Chronic hepatitis B and metabolic risk factors: A call for rigorous longitudinal studies

Wai-Kay Seto

ORCID number: Wai-Kay Seto (0000-0002-9012-313X).

Author contributions: Seto WK interpreted the literature and wrote the manuscript.

Conflict-of-interest statement: Wai-Kay Seto is an advisory board member and received speaker’s fees from AbbVie; he is also an advisory board member, received speaker’s fees and research funding from Gilead Sciences.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: August 29, 2018
Peer-review started: August 29, 2018
First decision: October 9, 2018
Revised: October 14, 2018
Accepted: October 21, 2018
Article in press: October 21, 2018
Published online: January 21, 2019

Abstract

Long-term nucleos(t)ide analogue therapy in chronic hepatitis B virus (HBV) infection is effective in suppressing viral replication and reducing liver-related complications. However, HBV-related liver events can still occur in different patient sub-groups. There is emerging evidence that, similar to chronic hepatitis C virus infection, metabolic risk factors may play a role in the disease process of chronic HBV. While the mechanistic nature of metabolic-HBV interactions remains uncertain, studies in different HBV-infected populations have demonstrated that hepatic steatosis, increased body-mass index, diabetes, or a combination of different metabolic risk factors are associated with an increased risk of hepatocellular carcinoma and cirrhosis. The impact of metabolic risk factors is especially prominent in patients with quiescent virological activity, including on-treatment patients with effective viral suppression. As the proportion of on-treatment chronic HBV patients increases worldwide, longitudinal studies determining the relative risks of different metabolic parameters with respect to clinical outcomes are needed. Future studies should also determine if metabolic-directed interventions can improve disease outcomes in chronic HBV.

Key words: Hepatitis B virus; Diabetes; Obesity; Steatosis; Non-alcoholic fatty liver disease; Body-mass index

Wai-Kay Seto, Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Wai-Kay Seto, Department of Medicine, the University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, Guangdong Province, China

Wai-Kay Seto, State Key Laboratory for Liver Research, the University of Hong Kong, Hong Kong, China

Corresponding author: Wai-Kay Seto, FRCP (C), MBBS, MD, Associate Professor, Doctor, Department of Medicine, the University of Hong Kong Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. wkseto@hku.hk

Telephone: +86-852-22553994
Fax: +86-852-28162863

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Metabolic risk factors, including hepatic steatosis, increased body-mass index
and diabetes, may be associated with worsened disease outcomes and reduced treatment
response in chronic hepatitis B. Their effect may be most pronounced in patients with
quiescent viral activity, including patients on long-term nucleos(t)ide analogue therapy.

Citation: Seto WK. Chronic hepatitis B and metabolic risk factors: A call for rigorous
longitudinal studies. World J Gastroenterol 2019; 25(3): 282-286
URL: https://www.wjgnet.com/1007-9327/full/v25/i3/282.htm
DOI: https://dx.doi.org/10.3748/wjg.v25.i3.282

INTRODUCTION

Affecting 248 million individuals worldwide, chronic hepatitis B virus (HBV)
infection is a leading cause of liver-related morbidity and mortality[1]. Current
nucleos(t)ide analogues, when taken long-term, can effectively suppress viral
replication, improve liver histology, and reduce liver-related complications[2]. Yet
nucleos(t)ide analogue therapy is never a “magic bullet” that can eliminate and
prevent all HBV-related complications, with the benefit of therapy mitigated in
certain patient sub-groups. For example, in an Asian population-based study,
nucleoside analogue failed to significantly reduce liver cancer incidence in elderly
chronic HBV patients[3].

Metabolic parameters have been demonstrated to play a prominent role in the
disease course of chronic hepatitis C virus infection[4]. The interaction of metabolic
factors with chronic HBV has been less extensively studied. Now, there is emerging
evidence on how metabolic risk factors may influence the natural history and
treatment response of chronic HBV (Figure 1), and these will be described in detail in
this editorial.

HEPATIC STEATOSIS

The impact of liver fat on the disease course of HBV is controversial. There are studies
indicating that steatosis may actually be protective. A cohort study from Taiwan
involving 83339 participants showed hepatitis B surface antigen (HBsAg)-positive
patients to have a lower risk of non-alcoholic fatty liver disease (NAFLD)
development compared to HBsAg-negative individuals[5]. Another study
demonstrated that a treatment-naïve chronic HBV patient with co-existing NAFLD
had significantly lower serum HBV DNA levels compared to chronic HBV without
steatosis, after adjusting for potential confounders[6].

