RESPONSE TO THE REVIEWERS (Manuscript ID: 75004)

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled "Hepatogenous Diabetes: Knowledge, evidence, and skepticism" (manuscript no 75004:, minireviews). These are very helpful for revising and improving our manuscript.

In the revised manuscript we have incorporated all the changes as suggested by the reviewers. Revised portion are marked underlined in the paper. Moreover, the revised manuscript has been edited for proper English language by a profession body (certificate included). Our point-by-point responses to the issues raised in the peer review report are as follows:

1.Response to reviewers' comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: It is an interesting article discussing hepatogenous diabetes (HD), a direct complication of liver cirrhosis with a high prevalence rate and strongly linked to its pathophysiological alterations and disease severity. Nevertheless, HD is still not recognized as a distinct entity by scientific organizations including American Diabetes Association and American Association for the Study of Liver Disease. In addition to the current knowledge and existence evidences about HD, this article also reviewed its clinical and therapeutic implications. The manuscript is well written in English and directly relevant to the clinical application.

Authors' response: Thank you for your valuable comments.

There are only minor suggestions as follows.

1.In the Introduction section, --- The liver plays a key role in glucose homeostasis by regulating multiple glucose metabolism --- [2-4]. The reference 4 is an article regarding nuclear magnetic resonance studies, not appropriate for this sentence.

Authors' response: Thank you for your suggestion. Reference 4 has been replaced with another suitable reference in the revised manuscript.

2.In the paragraph of DEFINITION AND CHARACTERISTICS OF HD, the authors stated that --- HD patients frequently have normal fasting blood glucose (FBG) levels but abnormal oral glucose tolerance tests (OGTTs) ---. Since hemoglobin A1c (HbA1c) is a common laboratory test in diabetes patients, the authors should revise this sentence as "--- normal FBG and HbA1c levels but abnormal ---".

Authors' response: We have modified the sentence as per the suggestion (change underlined).

3.Reference 110 should be Dig Liver Dis 2021;53:445-51.

Authors' response: Thank you for pointing out this error, and sorry for the mistake. We have now made the necessary correction

4.In Table 1, the cited reports should be starting from 2002 (at the top) to 2021 (at the bottom).

Authors' response: Suggestion accepted and necessary changes have been made (Table 2 now).

5.In Table 3, there is no abbreviation for AFP.

Authors' response: In the revised manuscript, the full form of AFP has been mentioned (table 4 now).

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

A. This is a challenging review. Authors tried the differentiation between T2DM and HD in cirrhotic patients to clear the criteria of HD. OGTTs was the useful tool to differentiate between them. However, it was difficult to understand the differences.

Authors' response Thank you for your comments. We agree that distinguishing HD from T2DM is challenging. OGTT is a useful tool in this regard; however, such differentiation is not usually considered in the routine clinical practise. For HD to be diagnosed, DM must have occurred after the onset of cirrhosis. There are a number of soft indicators that can help distinguishing HD from T2DM. In the revised manuscript, we have added a table depicting characteristics of diabetes in patients with cirrhosis that favour a diagnosis of HD and help differentiating it from T2DM (Table1).

B. First, although, authors mentioned that cirrhotic patients with DM showed poor prognosis, were there any differences in prognosis between T2DM and HD in cirrhotic patients?

Authors' response: As stated in the beginning of the section "clinical impact of DM on LC", (underlined), most published studies have not stratified DM into HD and T2DM, hence the individual impact of HD cannot be ascertained as of now. The data on direct head-to-head comparisons of prognostic importance T2DM and HD in patients with liver cirrhosis is not available. However, because HD is a direct complication of liver cirrhosis, it is likely to have a greater negative impact on prognosis of liver cirrhosis than T2DM. In two prospective studies, HD patients had a poorer survival rate than non-diabetic cirrhosis patients (references 25 and 114 of manuscript).

C. Next, the etiology of HCC was more important. In other words, hepatic fibrosis including portal hypertension could be improved in viral cirrhotic patients achieving sustained viral response. However, the improvement was not recognized in patients with metabolic cirrhosis. How about prevalence of HD in patients with viral cirrhosis and with metabolic cirrhosis?

