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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63926

Title: Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion

Reviewer's code: 05085789
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Senior Lecturer
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2021-02-06
Reviewer chosen by: AI Technique
Reviewer accepted review: 2021-02-07 02:09
Reviewer performed review: 2021-02-15 11:34
Review time: 8 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [Y] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

In the review article entitled "Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion", the authors outlined the relations between chronic hepatitis B (CHB) and hepatic steatosis and then insisted on the necessity of routine administering of concomitant NAFLD lifestyle management and disease screening to ensure better prognoses. While the findings of this study are of interest in a part, the current study is lacking the cutting edge to be accepted for publication. To overcome this limitation, authors are recommended to correct the manuscript according to the comments which are mentioned below. I am afraid to say, but I don't think that the present set of data are reliable enough to draw structural conclusions. [Comments] Concerning the Fig.1, authors need to show the PRISMA flow diagram showing how the studies included were selected for the meta-analysis. Authors also need to indicate the inclusion and exclusion criteria as well as the methods of data analysis. Without the information, the basic premise of this research will no longer be valid. In addition, each reference number and type of study design (e.g., retrospective or prospective) should be shown in the Fig.1.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63926

Title: Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion

Reviewer's code: 03765308
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Doctor, Professor
Reviewer's Country/Territory: Taiwan
Author's Country/Territory: China

Manuscript submission date: 2021-02-06
Reviewer chosen by: Man Liu
Reviewer accepted review: 2021-03-22 15:26
Reviewer performed review: 2021-03-27 00:54
Review time: 4 Days and 9 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

HBV and liver steatosis are two common etiologies of liver diseases. These two etiologies may be presented in the same patient. This review aims to understand the prevalence, out come and mechanism of these two diseases. The review is extensive and well organized. However, many literatures presented with controversy views. The readers may be unable to catch a clear concept. Comments: 1. In 1.1 prevalence and incidence of steatosis, the meta-analysis (13) and a study using proton-MRS showed a lower prevalence of NAFLD in CHB than in the control (14). These reports seem to be consistent. On the other hand, the incident of NAFLD showed controversy results. As a mater of fact, incidence of steatosis was significantly lower in CHB than in the control (40.6 vs 43.5 per 1000 person-years) in a Korea study (15). The reviewers compared the incidence of liver steatosis in an HBsAg carrier cohort from China (63.89 per 1000 person-years) with a meta-analysis from general population (overall 52.34 per 1000 person-years). They concluded that incidences of steatosis were similar. The later reference by Younossi ZM et al was not cited. This will make the reader think that these data were from the same study. In my point of view, different incidences from difference studies are difficult to be compared. Therefore, it will be more appropriated to conclude that the incidence of steatosis is lower in CHB than in the normal control. 2. In 1.2 the metabolic disfunction in CHB, the risk ratio of DM in HBsAg carriers were 1.23-1.90 (31-33). The risk of DM seems to be increased but difficult to be explained when there is a lower risk of steatosis in CHB. The reviewer mentioned 'In subgroups with older age or severe obesity, CHB patients no longer had higher risks of developing diabetes (32)'. This may be misleading. The true is after control of age, BMI and other factors, the risk of DM is higher in non-HBsAg carriers than in HBsAg carriers. In the reference 32, the risk of DM was not high in CHB after removed patients with liver

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cirrhosis. Liver is an important organ in glucose homeostasis. DM will occur mainly in CHB with decrease functional reserve of liver. 3. In 2.1 disease severity of CHB with NAFLD, there is no doubt that a patient with chronic hepatitis B and NASH will have a poor outcome. The key point of progression will be the inflammation activity. Inflammation induces by either HBV or steatosis will be difficult to differentiate without histology. In other aspect, some reports suggest steatosis may be a protestive factor for HBV (34,35,54). We should be aware that the inflammation induces by HBV are mainly before age 40. If HBV replication could be suppressed before age 40, the risk of fibrosis progression and/or HCC could be low. On the other hand, NASH is generally happened in older age with exception of lean NAFLD or MASH. In patients with NAFLD and low HBV replication phase, the outcome may be good and be able to clear HBsAg. 4. In the mechanism of interaction between HBV and steatosis, please mention T as the risk allele of rs1010023. Please add rs58542926 as the SNP of TM6SF2 you described. The T allele is a minor allele (7% globally). Therefore, may play a role of steatosis in minority.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63926

Title: Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion

Reviewer's code: 03734450
Position: Peer Reviewer
Academic degree: MD, MSc
Professional title: Associate Professor
Reviewer's Country/Territory: South Korea
Author's Country/Territory: China

Manuscript submission date: 2021-02-06
Reviewer chosen by: Man Liu
Reviewer accepted review: 2021-03-24 06:47
Reviewer performed review: 2021-03-27 05:33
Review time: 2 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This is a well-written article that comprehensively reviewed the relationship between HBV infection and hepatic steatosis. However, it would be better if some parts of the article are revised prior to publication. 1. Section 1.1 Explain in more detail for the readers on which clinical metabolic profiles, and in what extent, have been reported so far to be associated with the development of steatosis in CHB patients. 2. Sections 1.2 & 2.1 & 2.2 & 2.3 In these sections, conflicting evidences are suggested in a mixed-up manner which may lead to confusion of the readers. Please re-organize the contents for clarification. For example, in the order of pros – cons – the authors' overall stance in each section based on evidences to this date.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63926

Title: Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion

Reviewer's code: 04072104
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Chief Doctor, Doctor, Occupational Physician, Research Scientist
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2021-02-06

Reviewer chosen by: Man Liu

Reviewer accepted review: 2021-03-22 13:23

Reviewer performed review: 2021-03-27 13:38

Review time: 5 Days

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

It is an interesting a Review about "Chronic hepatitis B infection with concomitant hepatic steatosis: current evidence and opinion". My concern is determined in the following points. (1) In patients with NASH, liver fibrosis is the main determinant of mortality. In fibrosis development in NASH, triggers and consequences of hepatocytes-macrophage-hepatic stellate cell crosstalk is focused; pathways through which stressed and dead hepatocytes instigate the profibrogenic crosstalk with hepatic stellate cell and macrophages, including the reactivation of developmental pathways such as TAZ, Notch, and hedgehog; how clearance of dead cells in NASH via efferocytosis may affect inflammation and fibrogenesis. (2) Patients with CHB and liver steatosis should be closely monitored, irrespective of their viral load. (3) Proinflammatory Cytokines in NASH: Insulin resistance, in the setting of obesity, is characterized by low-grade inflammation that is associated with macrophage activation with release of proinflammatory cytokines including TNF-alpha and IL-6. TNF-alpha interacts with the NF-k-beta to promote apoptosis, inflammation, proliferation, and angiogenesis. IL-6 activates the signal STAT3, which promotes cell growth and differentiation. Above mentioned should be referred to.