant interaction variable, the odds of HS >2 increased significantly by 77% for each additional MetRF when controlled for age, sex and HBV treatment. In subjects without MetRFs, the odds ratio (OR) comparing groups differing by one international unit per mL of HBV DNA on a logarithmic scale was 1.00 (95% CI: 0.83–1.19, P=0.986). The exponentiated coefficient of the interaction variable between the number of MetRFs and the logarithm of HBV DNA plus one was estimated at 1.01 (95% CI: 0.94–1.08, P=0.839) (*Table 2*). Interpreted, the association in the odds of HS >2 and the number of MetRFs did not significantly change as the HBV VL increased when controlled for age, sex, and HBV treatment.

In the second model (*Table 3*), log odds of HS >2 was regressed over age, HBV treatment, BMI, TG, HDL-c, history of HTN, HA1c, log of HBV DNA plus one, and interaction variables between HBV DNA and BMI, TG, HDL-c, history of HTN, and HA1c respectively. In the setting of insignificant interaction variables, the odds of HS >2 does not change for each unit increase in log(HBV DNA) (OR =1.01; 95% CI: 0.24–4.00, P=0.990). Controlled for age, sex, and past HBV treatment, the individual metabolic risk factors were not associated with steatosis, nor was effect modification by viral load observed.

Table 1 Descriptive statistics stratified by HBV DNA detection

Variables	Overall (N=184)	HBV DNA not detected (N=73)	HBV DNA detected (N=111)	P value
Age (years), mean (SD)	51.7 (11.7)	53.2 (10.7)	50.7 (12.3)	0.160
Female, n (%)	73 (39.7)	23 (31.5)	50 (45.1)	0.092
Race, n (%)				0.222
White	38 (20.7)	17 (23.3)	21 (18.9)	
Black or African American	30 (16.3)	7 (9.6)	23 (20.7)	
Asian	107 (58.2)	46 (63.0)	61 (55.0)	
Other	9 (4.9)	3 (4.1)	6 (5.4)	
Body mass index (kg/m^2), median [IQR]	26.6 [23.6, 29.7]	26.5 [22.7, 28.9]	26.9 [24.2, 29.8]	0.312
History of hypertension, n (%)	72 (39.1)	30 (41.1)	42 (37.8)	0.773
Hemoglobin A1c (%), median [IQR]	5.7 [5.4, 6.0]	5.8 [5.4, 6.1]	5.6 [5.4, 5.9]	0.064
Total bilirubin (mg/dL), median [IQR]	0.5 [0.3, 0.6]	0.6 [0.4, 0.7]	0.5 [0.3, 0.6]	0.015
Alkaline phosphatase (U/L), median [IQR]	62.5 [51.8, 77.0]	69.0 [57.0, 83.0]	61.0 [50.0, 73.0]	0.025
Aspartate transaminase (U/L), median [IQR]	24.0 [20.0, 30.0]	25.0 [21.0, 31.0]	24.0 [20.0, 29.0]	0.270
Alanine transaminase (U/L), median [IQR]	22.5 [17.0, 35.0]	24.0 [19.0, 35.0]	21.0 [15.5, 36.5]	0.123
Triglycerides (mg/dL), median [IQR]	102.0 [70.0, 134.5]	99.0 [70.0, 176.0]	106.0 [70.5, 130.5]	0.427
HDL-c (mg/dL), median [IQR]	52.0 [43.0, 65.0]	49.0 [41.0, 58.0]	57.0 [43.0, 70.0]	0.004
LDL-c (mg/dL), median [IQR]	110.5 [87.0, 133.0]	106.0 [87.0, 130.0]	112.0 [88.0, 133.5]	0.680
Fibrosis stage, n (%)				0.034
F0	154 (83.7)	54 (74.0)	100 (90.1)	
F1	11 (6.0)	7 (9.6)	4 (3.6)	
F2	12 (6.5)	7 (9.6)	5 (4.5)	
F3	7 (3.8)	5 (6.9)	2 (1.8)	
History of receiving hepatitis B treatment, n (%)	84 (45.7)	65 (89.0)	19 (17.1)	<0.001
Steatosis stage greater than 2, n (%)	67 (36.4)	31 (42.5)	36 (32.4)	0.220

HBV DNA, hepatitis B viral deoxyribonucleic acid; SD, standard deviation; IQR, interquartile range; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Discussion

Our study does not find evidence of effect modification of HBV VL on the association between MetRFs and HS in non-cirrhotic and HBeAb positive CHB patients. In the absence of HBV VL, the presence of each additional MetRF increases the odds of HS >2 by 77%. The presence of HBV VL does not potentiate nor attenuate the association between MetRFs and HS [ratio of odds ratio (ROR) =1.01, 95% CI: 0.94–1.08, P=0.839].

Increasing prevalence of MetRFs in patients with concurrent NAFLD and CHB raises the importance of searching for synergistically deleterious effects. Our study suggests that MetRFs and HBV VL are independent entities without synergistic effects in the evolution of HS in non-cirrhotic and HBe antibody positive CHB patients. Our results support the conclusion that MetRFs rather than viremia contribute towards the progression of HS in patients with co-existing NAFLD and CHB (8,26,27).

