Editor of *World Journal of Diabetes*

Apr. 15th, 2021

Dear Editor,

We submit our revised manuscript titled "**The Role of Interferons in Diabetic Retinopathy**" to be considered for publication in *World Journal of Diabetes.* We thank the reviewer for the comments, and we have incorporated the suggestions in the revised manuscript.

We have corrected all the details that the reviewer pointed out. The changes are presented in yellow highlights. We believe that the revised manuscript has become more suitable for publication in your esteemed journal.

We look forward to your response, and please contact us if you would need anything further to make your decision.

Sincerely yours,

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The authors thank the reviewer for constructive comments and suggestions. We have revised the manuscript according to the comments. We address the reviewer’s comments in a point-by-point fashion and the specific changes have been highlighted in yellow in the manuscript.

Reviewer #1

1. Which would be the advantages of IFN as a biomarker? Compared to blood glucose levels and glycosylated hemoglobin.

Answer: Thanks for the suggestion. We really appreciate these important questions to be asked. In the review, we believe that IFN-γ may be a potential candidate biomarker of DR and greatly contribute to diagnosis, treatment, and prognosis. Compared with blood glucose and hemoglobin, IFN-γ has the advantage of being less susceptible to dietary changes and better reflecting inflammation of the eye, because IFN-γ is more stable and positive correlated with inflammatory cytokines, such as IL-1β and IL-3. We have added the necessary part in the revised manuscript (page 8, line 25 to line 29; page 13, line 29 to page 14, line 3 in the auto-edited manuscript file. page 14, line 28 to page 15, line 3 in the manuscript file).

2. When IFN should be determined to be considered effective for treatment. What about the procedures, and their levels?

Answer: Thanks for the suggestion. There are few cases of clinical use of IFN-α 2a in the treatment of DR, so criterion for when and how to implement and evaluate the therapeutic effect of IFN-α 2a is not unified now, which needs further exploration. Based on clinical data, the clinical effect of IFN-α 2a was only observed in patients after PRP and those with active neovascularization but not meet the criteria of PRP treatment. Meanwhile, clinicians should choose appropriate intervals to review the progress of the disease, such as glucose metabolism index, vision, visual field, neovascularization and fundus examination. We have included more information about IFNs in the treatment of DR in the introduction part of the revised manuscript (page 11, line 29 to page 12, line 14; page 13, line 3 to line 5 in the auto-edited manuscript file. page 12, line 19 to page 13, line 6; page 13, line 24 to line 27 in the manuscript file).

3. In the review, would be important to show a table indicating the normal IFN levels and their changes during retinopathy. How changes in IFN are related to glucose levels in diabetic situation?

Answer: Thanks for the suggestion. With the progression of diabetes, the expression of IFN-γ increases, and it is closely related to the blood glucose control of patients. IFN-α can be detected in aqueous humor samples of people without diabetes, but with the progress of diabetes, the concentration of IFN-α presents a gradual downward trend, and even rarely detected in DR stage. We have added a table and more information to show the changes of IFNs concentration as the disease

progresses in the revised manuscript (Table 2 in the table file. page 40, Table 2 in the manuscript file).

We would like to thank the Editor and Reviewer again for their valuable comments. We believe that the revised manuscript is now suitable for publication in *World Journal of Diabetes.*