Association between metabolic factors and chronic hepatitis B virus infection

Chien-Hsieh Chiang, Kuo-Chin Huang

Chien-Hsieh Chiang, Kuo-Chin Huang, Department of Family Medicine, National Taiwan University Hospital and College of Medicine, Taipei 100, Taiwan
Chien-Hsieh Chiang, Department of Community and Family Medicine, National Taiwan University Hospital Yun-Lin Branch, Yunlin 640, Taiwan
Kuo-Chin Huang, Graduate Institute of Clinical Medical Science, China Medical University, Taichung 404, Taiwan
Author contributions: Chiang CH and Huang KC designed the study and wrote the article.
Correspondence to: Kuo-Chin Huang, MD, PhD, Professor, Head, Department of Family Medicine, National Taiwan University Hospital and College of Medicine, 7 Chung Shan South Road, Taipei 100, Taiwan. bretthuang@ntu.edu.tw
Telephone: +886-2-23123456 Fax: +886-2-23118674
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Abstract
There are limited data regarding the relationship between chronic hepatitis B virus (HBV) infection and metabolic factors. This article aims to highlight the link of metabolic factors with hepatitis B surface antigen (HBsAg) serostatus, HBV load, and HBV-related hepatocellular carcinoma (HCC). Although HBsAg-positive serostatus was positively correlated with a high risk of metabolic syndrome in students, chronic HBV-infected individuals have high serum adiponectin levels. The androgen pathway in HBV carriers with a low body mass index is more triggered which leads to enhanced HBV replication. High HBV load was inversely associated with obesity in hepatitis B e antigen (HBeAg)-seropositive HBV carriers; while in HBeAg-seronegative HBV carriers, high HBV load was inversely related to hypertriglyceridemia rather than obesity. For overweight and obese HBV-infected patients, high HBV load was positively associated with serum adiponectin levels. Several large cohort studies have revealed a positive link of diabetes with incidence of HBV-related HCC. However, the association between incidence of HCC and metabolic factors other than diabetes is still inconclusive. More long-term prospective studies should elucidate the association of chronic HBV infection and its outcomes with metabolic factors in clinical practice.

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Key words: Hepatitis B surface antigen; Hepatitis B viral load; Hepatocellular carcinoma; Diabetes; Obesity; Adiponectin

Core tip: Facing the increasing burden of metabolic syndrome and chronic hepatitis B worldwide, this review tries to highlight the association of metabolic factors with chronic hepatitis B. Intriguingly, hepatitis B virus carriers are reported to have higher serum adiponectin levels, previously linked with individuals with low body mass index. Obesity and hypertriglyceridemia (metabolically bad factors) are inversely associated with high hepatitis B viral load; a crucial predictor for primary liver cancer. In contrast, serum adiponectin levels (a metabolically good factor) are positively related to high hepatitis B viral load in individuals with high body mass index.

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INTRODUCTION
Chronic hepatitis B virus (HBV) infection is well-known as a major risk factor for hepatocellular carci...
noma (HCC)[13,14]. The burden of obesity and metabolic syndrome has been increasing in recent decades[15]. Subsequently, there is growing concern regarding the association between metabolic factors and chronic HBV infection. This review article tries to highlight the association of metabolic factors with hepatitis B surface antigen (HBsAg) serostatus, HBV load, and HBV-related HCC.

METABOLIC FACTORS AND HBsAg SEROSTATUS

Chronic-HBV-infected university freshers (4475 men and 3751 women) had a higher risk of metabolic syndrome (OR = 1.58, 95%CI: 1.04-2.47) compared to individuals with seroprotective titers after HBV vaccination[6], after controlling for age, sex, body mass index (BMI), uric acid quartiles, smoking, alcohol consumption, and physical activity. However, another population-based cross-sectional study (53528 participants) showed that the likelihood of developing metabolic syndrome was lower in HBsAg-positive (n = 5995, 12.6%) than HBsAg-negative (adjusted OR = 0.84, 95%CI: 0.76-0.93) adults after controlling for age and sex[7]. High triglyceride level (≥ 150 mg/dL) (adjusted OR = 0.65, 95%CI: 0.60-0.69) and high blood pressure (adjusted OR = 0.89, 95%CI: 0.83-0.94) were inversely associated with being HBsAg-positive. One of the probable explanations of the inconsistency between the above student- and population-based studies is the different age compositions (freshers vs 30-79 years) and comparison groups (individuals with seroprotective titers after HBV vaccination vs being HBsAg positive). It is worth mentioning that being positive for hepatitis C virus (HCV) antibody was positively associated with reduced high-density lipoprotein (adjusted OR = 1.61, 95%CI: 1.37-1.88), while inversely associated with high triglyceride level (adjusted OR = 0.63, 95%CI: 0.55-0.71) according to the population-based study[7]. Thus, the likelihood of developing metabolic syndrome in HCV carriers (n = 1792, 3.8%) was similar to that in non-HCV carriers.

