Dear Editor and Reveiwers,

Please find enclosed the edited manuscript in Word format (file name: 8614-revision.doc).

Title: Potential Roles of Glucagon-like Peptide-1-based Therapies in Treating Non-alcoholic Fatty Liver Disease

Author: Ye Liu, Rui Wei, Tianpei Hong

Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of the reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

All the important revision has been highlighted with red in the manuscript.

Response to Referee 1 (NO. 02860590)

Q1. Although the authors have done an extensive discussion regarding clinical utility of the GLP-1-based therapies, the authors do not address the potential adverse effects of these new therapies. Can the authors please provide a paragraph regarding possible side effects of GLP-1 class of drugs? ? Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011 Jul;141(1):150-6. doi: 10.1053/j.gastro.2011.02.018. Epub 2011 Feb 18. PubMed PMID: 21334333. **A1**: As suggested, we have added the section "***Safety issues of GLP-1-based therapies***", which focuses on the safety of GLP-1-based agents, especially on their association with pancreatitis and cancer, which was discussed in the study mentioned by the referee.

Page 12, the last paragraph

Response to Referee 2 (NO. 02540407)

Q1. It would be impressive if the authors could have include couple of figures showing the functions and the mechanistic role of GLP-1 or its analogue/inhibitors in NAFLD or NASH or other diseases, which are relevant to NAFLD.

A1: We have added "Figure 1" to the revised version to illustrate the functions and potential mechanistic roles of GLP-1 and GLP-1 receptor agonists or DPP-4 inhibitors in NAFLD.

Page 18

Q2. I think the title could be modified.

A2: The title has been modified to "Potential Roles of Glucagon-like Peptide-1-based Therapies in Treating Non-alcoholic Fatty Liver Disease".

Q3. Author should also discuss the recent works done by Bernsmeier et al and Zhang et al (Plos One 2014& Liv Int 2013, respectively) into the manuscript.

A3: We have added a discussion of Bernsmeier's study at the beginning of the section "*GLP-1 levels and DPP-4 expression in NAFLD*" on page 7**.** Zhang's work was referenced and discussed in our initial manuscript in the following sections: "***Evidence from animal studies***" (page 11), "***Attenuation of insulin resistance in the liver by GLP-1-based therapies***" (page 14), "***Suppression of oxidative stress in the liver by GLP-1-based therapies***" (page 14) and "***Regulation of lipid metabolism-related gene expression in the liver by GLP-1-based therapies***" (page 15).

Q4. Discuss the role of GLP-1 and its inhibitor or promoter in the pathogenesis of obesity, NASH or fibrosis would give the clear picture.

A4: We have added a detailed discussion of the beneficial effect of GLP-1 and GLP-1-based agents on body weight in the 2nd paragraph of the Introduction. In fact, the role of GLP-1 in the pathogenesis or development of NAFLD and NASH has not been well established, and we believe that discussion of their relationship will be of interest. As we

reviewed in our paper, some studies have shown that the change in GLP-1 levels or GLP-1R expression on hepatocytes in NAFLD points to a link between GLP-1 signalling and the disease. Moreover, data from both preclinical and clinical studies suggest that NAFLD may benefit from GLP-1-based therapies, and promote the idea that GLP-1 or GLP-1-based therapies may play a role in the development or treatment of NAFLD.

Q5. Page No. 10, first paragraph, line 2&4 "wide type" Has to be changed as "wild-type"
A5: We have changed "wide type" to "wild-type" throughout.

Q6. Some English inadequacies need to be corrected.
A6: Our manuscript has been "polished" by a professional English language editing company, as recommended by the editors.

Response to Referee 3 (NO. 02860705)

Q1. pag.5 line 10 (As novel anti-diabetic treatment options, glucagon-like peptide-1 (GLP-1).....and pag. 5 line 12 GLP-1 is an incretin hormone secreted.....): which is the link between NAFLD and T2DM. Describe in detail. Describe better and in detail GLP-1, and active and inactive GLP1 its involvement and its mechanism.
A1: We describe in detail the involvement and mechanisms of active and inactive GLP-1 in the 2nd paragraph of the Introduction.

Page 6, Paragraph 2

Q2. Pag. 6 line 5 (For example, one important factor is elevated serum level of GLP-1 as a result of the changed .....): Explain better.
A2: We have expanded the explanation of elevated serum levels of GLP-1 after bariatric surgery in section "***Observations from bariatric surgery***".

Page 7

Q3. Pag. 6 last line (GLP-1 receptor (GLP-1R) could be detected in human liver biopsy....): Why are you talking about this receptor. What's known in letterautre about glp receptor

and nafld

A3: We discuss the GLP-1R because GLP-1 exerts its effect mainly through its receptor. Therefore, if GLP-1R could be detected in the liver, more specifically on hepatocytes, it raises the possibility that GLP-1 would exert a direct effect on hepatocytes via functional GLP-1R.

We also discuss the relationship of GLP-1R and NAFLD in the later part of the article (section "***POTENTIAL MECHANISMS OF GLP-1-BASED THERAPIES IN AMELIORATING NAFLD***", page 13).

Response to Referee 4 (NO. 02821572)

Q1. Introduction: line 4 of first paragraph: I suggest removing "However".

A1: We have removed "However".

Q2. Introduction: second paragraph, line 6, "proved"should be "proven"?

A2: We have replace "proved" with "proven".

Q3. Page 6, second paragraph: "Sarah et al": Please cite the last name of the author.

A3: We have replaced "Sarah et al" with "McDonald et al".

Q4. The author noticed that, in rat NAFLD model, GLP-1R expression is down-regulated (REF14). The author also noticed that NAFLD patients exhibited elevated GLP-1 expression (REF32). How would the author relate these two findings?

A4: The down-regulated GLP-1R expression in NAFLD implies the deficiency of GLP-1 signalling in the liver in the development of NAFLD. On the other hand, in the paediatric non-alcoholic fatty liver disease, the elevated GLP-1 expression in hepatic progenitor cells (not serum GLP-1 levels or elevated GLP-1R expression) could be considered a compensational mechanism of hepatocytes responding to the oxidative stress in the paediatric NAFLD subjects. Therefore, these findings are not conflicting.

Q5. When reviewing human studies, I wonder whether it is helpful/useful/possible to

discuss prospective placebo controlled trials separately from other types of studies (make subsections)?

A5: According to the published studies, only the Liraglutide Effect and Action in Diabetes (LEAD) program is composed of prospective placebo-controlled trials. We have rearranged our paper and discussed the LEAD study separately from other types of studies (see section "***Evidence from prospective placebo-controlled trials***").

Page 10

Q6. When reviewing human studies, I wonder whether it is helpful/useful/possible to discuss adult studies separately from pediatric studies (make subsections)? This is because adult NAFLD and pediatric NAFLD is substantially different in some aspects.

A6: We appreciate your recommendation concerning the discussion of paediatric NAFLD studies. However, we decided not to discuss paediatric NAFLD itself in this article. What we do discuss is the possibility that hepatic progenitor cells could express GLP-1 when NAFLD develops, which suggests a protective role of GLP-1 by inducing the resistance of hepatic progenitor cells to oxidative stress in the process of paediatric NAFLD. Therefore, we believe that inserting this discussion in the section of "***Suppression of oxidative stress in the liver by GLP-1-based therapies***" will be acceptable.

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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