

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2019 January 21; 25(3): 282-397



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*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, etc. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Report® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35<sup>th</sup> among 80 journals in gastroenterology and hepatology (quartile in category Q2).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: Yan Huang

Proofing Editorial Office Director: Ze-Mao Gong

**NAME OF JOURNAL***World Journal of Gastroenterology***ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Subrata Ghosh, Andrzej S Tarnawski

**EDITORIAL BOARD MEMBERS**<http://www.wjgnet.com/1007-9327/editorialboard.htm>**EDITORIAL OFFICE**

Ze-Mao Gong, Director

**PUBLICATION DATE**

January 21, 2019

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

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**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.

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**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

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### 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

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**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<sup>[1]</sup>. Current nucleos(t)ide analogues, when taken long-term, can effectively suppress viral replication, improve liver histology, and reduce liver-related complications<sup>[2]</sup>. 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<sup>[3]</sup>.

Metabolic parameters have been demonstrated to play a prominent role in the disease course of chronic hepatitis C virus infection<sup>[4]</sup>. 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<sup>[5]</sup>. 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<sup>[6]</sup>.

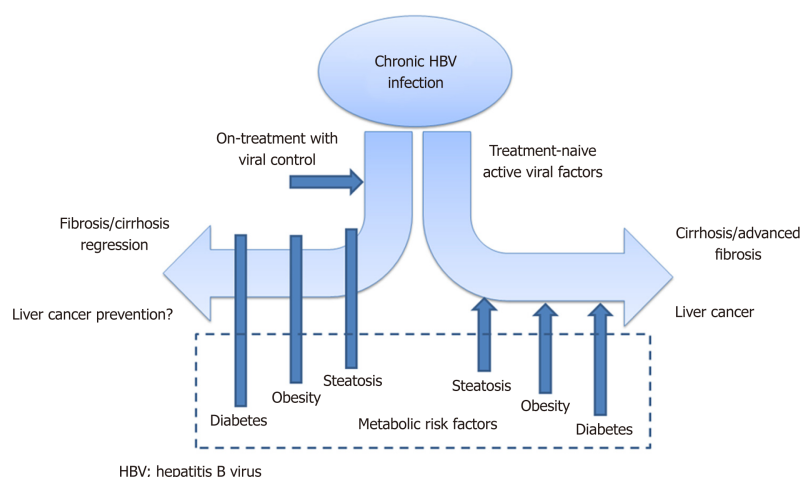
Paradoxically, there is evidence that co-existing hepatic steatosis may contribute to the chronic HBV disease process. A study employed the noninvasive quantification of steatosis using controlled attenuation parameter (commonly known as CAP) measurements, with standardized cut-off values used to categorize steatosis severity<sup>[7]</sup>. Severe steatosis (CAP  $\geq$  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<sup>[8]</sup>.

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%<sup>[9]</sup>, while more than a quarter of chronic HBV patients have concomitant NAFLD<sup>[10]</sup>.

## 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  $\geq$  30 kg/m<sup>2</sup>) 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<sup>[11]</sup>. 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 ( $\geq 25$  kg/m<sup>2</sup>) 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<sup>[2]</sup>. Results were also similar in another study involving Asian on-treatment patients with paired transient elastography over a median duration of 87.5 mo<sup>[12]</sup>.

Obesity is associated with adipokine dysregulation, including reduced adiponectin and increased leptin production, which leads to enhanced liver fibrogenesis<sup>[13]</sup>. However, it remains unclear whether this adipokine dysfunction has any mechanistic interaction with HBV. With the prevalence of obesity in HBV-endemic regions increasing<sup>[14]</sup>, 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<sup>[15]</sup>, which can be linked with the severity of liver disease in chronic HBV infection<sup>[16]</sup>. Diabetic chronic HBV patients have an increased chance of alanine aminotransferase elevation and liver damage compared to non-diabetic patients<sup>[17]</sup>. Diabetes also increases the risk of HBV-related cirrhotic decompensation<sup>[18]</sup> and liver-related mortality<sup>[19]</sup>.

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<sup>[20]</sup>. 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)<sup>[21]</sup>.

## 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<sup>[22]</sup>. 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)<sup>[23]</sup>.

## 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 unable to support the full HBV life cycle, restricting the study of host-viral interactions<sup>[24]</sup>.

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<sup>[8,12,23]</sup>, 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<sup>[25]</sup>, 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.

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