There have been controversial results. A hospital-based cross-sectional study (243 men and 264 women; mean age: 46.6 years) showed no significant relationship between chronic HBV infection and insulin resistance or ultrasonographic hepatic steatosis[8]. Another cross-sectional population study reported that HBV-infected Hong Kong Chinese (n = 91) had lower intrahepatic triglyceride content measured by proton-magnetic resonance spectroscopy (P < 0.001), lower serum triglycerides (P < 0.001), lower metabolic syndrome (11.0% vs 20.2%, P = 0.034), and a lower risk of fatty liver (adjusted OR = 0.42, 95%CI: 0.20-0.88) than controls (n = 922)[8]. The association of HBV with selected adipokines is also under investigation. For example, adiponectin possesses anti-inflammatory effects and is inversely associated with BMI, type 2 diabetes and several metabolic disorders[10]. Recently, we demonstrated that HBV-infected individuals, though heavier than healthy controls, had higher serum adiponectin levels (P < 0.0001) and a higher proportion of adiponectin levels over the 75th percentile (adjusted OR = 4.25, 95%CI: 2.36-7.66) after controlling age, sex, BMI, and insulin resistance index[11]. The link between HBsAg serostatus and metabolic factors should be further clarified from the perspective of HBV load.

METABOLIC FACTORS AND HEPATITIS B VIRAL LOAD

Some animal models considered HBV a “metabolovirus” because the gene expression of HBV and key metabolic genes in hepatocytes was shown to be similarly regulated[12]. The androgen production in HBV carriers with a low BMI (< 23 kg/m²) was more triggered and up-regulated HBV replication, as shown in a transcriptional animal model and a campus-based study[13,14]. A Taiwanese community-based study including 3587 HBV-infected participants revealed that high HBV load was inversely associated with extreme obesity (adjusted OR = 0.17, 95%CI: 0.05-0.63) and central obesity (adjusted OR = 0.44; 95%CI: 0.25-0.78) in HBsAg-seropositive patients; while high HBV load was inversely associated with hypertriglyceridemia (adjusted OR = 0.74, 95%CI: 0.61-0.89) in HBsAg-seronegative patients[15]. Liver steatosis was neither associated with HBV load in HBsAg-seropositive patients (adjusted OR = 1.46, 95%CI: 0.90-2.36) nor in HBsAg-seronegative patients (adjusted OR = 0.88, 95%CI: 0.72-1.08). The above findings altogether implicate that metabolically bad factors (obesity and hypertriglyceridemia) may cause liver damage through hepatic steatosis and oxidative stress, independently of HBV replication.

Although adipokines were observed to contribute to histological liver injury of chronic HBV-infected patients hospitalized for liver biopsy[16], an experimental animal model demonstrated that HBV replication boosted the increase in circulating adiponectin levels through activation of peroxisome proliferator-activated receptor (PPAR) gene expression. Reciprocally, adiponectin and PPARγ agonist treatment triggered HBV replication[17]. Consistently, we also revealed that the logarithmic transformation of HBV load was positively associated with serum adiponectin levels, but only in patients with a higher BMI (BMI ≥ 23 kg/m²) (P = 0.018) adjusted for age, sex, BMI, HBsAg serostatus, liver function, and homeostasis model assessment of insulin resistance[18]. In patients with a lower BMI, HBV load tended to be up-regulated by the activated androgen production more than the adiponectin pathway[19]. More elucidation of adiponectin pathways in HBV carriers may help develop adjuvant treatments of HBV infection in the future.

METABOLIC FACTORS AND HBV-RELATED HCC

The potential link between diabetes mellitus and metabolic factors with HBV-related HCC has aroused increasing concern[20,21], not necessarily related to serum HBV
load, a well-known risk factor of HCC\(^{22,34}\). For example, a long-term community-based cohort revealed that HBV-related HCC risk was associated with diabetes (adjusted OR = 2.27, 95\%CI: 1.10-4.66) rather than extreme obesity (adjusted OR = 1.36, 95\%CI: 0.64-2.89)\(^{19}\). However, the study performed no adjustment of hepatitis B viral load or HBsAg serostatus.