The published studies reported that hepatitis B viremia

Table 2 Results of first multivariate regression predicting hepatic steatosis

Variables	Exponentiated coefficient	Std. Error	2.50%	97.50%	P value
(Intercept)	0.11	0.99	0.01	0.69	0.022
Age	1.01	0.02	0.98	1.04	0.719
Hepatitis B treatment	1.38	0.41	0.62	3.09	0.429
Sex	0.79	0.37	0.38	1.64	0.528
Number of metabolic risk factors (MetRF)	1.77	0.20	1.20	2.69	0.005
Log(HBV DNA)	1.00	0.09	0.83	1.19	0.986
Number of metabolic RF:Log(HBV DNA)	1.01	0.04	0.94	1.08	0.839
Number of observations			184		

Std. Error, standard error; HBV DNA, hepatitis B viral deoxyribonucleic acid.

Table 3 Results of second multivariate regression predicting hepatic steatosis

Variables	Exponentiated coefficient	Std. Error	2.50%	97.50%	P value
(Intercept)	0.00	3.95	0.00	0.13	0.018
Age	1.00	0.02	0.96	1.03	0.888
Sex	0.76	0.42	0.33	1.72	0.517
Hepatitis B treatment	1.68	0.43	0.72	3.95	0.232
BMI	1.11	0.06	0.99	1.25	0.083
TG	1.01	0.00	1.00	1.01	0.138
HDL-c	1.01	0.02	0.97	1.05	0.654
HTN	1.63	0.51	0.60	4.48	0.337
Hemoglobin A1c (HA1c)	2.23	0.53	0.82	6.68	0.131
Log(HBV DNA)	1.01	0.72	0.24	4.00	0.990
BMI:Log(HBV DNA)	1.00	0.01	0.98	1.02	0.851
TG:Log(HBV DNA)	1.00	0.00	1.00	1.00	0.486
HDL-c:Log(HBV DNA)	1.00	0.00	0.99	1.01	0.793
HTN:Log(HBV DNA)	0.97	0.10	0.80	1.17	0.756
HA1c:Log(HBV DNA)	0.99	0.08	0.85	1.18	0.908
Number of observations			184		

Std. Error, standard error; BMI, body mass index; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; HTN, history of hypertension; HBV DNA, hepatitis B viral deoxyribonucleic acid.

was not associated with increase in severity of HS in patients with or without MetRFs (5,20,22,27-30). Hui *et al.* demonstrated in a multivariate analysis that HBV VL was lower in treatment-naïve adult patients with HS than in healthy controls (OR 0.859, 95% CI: 0.743–0.994, P<0.050). In that study, there was a stepwise decrease in median HBV DNA levels with increased steatosis severity (3.1 and 2.6 log IU·mL^{-1} in no steatosis and severe steatosis, respectively, P=0.032) (5). Wang *et al.* and Zheng *et al.* also showed an inverse relationship between HBV VL and HS in their pediatric (OR 0.376, 95% CI: 0.173–0.818) and adult patients (MD –0.38, 95% CI: –1.16 to 0.42), respectively

(28,29). Whereas in other studies, no association was found between HBV VL and HS (8,22,30). In Zhu *et al.*'s large population-based cohort study, 283 out of the 2,393 Chinese adult CHB patients developed NAFLD. The incidence of NAFLD, detected by sonogram, was not associated with viral factors except a negative relationship between detectable HBV VL with incidental NAFLD in patients with concurrent type 2 diabetes mellitus (HR 0.37; 95% CI: 0.14–0.98) (27). Our study not only reveals the lack of basic correlations between HBV viremia and severity of HS, but also provides evidence for lack of interactions between HBV VL and MetRFs in the progression of HS. This may further strengthen the assumption that HBV viremia and MetRFs act as independent modulators in the progression of NAFLD.

This study has several limitations. Retrospective data collection is limited by the availability of information on the electronic medical records. CAP has been reported to have reduced diagnostic accuracy in patients with obesity (25,31,32). It may also be affected by variations in geographic regions, cutoffs, and age (25). In addition, we focused our analysis on subjects with positive HBeAb with the intent to investigate patients in the immune-active phase. CHB is a vastly heterogenous disease with a wide range of patient demographic and stages of disease. By focusing on one particular phase of the disease progression, we intended to minimize the confounding factors. Consequently, the generalizability of our study is limited to a small number of non-cirrhotic and HBeAb positive CHB patients.

Conclusions

In conclusion, our study among non-cirrhotic HBeAb positive CHB patients demonstrated that the odds of HS are affected by metabolic risk factors and not by hepatitis B viremia. Moreover, there was no effect modification between metabolic risk factors and viral load on the odds of steatosis. Larger studies, including different phases of CHB are warranted to further explore the role of HBV in NAFLD patients.

Acknowledgments

Thanks to Qiu He, MD in participation of early phase of data collection. The abstract was virtually presented as e-poster at 2021 Liver Meeting with AASLD.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-44/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-44/dss

Peer Review File: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-44/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-44/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Boards and Ethics Committees (Northwell IRB: #21-0663), and individual consent for this retrospective analysis was waived.

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doi: 10.21037/tgh-22-44
Cite this article as: Shi MY, Wong C, Lee TP. Effect modification of hepatitis B viral load on the association between metabolic risk factors and hepatic steatosis. Transl Gastroenterol Hepatol 2023;8:6.