Paradoxically, there is evidence that co-existing hepatic steatosis may contribute to
the chronic HBV disease process. A study employed the noninvasive quantification of
steatosis using controlled attenuation parameter (commonly known as CAP)
measurements, with standardized cut-off values used to categorize steatosis
severity[7]. Severe steatosis (CAP ≥ 280 dB/m) was found to be independently
associated with increased liver fibrosis in both treatment-naïve patients and on-
treatment patients achieving long-term virological suppression. The results suggest
that even during quiescent viral activity, fibrogenesis can still develop in the presence
of hepatic steatosis[8].

The above findings will require longitudinal validation in the clinical setting, as
well as mechanistic studies for any HBV-steatosis interaction. Nonetheless, the
management implications can be potentially huge, since both chronic HBV and
NAFLD are common diseases. In Asia, the prevalence of NAFLD is greater than
30%[9], while more than a quarter of chronic HBV patients have concomitant
NAFLD[10].

OBESITY

An increased body-mass index (BMI) has been demonstrated to worsen the disease
outcome of chronic HBV. In a population-based study involving 2903 HBsAg-positive
men after a mean follow-up of 14.7 years, obesity (BMI ≥ 30 kg/m²) was associated
with increased risk of both hepatocellular carcinoma (HCC) and liver-related
Figure 1 Potential association of metabolic risk factors with the natural history and treatment response of chronic hepatitis B virus infection. HBV: Hepatitis B virus.

mortality. Obesity also diminishes treatment response by lessening fibrosis regression during long-term nucleos(t)ide analogue therapy. In a study with paired liver biopsies over a course of five years, increased BMI (≥ 25 kg/m²) in HBV-infected patients of majority European descent was associated with persistent severe fibrosis or cirrhosis during treatment when compared to patients with normal BMI. Results were also similar in another study involving Asian on-treatment patients with paired transient elastography over a median duration of 87.5 mo.

Obesity is associated with adipokine dysregulation, including reduced adiponectin and increased leptin production, which leads to enhanced liver fibrogenesis. However, it remains unclear whether this adipokine dysfunction has any mechanistic interaction with HBV. With the prevalence of obesity in HBV-endemic regions increasing, studies specifically concentrating on the obese HBV population will be needed.

DIABETES MELLITUS

Diabetes has a synergistic impact on the disease course of chronic HBV. While the exact mechanism remains unclear, hyperglycemia activates oxidative stress, which can be linked with the severity of liver disease in chronic HBV infection. Diabetic chronic HBV patients have an increased chance of alanine aminotransferase elevation and liver damage compared to non-diabetic patients. Diabetes also increases the risk of HBV-related cirrhotic decompensation and liver-related mortality.

Large-population cohort studies have further established the association of diabetes with liver-related clinical outcomes. A cohort study involving 23,820 Taiwan residents and a mean follow-up duration of 14 years found that diabetes independently increased the risk of HCC in HBsAg-positive individuals. In addition, in a recent study involving 512,891 Chinese adults (both HBsAg-positive and -negative) with a median follow-up duration of 10.1 years, the presence of diabetes significantly increased the risk of HCC and cirrhosis (adjusted hazards ratios of 1.49 and 1.87, respectively). In addition, in patients without previously diagnosed diabetes, an increase of plasma glucose levels by 1 mmol/L, even in the non-diabetic range, significantly increased the probability of HCC and cirrhosis (adjusted hazards ratios of 1.04 and 1.07, respectively).

METABOLIC RISK FACTORS IN COMBINATION

The combination of different metabolic risk factors in HBV-infected patients can increase the risk of liver-related events. Metabolic syndrome, which is a combination of increased waist circumference or obesity with the presence of different metabolic risk factors (hyperglycemia, hyperlipidemia, hypertriglyceridemia or hypertension) is a known risk factor for the development of HBV-related fibrosis progression. More recently, a Taiwanese study followed up with 1690 men with chronic HBV infection for a median duration of 19 years. Having three or more metabolic risk factors
(including diabetes, obesity, hypertriglyceridemia, hypercholesterolemia or hypertension) increased the risk of HCC and liver-related death (hazards ratios of 2.32 and 2.72, respectively). Notably, in patients with available virological data, the risk of HCC among patients with three or more metabolic risk factors was especially accentuated when serum HBV DNA was less than 2000 IU/mL (hazards ratio of 14.38) [23].

CONCLUSION

HBV and metabolic risk factors: Partners in crime?

