April 14th, 2020

Re: Manuscript No. 54800

Dear Editor,

thank you for your letter of 13th April and the possibility of resubmitting our revised manuscript titled "Post-transplant diabetes mellitus and preexisting liver disease - a bidirectional relationship affecting treatment and management" for consideration for publication in the *World Journal of Gastroenterology*.

We have carefully considered the reviewers' comments, and have revised the manuscript accordingly. The changes are marked **in red** in the revised manuscript. Below are the answers to specific reviewers' comments.

Reviewer #1: ID 00000663

A well-detailed analysis of the intertwining relationship between diabetes and advanced liver disease in pre- and post-transplant patients. The authors dedicate most of their interest to NAFLD and post-NAFLD area, which is reasonable nowadays considering the importance and burden of disease. The references are generally up-to-date in a fast evolving area. I have only minor comments to increase interest and readability. Although NAFLD takes the stage, there is scarce consideration to problems with HCV, no mention of the problems related to HB virus (mainly in post-transplanted patients) or in other less common diseases (e.g., hemochromatosis). A few lines might be included to expand these areas.

> We agree with your comment, and we have expanded the discussion on other etiologies such as alcohol, hemochromatosis, HCV and HBV in the Section - Diabetes mellitus and Liver Cirrhosis, pages 8-10.

In particular, post-transplant weight gain remains a problem for most patients, and the reasons for it – and treatment, including psychological distress and post-survivor euphoria – might be more extensively dealt with.

> Thank you for this comment. We have added the part about the post-transplant weight gain according to your suggestion in the *NAFLD and liver transplantation* Section, pages 12-13.

There is no mention of the problems associated with pre-transplant bariatric surgery, an issue which might become crucial in next years, considering the role of bariatric surgery in curing and preventing diabetes.

> The issue of bariatric surgery has been additionally addressed in section "T2DM treatment in the context of NAFLD", paragraphs 4, 5 and 6.

The role of TZD in the management of liver disease should be extensively reconsidered (see and quote: Yen, Fu-Shun et al, Liver Int. 2020 Jan 21. doi: 10.1111/liv.14385.) •

According to your remark we have extensively addressed the role of thiazolidinediones and quoted suggested reference. Please see Section T2DM treatment in the context of NAFLD, pages 14, 15.

Figure. There is a lot of unused space and character is small. Consider redrawing

We have modified the Figure and hopefully improved it.

Reviewer #2: ID 00058696

1. There is no description of the methods used by the authors to obtain/collect/sort the information that they present herein.

This paper is narrative review therefore no methodology description is warranted. This is a critical review end overview of the published literature regarding topic in question. This has been inserted in the Introduction section, last paragraph.

2. Do the authors intend to describe only treatments that involve prescription medications in this minireview? If yes, then the Title should be changed and the authors could consider "affecting pharmacologic treatment" as the end of their Title.

We have also included an extensive section on the role of bariatric surgery in treatment and management of preexisting liver disease and PTDM as well as paragraph regarding importance of lifestyle changes according to your suggestions. Therefore we feel that the title of this mini review should stay as it is.

3. This manuscript is presently difficult to read because the authors have not summarized important concepts that are being discussed in either Tables or Figures.

According to the reviewer's suggestions we have revised the whole manuscript and hopefully made significant improvements in the text. We have added additional Table which simplifies proven and possible effects of the mentioned drugs, and we have modified the Figure that was present earlier.

4. The authors should spell out more terms rather than use non-standard abbreviations. LT for liver transplantation should not be abbreviated (it usually means long term). IR to a gastrointestinal physician refers to "Interventional Radiology", etc.

The abbreviations in question are commonly used in reviewed published literature and all abbreviations are clarified when mentioned in the manuscript for the first time.

5. Please use a spell check in your word processing program. (see last sentence in Abstract: "patophysiology" should be pathophysiology and "oxydative" should be oxidative.

This has been corrected according to your remark.