The relationship between HCC and metabolic factors other than diabetes, however, is more inconclusive. A large European cohort study of 289273 men has reported an inverse link between cancer occurrence of the liver and intrahepatic ducts and serum total cholesterol\(^{20}\). Tsan et al\(^{26,27}\) analyzed a National Health Insurance claims database and found protective effects of statins on HBV- and HCV-related HCC incidence. Notably, secondary data analyses using claims database in Taiwan usually lack important confounding information including BMI, blood pressure, liver function, cigarette or alcohol habits, and medication adherence. Besides, clinicians may decide to withhold or withdraw statins for patients with abnormal liver function, though some human trials of statins were shown to improve hepatic steatosis and hepatic fibrosis\(^{28}\). This concern in real practice might confound the true protective role of statins in HBV- and HCV-related HCC incidence.

High triglyceride levels (≥150 mg/dL) were inversely associated with subsequent HBV-related HCC incidence (adjusted OR = 0.60, 95\%CI: 0.40-0.90)\(^{15}\). This finding is consistent with the inverse association between serum triglycerides and HBV load in HBeAg-seronegative patients\(^{15}\). HBV X protein could inhibit the secretion of apolipoprotein B, located on the surface of every triglyceride-rich very-low-density lipoprotein particle\(^{29}\). Once HBV actively replicates, HBV X protein increases rapidly and impairs the production of very-low-density lipoprotein and circulating triglycerides. However, an animal study reported fibrate-induced anti-proliferative effects in cultured human HCC cells\(^{29}\). The investigators demonstrated that the protective effects were independent of the PPAR\(\alpha\) pathway. There are still no prospective human studies prospectively exploring fibrate use and HCC occurrence in HBV-infected individuals.

**CONCLUSION**

The controversy regarding the association between the presence of HBsAg and metabolic factors should be further understood from the perspective of HBV load. High HBV load was inversely associated with obesity in HBeAg-seropositive HBV carriers; while in HBeAg-seronegative individuals, high HBV load was inversely related to hypertriglyceridemia. HBV replication did not interact with obesity or hypertriglyceridemia to cause liver damage. The activation of PPR\(\alpha\) gene expression at a high BMI and androgen pathway at a low BMI might be associated with high HBV load. Among metabolic factors, diabetes has been the best known risk factor of HBV-related HCC. More better-designed long-term prospective research should focus on elucidating association of metabolic factors with chronic HBV infection and its relevant outcomes.