Despite the emerging evidence of metabolic risk factors being associated with HBV-related outcomes, one fundamental question remains unanswered: are HBV and metabolic-related liver injury synergistic, or simply two unrelated and different disease processes? Mechanistic studies to investigate their interaction are technically difficult, mainly due to the limitations of current HBV animal models which are inadequate to model HBV infection in humans. Nonetheless, the more important clinical question will be the magnitude of impact of different metabolic risk factors on HBV-related clinical outcomes. From available evidence, this impact is especially prominent in quiescent HBV disease [23,24], either in treatment-naïve patients with intrinsically low HBV DNA levels or in nucleos(t)ide analogue-treated patients with effective virological suppression. The proportion of patients receiving long-term treatment is increasing worldwide [25], while at the same time, the HBV patient cohort is ageing, suggesting that the concomitant presence of metabolic risk factors will increase. Taken together, these data suggest that the metabolic impact on the disease course of HBV will become more and more predominant. Finally, well-designed longitudinal studies will be needed to determine whether interventions directed at metabolic risk factors e.g., glycemic control in diabetes or weight loss, can improve HBV-related outcomes. Clinical data on this metabolic-HBV interaction will prove useful if we are to meet the World Health Organization’s objective in removing HBV as a public health threat by 2030.

REFERENCES

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015; 386: 1546-1555 [PMID: 26231439 DOI: 10.1016/S0140-6736(15)61422-X].

2. Marcellin P, Gane E, Buti M, Afdhal N, Severt W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Aguilar Schall R, Bornstein JD, Kritinos KM, Subramanian GM, McHutchinson JC, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. Lancet 2013; 381: 466-475 [PMID: 23234725 DOI: 10.1016/S0140-6736(12)64125-1].

3. Seto WK, Lau EH, Wu JT, Hung IF, Leung WK, Cheung KS, Fung J, Lai CL, Yuen MF. Effects of nucleoside analogue prescription for hepatitis B on the incidence of liver cancer in Hong Kong: a territory-wide ecological study. Aliment Pharmacol Ther 2017; 45: 501-509 [PMID: 27976416 DOI: 10.1111/apt.13985].

4. Serfaty L. Metabolic Manifestations of Hepatitis C Virus: Diabetes Mellitus, Dyslipidemia. Clin Liver Dis 2017; 21: 475-486 [PMID: 28695557 DOI: 10.1016/j.cld.2017.07.004].

5. Joo EJ, Chang Y, Yoon JS, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: A cohort study. Hepatology 2017; 65: 828-835 [PMID: 28035771 DOI: 10.1002/hep.29117].

6. Hui RWH, Seto WK, Cheung KS, Mak LY, Liu KSH, Fung J, Wong DK, Lai CL, Yuen MF. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. J Viral Hepat 2018; 25: 97-104 [PMID: 28772340 DOI: 10.1111/jvhe.12766].

7. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Ledinghen V, Kumar M, Lupsov-Platon M, Han KH, Cardoso AC, Ferreira G, Chan WK, Wong VW, Myers RP, Chayama K, Friedrich-Rust M, Beaugrand M, Shen J, Hirjai JB, Sarin SK, Badea R, Jung KS, Marcellin P, Filić C, Mahadeva S, Wong CL, CroTTY P, Masuki K, Rojunga J, Bedossa P, Keim V, Wiegand J. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017; 66: 1022-1030 [PMID: 28059099 DOI: 10.1016/j.jhep.2016.12.022].

8. Seto WK, Hui RWH, Mak LY, Fung J, Cheung KS, Liu KSH, Wong DK, Lai CL, Yuen MF. Association Between Hepatic Steatosis, Measured by Controlled Attenuation Parameter, and Fibrosis Burden in Chronic Hepatitis B. Clin Gastroenterol Hepatol 2018; 16: 575-583.e2 [PMID: 28970146 DOI: 10.1016/j.cgh.2017.09.044].

9. Seto WK, Yuen MF. Nonalcoholic fatty liver disease in Asia: emerging perspectives. J Gastroenterol 2017; 52: 164-174 [PMID: 27637587 DOI: 10.1007/s00535-016-1264-3].

10. 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 [PMID: 21649726 DOI: 10.1111/j.1440-1746.2011.06801.x].

11. Yu MW, Shih WL, Lin CL, Liu CJ, Jian JW, Tsai KS, Chen CJ. Body-mass index and progression of hepatitis B: a population-based cohort study in men. J Clin Oncol 2008; 26: 3556-3562 [PMID: 18700392].
Seto WK. Chronic HBV and metabolic risk factors

12 Seto WK, Fung J, Cheung KS, Mak LY, Hui RW, Liu KS, Lai CL, Yuen MF. Body-mass index is associated with fibrosis regression during long-term nucleoside analogue therapy in chronic hepatitis B. *Aliment Pharmacol Ther* 2016; 44: 1071-1079 [PMID: 27692292 DOI: 10.1111/apt.13804]

