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**Diabetes and fatty liver: involvement of incretin and its benefit for fatty liver management**

Wibawa IDN et al. Incretin on fatty liver disease

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We really appreciate for the valuable comments by all the reviewers. We have responded their comments and improved our manuscript according to their suggestions.

### **Reviewer 1**

I Dewa Nyoman Wibawa and collaborators present a comprehensive review on discussion the relationship between the incretin hormones and fatty liver disease related to metabolic factors, focusing on the mechanism and clinical effect of incretin hormones in improving fatty liver disease. The article needs to be revised as follows : 1. This review mainly focuses on non-alcoholic fatty liver disease caused by diabetes and obesity. Therefore, some general definitions of “fatty liver disease” in this review need

to be replaced by more appropriate professional terms (such as NAFLD). 2.The sentence “the two conditions” in the ABSTRACT needs to be specified. 3.In the INTRODUCTION, the description of the diagnosis of non-alcoholic fatty liver disease is excessive and can be replaced with an epidemiological description of non-alcoholic fatty liver disease. 4.Punctuation errors in the text need to be reasonably corrected, such as “? oxidative stress [2]” and “[22,23]”. 5.In the INTRODUCTION, the sentence “Incretin hormones influence glucose homeostasis and are involved with the pathophysiology of type 2 diabetes mellitus” repeats with the expression in the following: “Incretin hormones play significant roles in glucose homeostasis and the pathophysiology of type 2 diabetes mellitus”, it is more appropriate to replace or delete it. 6.The Figure and Table in the review need to be annotated in detail. 7.The expression of "adiposity hypertrophy" should be changed to "adipocyte hypertrophy". 8.The specific process described in the sentence "Further dysregulation causes the increase of free fatty acids." should be elaborated. 9.The sentence "Numerous studies with insulin treatment to control hyperglycemia to reach a near-normal value of glucose concentrations may improve the insulinotropic of GIP and GLP-1 in T2DM patients, indicating improvement of the incretin effects" is not clearly expressed. 10.The sentence "Even though the excretion of incretin is more or less normal in T2DM patients" is not clearly expressed. 11.In the section of DIABETES, INCRETIN HORMONE AND FATTY LIVER DISEASE, there are a lot of contents about the regulation of incretin hormones in diabetes, but there are too few descriptions about how incretin hormones can benefit fatty liver disease. 12.The CONCLUSION is too brief, which can be supplemented for pharmacological characteristics of incretin hormones, advantages and defects compared with other treatment modalities, current clinical research and mechanism research progress, research limitations and specific limitations, as well as suggestions for future research direction and practice through this review.

***Response:***

Thank you for your suggestion to enhance the quality of this manuscript. We have revised the manuscript according to the suggestions. We have responded to the suggestion with point-by-point response.

1. *This review mainly focuses on non-alcoholic fatty liver disease caused by diabetes and obesity. Therefore, some general definitions of “fatty liver disease” in this review need to be replaced by more appropriate professional terms (such as NAFLD).*

**Response:** Thank you for your suggestion. We have revised the manuscript according to your suggestion.

2. *The sentence “the two conditions” in the ABSTRACT needs to be specified.*

**Response:** Thank you for your suggestion. We have revised the manuscript according to your suggestion.

3. *In the INTRODUCTION, the description of the diagnosis of non-alcoholic fatty liver disease is excessive and can be replaced with an epidemiological description of non-alcoholic fatty liver disease.*

**Response:** Thank you for your suggestion. We have revised the manuscript according to your suggestion.

4. *Punctuation errors in the text need to be reasonably corrected, such as “? oxidative stress [2]” and “[22,23]”*

**Response:** Thank you. We have revised these punctuation errors.

5. *In the INTRODUCTION, the sentence “Incretin hormones influence glucose homeostasis and are involved with the pathophysiology of type 2 diabetes mellitus” repeats with the expression in the following: “Incretin hormones play significant roles in glucose homeostasis and the pathophysiology of type 2 diabetes mellitus”, it is more appropriate to replace or delete it.*

**Response:** Thank you for your suggestion. We decided to delete the statement of *“Incretin hormones play significant roles in glucose homeostasis and the pathophysiology of type 2 diabetes mellitus”*

6. *The Figure and Table in the review need to be annotated in detail*

**Response:** Thank you for your suggestion. We added more detailed annotation for each Figure.

7. *The expression of "adiposity hypertrophy" should be changed to "adipocyte hypertrophy"*

**Response:** Thank you for your suggestion. We have revised the manuscript according to your suggestion.

8. *The specific process described in the sentence "Further dysregulation causes the increase of free fatty acids." should be elaborated*

**Response:** Thank you for your suggestion. We have elaborated in more detail in the revised manuscript.

9. *The sentence "Numerous studies with insulin treatment to control hyperglycemia to reach a near-normal value of glucose concentrations may improve the insulinotropic of GIP and GLP-1 in T2DM patients, indicating improvement of the incretin effects" is not clearly expressed.*

**Response:** Thank you. We have replaced the sentence with *“Numerous studies with insulin treatment to control hyperglycemia to reach a near-normal value of glucose concentrations have been done. Insulin treatment may improve the insulinotropic of GIP and GLP-1 in T2DM patients, therefore leads to improvement of the incretin effects”* to clearly expressed the meaning of the sentence.

10. *The sentence "Even though the excretion of incretin is more or less normal in T2DM patients" is not clearly expressed.*

**Response:** Thank you. We have replaced the sentence with “*Even though the excretion of incretin is approximately normal in T2DM patients*”.

11. *In the section of DIABETES, INCRETIN HORMONE AND FATTY LIVER DISEASE, there are a lot of contents about the regulation of incretin hormones in diabetes, but there are too few descriptions about how incretin hormones can benefit fatty liver disease.*

**Response:** Thank you for your suggestion. We have added additional paragraph to describe how incretin hormones benefit NAFLD patients. However, the evidence-based aspect described more detailed in the next section of CLINICAL ASPECT OF GLP-1 IN FATTY LIVER DISEASE.

12. *The CONCLUSION is too brief, which can be supplemented for pharmacological characteristics of incretin hormones, advantages and defects compared with other treatment modalities, current clinical research and mechanism research progress, research limitations and specific limitations, as well as suggestions for future research direction and practice through this review.*

**Response:** Thank you for your suggestion. We have revised the conclusion in the revised manuscript.

## **Reviewer 2**

The following paragraphs may be added as separate sub headings and latest information to be please provided. 1. Incretin and HbA1c as a measure of good, fair and poor glycemic control 2. Comparison of incretin status in response to oral and parenteral glucose infusion 3. Incretin and Insulin sensitivity with special reference to the various indices such as HOMA Beta, QUICKI etc. 4. Incretin and Insulin resistance 5.

Incretin and liver enzymes 6. Dual Incretin receptor agonists that target GLP 1 and GIP  
7. Incretin based therapy especially under conditions such as Metformin failure

***Response:***

Thank you for your suggestion to enhance the quality of this manuscript. We have revised the manuscript according to the suggestions. We provide those information's as new paragraphs in their respective appropriate location rather than as separate sub-section.

**Reviewer 3**

The manuscript is overall well written. I recommend acceptance after minor language revision.

***Response:***

Thank you for your review.