Authors' response: Overall, the prevalence of DM varies depending on the etiology of liver cirrhosis. In a recent meta-analysis, patients with NAFLD-cirrhosis had the highest pooled prevalence of DM (56.1%), while patients with HCV and HBV cirrhosis had 32.2% and 22.2%, respectively [Ref 21, *Diabetes* Metab Res Rev. 2019; **35**: e3157]. Due to multiple shared risk factors, the prevalence of DM is higher in metabolic cirrhosis than in viral cirrhosis. However, because HD In its true sense refers to diabetes induced by liver dysfunction regardless of the cause, the etiology of cirrhosis may have little bearing on the occurrence of HD. The incidence of HD was unaffected by the etiology of cirrhosis in a longitudinal study by Gentile S et al. [Ref 26, Diabetes Res Clin Pract. 1993; **22**: 37-44]. Another study found no independent link between the incidence of HD and the etiology of LC [Ref no 29, Dig Dis Sci. 2013; **58**: 3335-41]. We agree with the reviewer that in viral-induced liver cirrhosis, HD may be reversible due to the possibility of fibrosis and portal hypertension alleviation with successful antiviral treatment. (changes underlined, section: PREVALENCE OF HD IN LC**)**

D. In addition, how about the strategy of treatment for two types of cirrhotic patients?

Authors' response: There are no standardized guidelines for managing diabetes in cirrhosis patients. Currently, T2DM and HD are being treated in a similar manner. However, because the pathophysiology of T2DM and HD differs, the therapeutic approach may need to be adjusted. Several pathophysiological changes produced by cirrhosis, such as degree of hepatic dysfunction, large portosystemic shunt, sarcopenia, gut dysbiosis, and hyperammonemia, all of which have an indirect impact on HD, could influence treatment choices, including drug selection.

Because HD is a direct complication of LC and is associated with severity of cirrhosis, improving hepatic dysfunction and portal hypertension should be one of the important goals of HD treatment. Etiology-specific therapy (for HCV, hepatitis B, autoimmune hepatitis, etc.) and non-selective β-blocker to control portal hypertension may play a role in preventing, delaying, or attuning HD in LC patients. In a recent prospective study of 96 acute-on-chronic liver failure patients, 51 (53.1%) of whom had new-onset diabetes, most likely HD, the glycemic indices improved in one-third of patients following improvement of their liver function without taking anti-hyperglycemic medication [Hepatol Int. 2021 Oct;15(5):1093-1102]. (Underlined in Treatment section)

E. Minor; Semi-titles of in text were complicated; beta-cell dysfunction was one of the pancreatic dysfunctions?

Authors' response: Thank you for your suggestion. We have made suitable correction by including the paragraph of beta-cells dysfunction in the section on pancreatic dysfunction.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Authors' response: The revised manuscript has been edited for proper English language by a profession body and a high quality has been achieved (certificate included).

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This manuscript explored current information on hepatic-derived diabetes, including evidence for its existence and clinical significance. Please indicate whether there is a difference in prognosis between T2DM and HD in patients with cirrhosis, the prevalence of HD in patients with viral and metabolic cirrhosis, and treatment strategies for patients with two types of liver cirrhosis.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Authors' response: Thank you for your valuable comments. The revised manuscript has been edited for proper English language by a profession body and a high quality has been achieved.

Regarding the prognostic differences, We have stated in the beginning of the section "clinical impact of DM on LC", that most published studies have not stratified DM into HD and T2DM, hence the individual impact of HD cannot be ascertained as of now. However, because HD is a direct complication of liver cirrhosis, it is likely to have a greater negative impact on prognosis of liver cirrhosis than T2DM. In two prospective studies, HD patients had a poorer survival rate than non-diabetic cirrhosis patients (references 25 and 114 of manuscript).

Regarding the prevalence, the overall prevalence of DM is higher in metabolic cirrhosis than in viral cirrhosis (56.1% vs. 22-32%, Ref 21, *Diabetes* Metab Res Rev. 2019; **35**: e3157]. However, because HD In its true sense refers to diabetes induced by liver dysfunction regardless of the cause, the etiology of cirrhosis may have little bearing on the occurrence of HD. The incidence of HD was unaffected by the etiology of cirrhosis in a longitudinal study by Gentile S et al. [Ref 26, Diabetes Res Clin Pract. 1993; **22**: 37-44]. Another study found no independent link between the incidence of HD and the etiology of LC [Ref no 29, Dig Dis Sci. 2013; **58**: 3335-41].

Regarding treatment strategies, no standardized guidelines for managing diabetes in cirrhosis patients. Currently, T2DM and HD are being treated in a similar manner. However, because the pathophysiology of T2DM and HD differs, the therapeutic approach may need to be adjusted. Because HD is a direct complication of LC and is associated with severity of cirrhosis, improving hepatic dysfunction and portal hypertension should be one of the important goals of HD treatment. Etiology-specific therapy (for HCV, hepatitis B, autoimmune hepatitis, etc.) and non-selective β-blocker to control portal hypertension may play a role in preventing, delaying, or attuning HD in LC patients.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Hepatology.

Authors' response: Thank you for your acceptance of our paper for the esteemed journal – World Journal of Hepatology

Best regards,

Ramesh Kumar,

MD, DM, **Associate Professor, Head**,

Department of Gastroenterology, 4t floor, OPD Block,

All India Institute of Medical Sciences, Patna-801507, India.,

Email docrameshkr@gmail.com