13 Saxena NK, Anania FA. Adipocytokines and hepatic fibrosis. *Trends Endocrinol Metab* 2015; 26: 153-161 [PMID: 25656826 DOI: 10.1016/j.tendo.2015.01.002]

14 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Aberra SF, Abraham JP, Abu-Rmeileh NM, Achocki T, Ailluhrainan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Gazzano NA, Ammar W, Anwar P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabbadkar KC, Dandona L, Davis A, Dayama A, Dharumaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hatefi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Ikiriso BT, Ikeda N, Islam F, Jahangir E, Jassal SK, Joe SH, Jeffreys M, Jonas JB, Kabagambe EK, Khaliﬁ SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Koku było Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayanan KM, Nelson EL, Neushoff ML, Nisar MI, Oktubo T, Oli SO, Pedroza A, Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384: 766-781 [PMID: 24880830 DOI: 10.1016/S0140-6736(14)60460-8]

15 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; 295: 1681-1687 [PMID: 16609090 DOI: 10.1001/jama.295.14.1681]

16 Bolukbas C, Bolukbas FF, Horoz M, Mazar C, Celik H, Erel O. Increased oxidative stress associated with the severity of the liver disease in various forms of hepatitis B virus infection. *BMJ Infect Dis* 2005; 5: 95 [PMID: 16262897 DOI: 10.1186/1471-2334-5-95]

17 Khalili M, Lombardo M, Chung RT, Terrault NA, Ghany MG, Kim WR, Lau D, Lisker-Melman M, Sanyal A, Lok AS; HBRN. Diabetes and prediabetes in patients with hepatitis B residing in North America. *Hepatology* 2015; 62: 1364-1374 [PMID: 26302728 DOI: 10.1002/hep.28110]

18 Huang YW, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT, Yang SS, Kao JH. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. *Clin Infect Dis* 2013; 57: 1695-1702 [PMID: 24051864 DOI: 10.1093/cid/cit603]

19 Hsiang JC, Gane EJ, Bai WW, Gerred SJ. Type 2 diabetes: a risk factor for liver mortality and complications in hepatitis B cirrhosis patients. *J Gastroenterol Hepatol* 2015; 30: 591-599 [PMID: 25250942 DOI: 10.1111/jgh.12790]

20 Chen CL, Yang HI, Wang WS, Liu CJ, Chen PJ, You SL, Wang LY, Sun CA, Lu SN, Chen DS, Chen CL. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008; 135: 111-121 [PMID: 18505600 DOI: 10.1053/j.gastro.2008.03.073]

21 Pang Y, Kartsonaki C, Turnbull I, Guo Y, Clarke R, Chen Y, Bragg F, Yang I, Bian Z, Millwood IY, Hsiao J, Han X, Zang Y, Chen J, Li L, Holmes MV, Chen Z. Diabetes, Plasma Glucose, and Incidence of Fatty Liver, Cirrhosis, and Liver Cancer: A Prospective Study of 0.5 Million People. *Hepatology* 2018; 68: 1308-1318 [PMID: 29734463 DOI: 10.1002/hep.30083]

22 Wong GL, Chan HL, Yu Z, Chan AW, Choi PC, Chim AM, Chan HY, Tse CJ, Wong VW. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B–a prospective cohort study with paired transient elastography examinations. *Aliment Pharmacol Ther* 2014; 39: 883-893 [PMID: 24612251 DOI: 10.1111/apt.12686]

23 Yu MW, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of Metabolic Risk Factors on Risk of Hepatocellular Carcinoma and Liver-Related Death in Men With Chronic Hepatitis B: A Large Cohort Study. *Gastroenterology* 2017; 153: 1006-1017.e5 [PMID: 28711626 DOI: 10.1053/j.gastro.2017.07.001]

24 Trotzer V. Viral hepatitis: The bumpy road to animal models for HBV infection. *Nat Rev Gastroenterol Hepatol* 2017; 14: 327-328 [PMID: 28400622 DOI: 10.1038/nrgastro.2017.44]

25 Spradling PR, Xing J, Rupp LB, Moorman AC, Gordon SC, Teshale ET, Lu M, Boscaino JA, Schmidt MA, Trinacty CM, Holmberg SD: Chronic Hepatitis Cohort Study Investigators. Distribution of disease phase, treatment prescription and severe liver disease among 1598 patients with chronic hepatitis B in the Chronic Hepatitis Cohort Study, 2006-2013. *Aliment Pharmacol Ther* 2016; 44: 1080-1089 [PMID: 27640985 DOI: 10.1111/apt.13802]

P- Reviewer: Raghow R, Schuurman HJ
S- Editor: Wang XJ L- Editor: Filipodia E- Editor: Huang Y