6. In "Non-alcoholic fatty liver disease (NAFLD)", paragraph 4 starting with "Obesity and insulin resistance": the authors state "it has been recognized that hepatic inflammation and fibrosis can exist without steatosis"; this sentence needs to be rewritten or clarified since every gastrointestinal physician knows that the authors could be referring to, for example, chronic Hepatitis C or chronic Hepatitis B.

This sentence has been clarified that it refers to NAFLD and the concept has been explained in more detail with additional reference for interested readers.

In this section, the authors provide no overview of the important information about treatment of NASH-induced cirrhosis in individuals with obesity by a joint Vertical Sleeve Gastrectomy-Liver Transplantation approach.

This particular issue of bariatric surgery has been addressed in section "T2DM treatment in the context of NAFLD" paragraphs 4, 5 and 6.

7. In "Diabetes mellitus and NAFLD – cardiovascular disease equivalents?", in paragraph 2, the authors discuss an "intimate relationship"; are the authors referring to obesity-dependent or obesity independent relationships?

This concept has been further explained, but more detailed discussion on this interesting topic is beyond the scope of this manuscript.

8. In "Diabetes mellitus and liver cirrhosis"; sentence 1: the usual considered sequence is inflammation, necrosis, and fibrogenesis. In paragraph 2, the authors use the abbreviation NAFL but do they mean NAFLD? In the last paragraph of this section, the authors discuss "death rates are higher in cirrhotic patients with DM". The authors should expand upon whether they are referring to controlled or to poorly controlled type 2 diabetes, since there is long-standing literature examining neutrophil function in the presence of chronic hyperglycemia.

We have corrected the sequence and the abbreviation. As you suggested we added the text regarding the quality of glucoregulation (both poorly and well controlled DM) and its effect on consequences of chronic liver disease with appropriate references.

9. In "T2DM treatment in the context of NAFLD, paragraph 2: "weight loosing effect" should be weight losing effect and "ramdomized" should be randomized. The authors make no mention of the potential for weight loss programs as potential therapy (physicians have additional options available other than prescription medications).

This issue has been addressed in section "T2DM treatment in the context of NAFLD" paragraph 2 according to your suggestion.

10. In"GLP-1RA in the treatment of NAFLD", paragraph 2, sentence 2: "achieving normalization of ALT"; this reference is from 2014. The more recent American College of Gastroenterology guidelines for "normal" levels of transaminases reduced the "normal" levels of ALT and so the authors should either consider the term reduction rather than "normalization" or provide information supporting declines in ALT levels to within the newer normal ALT range.

This has been corrected according to your suggestion, the term reduction was used instead normalization.

In paragraph 4, the authors state that "it shows superiority over liraglutide in terms of weight loss": the authors should either define the term "superiority", or let the reader know that they are actually referring to a difference in weight loss of 2 to 3 lbs. (which is unlikely to be of any clinical significance for gastroenterologists treating individuals with NASH).

Although it may be of no clinical consequence, the difference in body weight was statistically significant in PIONEER 4 between liraglutide sc and oral semaglutide. This was corrected according to your suggestion.

11. In "Post-transplant diabetes mellitus in LT patients", in paragraph 2 there is a very long and very complex sentence; it might be better understood if the authors place a comma between "cardiovascular mortality" and "this therapeutic option has its merits".

This has been corrected according to your suggestion.

In paragraph 4, the authors mention "are gastrointestinal (GI) [why is this abbreviation added here?] side effects"; authors please specify these GI side effects.

The GI abbreviation was deleted and GI side effects have been specified, nausea, vomiting, diarrhea

We corrected several typos and additionally revised manuscript for grammar and language.

In conclusion, we thank the reviewers for recognizing the presented mini-review as a good scientific effort, as well as for the useful and constructive comments, which made us think more critically about the presentation of our data. We hope that we have improved the consistency, clarity and interpretation of data in the revised manuscript and that the revised manuscript will meet the reviewers' requirements and be suitable for publication in the *World Journal of Gastroenterology*.

Thank you again for the privilege of submitting our work to *World Journal of Gastroenterology*.

Sincerely,

Anna Mrzljak, MD, PhD, FEBGH, FEBTM