**REFERENCES**

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; 365: 1118-1127 [PMID: 21922124 DOI: 10.1056/NEJMra1001683]
2. Liao SF, Yang HI, Lee MH, Chen CJ, Lee WC. Fifteen-year population attributable fractions and causal pies of risk factors for newly developed hepatocellular carcinomas in 11,801 men in Taiwan. *PloS One* 2012; 7: e34779 [PMID: 22506050 DOI: 10.1371/journal.pone.0034779]
3. Wen CP, Lin J, Yang YC, Tsao MK, Tsao CK, Etzel C, Huang M, Hsu CY, Ye Y, Mishra L, Hawk E, Wu X. Hepatocellular carcinoma risk prediction model for the general population: the predictive power of tumamisanes. *J Natl Cancer Inst* 2012; 104: 1599-1611 [PMID: 23075439 DOI: 10.1093/jnci/djs572]
4. Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009; 373: 582-592 [PMID: 19217993 DOI: 10.1016/S0140-6736(09)61207-3]
5. Huang KC. Obesity and its related diseases in Taiwan. *Obes Rev* 2008; 9 Suppl 1: S2-34 [PMID: 18307696 DOI: 10.1111/j.1467-789X.2007.00435.x]
6. Yen SL, Chiu TY, Lin YC, Lee YC, Lee LT, Huang KC. Obesity and hepatitis B infection are associated with increased risk of metabolic syndrome in university freshmen. *Int J Obes* (Lond) 2008; 32: 474-480 [PMID: 17955029 DOI: 10.1038/sj.ijo.0803573]
7. Jan CF, Chen CJ, Chiu YH, Chen LS, Wu HM, Huang CC, Yen MF, Chen TH. A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-Based Integrated Screening study No. 10). *Int J Obes* (Lond) 2006; 30: 794-799 [PMID: 16404404 DOI: 10.1038/sj.ijo.0803020]
8. Wang CC, Hsu CS, Liu CJ, Kao JH, Chen DS. Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. *J Gastroenterol Hepatol* 2008; 23: 779-782 [PMID: 18028349 DOI: 10.1111/j.1440-1746.2007.05216.x]
9. Wong VW, Wong GL, Chu WC, Chim AM, Ong A, Yeung DK, Ku KK, Chu SH, Chan HY, Woo J, Chan FK, Chan HL. Hepatitis B virus infection and fatty liver in the general population. *J Hepatol* 2012; 56: 533-540 [PMID: 22027575 DOI: 10.1016/j.jhep.2011.09.013]
10. McManus DD, Lyass A, Ingelsson E, Massaro JM, Meigs JB, Aragam J, Benjamin EJ, Vasan RS. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. *Obesity (Silver Spring)* 2012; 20: 1882-1888 [PMID: 23150435 DOI: 10.1038/oby.2011.1032]
11. Chiang CH, Lai JS, Hung SH, Lee LT, Sheu JC, Huang KC. Serum adiponectin levels are associated with hepatitis B viral load in overweight to obese hepatitis B virus carriers. *Obesity (Silver Spring)* 2013; 21: 291-296 [PMID: 23404868 DOI: 10.1002/oby.20000]
12. Shlomai A, Shaul Y. The metabolic activator FOXO1 binds hepatitis B virus DNA and activates its transcription. *Biochem Biophys Res Commun* 2009; 381: 544-548 [PMID: 19235123 DOI: 10.1016/j.bbrc.2009.07.087]
13. Chiang CH, Lai JS, Shou JC, Yen LL, Liu CJ, Huang KC. The risky body mass index ranges for significant hepatitis B viral load: A campus-based study. *Obes Res Clin Pract* 2012; 6: e1-e90 [PMID: 2433171 DOI: 10.1016/j.orcp.2011.04.005]
14. Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, Chen P. Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. *Hepatology* 2009; 50: 1392-1402 [PMID: 19670412 DOI: 10.1002/2009.bep.22163]
15. Chiang CH, Yang HL, Chen CL, Lu SN, Wang LY, You SL, Su J, Iloeje UH, Chen CJ. Association between obesity, hypertriglyceridemia and low hepatitis B viral load. *Int J Obes* (Lond) 2013; 37: 410-415 [PMID: 22531094 DOI: 10.1038/ijo.2012.63]
and outcomes in chronic hepatitis B. Hepatology 2009; 49: 572-584 [PMID: 19399801 DOI: 10.1002/hep.22884]

24 Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]

25 Strohmaier S, Edlinger M, Manjer J, Stocks T, Bjørge T, Borena W, Häggström C, Engeland A, Nagel G, Almquist M, Selmer R, Tretli S, Concín H, Hallmans G, Jonsson H, Stattin P, Ulmer H. Total serum cholesterol and cancer incidence in the Metabolic syndrome and Cancer Project (Me-Can). PLoS One 2013; 8: e54242 [PMID: 23372693 DOI: 10.1371/journal.pone.0054242]

26 Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. J Clin Oncol 2013; 31: 1514-1521 [PMID: 22271485 DOI: 10.1200/jco.2011.36.0917]

27 Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. J Clin Oncol 2012; 30: 623-630 [PMID: 22271485 DOI: 10.1200/jco.2011.36.0917]

28 Nseir W, Mograbi J, Ghali M. Lipid-lowering agents in non-alcoholic fatty liver disease and steatohepatitis: human studies. Dig Dis Sci 2012; 57: 1773-1781 [PMID: 22419057 DOI: 10.1007/s10620-012-2118-3]

29 Kang SK, Chung TW, Lee YJ, Lee YC, Morton RE, Kim CH. The hepatitis B virus X protein inhibits secretion of apolipoprotein B by enhancing the expression of N-acetylglucosaminylltransferase III. J Biol Chem 2004; 279: 28106-28112 [PMID: 15123606 DOI: 10.1074/jbc.M403176200]

30 Yamasaki D, Kawabe N, Nakamura H, Tachibana K, Ishimoto K, Tanaka T, Aburatani H, Sakai J, Hamakubo T, Kodama T, Doi T. Fenofibrate suppresses growth of the human hepatocellular carcinoma cell via PPARα-independent mechanisms. Eur J Cell Biol 2011; 90: 657-664 [PMID: 21514001 DOI: 10.1016/j.ejcb.2011.02.005]

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