June 10th, 2022
Editorial Office
World Journal of Diabetes
Manuscript NO: 77417

Dear Editors-in-Chief,

Thank you very much for your decision letter and suggestions regarding our manuscript entitled “Role of insulin in pancreatic microcirculatory oxygen profile and bioenergetics” (NO: 77417). We also thank the reviewers for the constructive, positive comments and helpful suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red font in the revised manuscript. In addition, point-by-point responses to the comments are attached below this letter.

If you have any further questions, please do not hesitate to let us know. Look forward to hearing from you.

With best regards,

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Response to the reviewers' comments on scientific quality:

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: In the present manuscript entitled "Role of insulin in pancreatic microcirculatory oxygen profile and bioenergetics" the authors investigated how insulin administration could improve integrated pancreatic microcirculatory oxygen profile and bioenergetics and found that glucotoxicity induced deterioration of pancreatic microcirculatory oxygen profile and bioenergetics is restored by insulin. This is an interesting study, and most of the methodology used is well described and the findings can offer considerable contribution in the field.
Response: We warmly thank you for your positive comments on our manuscript.

Nevertheless, I have few concerns with the manuscript in its current form:
1.there are some typo mistakes through the manuscript. Please read and correct them
Response: Thank you for your careful review. We apologize for these language errors. A further language polishing has been performed by *American Journal Experts* (AJE) recommended by the editorial office of *the World Journal of Diabetes* to ensure the typo, grammatical, syntactical, formatting, and other related mistakes are resolved. Thank you for your help.

2. The number of mice per group (n=3) is very small for a powerful statistics.
Response: Thank you for your comment. Although the number of mice per group is three when we detect the integrated pancreatic microcirculatory oxygen profile including hemoglobin oxygen saturation (SO_2), the relative amount of hemoglobin (rHb), and partial pressure of oxygen (PO_2). These parameters were measured at three random sites of the pancreas in each mouse. That is, in this study, data from 9 independent detections were collected to determine a microcirculatory oxygen parameter. We have supplemented the information in the MATERIALS AND METHODS section. Thank you for your help.

3. the amount of insulin administrated in both in vivo and in vitro models should be referenced.
Response: Thank you for your critical comments. *In vivo*, to maintain the blood glucose of the diabetic mice within the normal range, 1.5 IU/day of insulin was injected s.c. *In vitro*, the endothelial cells were treated with high glucose (25 mmol/L) plus 10^{-8} mol/L insulin for 24 h. These doses of insulin were chosen according to our previous experiments. In the revised manuscript, we added a reference on this issue according to your suggestion (Ref. 10). Thank you for your help.

Again, on behalf of all authors, I want to thank you for the helpful comments and suggestions. These comments and suggestions indeed dramatically improve our present work. If you have more queries or any comments, please feel free to let us know. Thank you so much for your help.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: This manuscript is interesting to explain the mechanism of deleterious effect of diabetes in an animal model and restauration of function for insulin. Results are relevant so, some issues need to be clearer. Since the sample size is small (three animals per group), which was the efficiency of STZ to induce diabetes at that concentration? There was animal replacement?
Response: Thank you for your professional comments. The efficiency of STZ to induce type 1 diabetic mouse model is 100% in the current experiences by daily i.p. injection of a small dose of streptozotocin for 5 consecutive days. Furthermore, in our previous observation, daily i.p. administration of STZ for 5 consecutive days at a concentration of 40 mg/kg was sufficient to induce diabetes in 90 % ~ 100 % of male mice but only 30 % ~ 35 % of female mice, which may be related with estrogenic hormone. Additionally, in the current study, there was no animal replacement. We apologize for this confusion, and we have included this information in the RESULTS section. Thank you for your help.

Which are advantages of this animal model of diabetes induction respecting others?
Response: Thank you for your critical comment. Currently, multiple administration of low-dose streptozotocin (STZ) is a well-established practice and a cost-effective, time-saving, convenient platform for the studies of the pathogenesis of diabetes. This model has two major advantages: (1) the STZ-induced type 1 diabetic model close resemblance to human T1DM with chronic pancreatic islet inflammation, insulitis, and insulin deficiency, and (2) STZ recognizes the GLUT2 receptor that is abundant in β cell plasma membranes. β cell is a specific target of STZ, rather than islet microvascular endothelial cells. Therefore, STZ-involved type 1 diabetic animal models have been useful in elucidating the mechanisms of diabetic microvascular endothelial pathogenesis. We have supplemented the advantages and reasons that we select the STZ-induced type 1 diabetic model. Please see the DISCUSSION section.

Which were the main limitations of this study?

Response: Thank you for your professional comment. There are several limitations in this study. First, the sample size of mice in each group was limited. Although pancreatic microcirculatory oxygen profile was measured at three random sites of the pancreas in each mouse, and a total of 9 independent detections were collected to determine a microcirculatory oxygen parameter, a large sample size is preferred to ensure the data are representative. Second, in an interdependent functional relationship with β cells, IMECs are involved not only in the delivery of oxygen, but affect adult β cell function and promote β cell proliferation via vasoactive substances. However, the phenotypic and functional crosstalk between IMECs and islet β cells are not involved in our study. We have supplemented a limitation paragraph in the Discussion section. Thank you for your help.

Again, on behalf of all authors, I want to thank you for the helpful suggestions. These comments indeed dramatically improve our present work. If you have more queries or any comments, please feel free to let us know. Thank you so much for your help.

Reviewer #3:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (High priority)

Specific Comments to Authors: very nice
Response: We warmly thank you for your positive comments on our manuscript. A further language polishing has been performed to improve the language quality of our manuscript. Thank you for your help.

Response to the editorial office's comments:

(1) Science editor:

The manuscript is of interest and the study is well designed. However, results are limited by the low number of animals per group. Strength and limitations of the study should be clearly reported. The English language should be revised throughout the manuscript.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)
Response: Thank you for your professional and helpful comments. Although the number of mice per group is three when we detect the integrated pancreatic microcirculatory oxygen profile including hemoglobin oxygen saturation (SO_2), the relative amount of hemoglobin (rHb), and partial pressure of

oxygen (PO_2). These parameters were measured at three random sites of the pancreas in each mouse. That is, in this study, data from 9 independent detections were collected to determine a microcirculatory oxygen parameter. We have supplemented this information in the MATERIALS AND METHODS section. Furthermore, we have supplemented some descriptions about the strength and limitations of the current manuscript in the Discussion section. Meanwhile, to improve the language quality of our manuscript, further language polishing has been performed by *American Journal Experts* (AJE) company according to your suggestion. Again, thank you for your help.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: Thank you for your careful review. We have checked the presentation of figures and reorganized the figures in a decomposable PowerPoint file. The figures are all original and we have added the copyright information according to your suggestion.

Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitation analysis.com/.

Response: Thank you for your suggestions. This citation analysis database is absolutely an intelligent and convenient tool to further improve the content of our manuscript. We have searched the results from the keywords including "Diabetes mellitus", "Glucotoxicity", "Endothelial cells", "Microcirculation", "Mitochondria", and "Bioenergetics". According to this important information, we have updated two references (Refs. 7, 8) in the INTRODUCTION section.

Again, on behalf of all authors, I want to thank you for the suggestions and corrections. These comments indeed dramatically improve our present work. If you have more queries or any comments, please feel free to let us know. Thank you so much for your help.