

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Exenatide once weekly combined with metformin reduced glycemic variability in type 2 diabetes by using flash glucose monitoring system" (ID: 57884). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope to meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

**Reviewer #1:**

Thanks for all your feedback and suggestions. We will carefully incorporate them into our paper.

1. The reviewer's comment: This clinical trial is actually a prospective, interventional study that can either be described as a case-crossover study or a pre-post study. The authors' designation and description need to be changed.

Response: It is really true as reviewer suggested that this clinical trial can be described as a pre-post study, which I have written in the first sentence of the materials and methods section (Line 184 in Page 8)

2. The reviewer's comment: The authors need to review all of their statistics. Using data from Table 4 with a standard on-line paired t-test calculator, non-significant p values are the result of the ad hoc analysis.

Response: Thank you for your valuable advice. We have recalculated and analyzed our data and found that the data and statistical results are correct. We are willing to provide the original data for further verification if necessary

3. The reviewer's comment: No *P* values are presented in the Abstract and the Abstract should be acceptable for evaluation without requiring a complete analysis of the entire manuscript.

Response: We are very sorry for our negligence of *P* value in the abstract. Following your advice, the *P* value has been added to the corresponding location (Line 102,104,109,114 and 116 in Page 5). At the same time, we simplify the research objectives and methods in the abstract, delete some meaningless results and conclusions, and merge some data in the results section to describe, so that the abstract can be evaluated without a complete analysis of the entire manuscript.

4. The reviewer's comment: The Abstract is too long and should be shortened.

Response: Thank you for your suggestion. We have cut out some of the inessential content and kept the important conclusions so that the abstract is both concise and quick for the reader to understand.

5. The reviewer's comment: The authors use abbreviations in a manner that makes it difficult to read their manuscript. There is an undefined abbreviation in the first line of their Abstract. There are too many abbreviations in the Results section. Undefined abbreviations are used in Figure 1, Table 1, and Table 2.

Response: Thank you for your comments, which have given us a better understanding of the use of abbreviations in the manuscript. First, I have reviewed all the abbreviations in the manuscript again and defined the abbreviations where they first appeared. The words or phrases, which appeared three times or more in the abstract or text, were defined as abbreviations. Secondly, I have deleted some abbreviations in the RESULT section, such as PT1 and eHbA1c, but I still keep the abbreviations of GV parameters. Because, it is the main evaluation parameter of this study, which occurs frequently; and on the other hand, the phrase length is relatively long, which is not easy for readers to read quickly. In order to make it easier for readers to read, I have added abbreviations section and sorted them in alphabetical order. Finally, I have defined the abbreviations in Figure 1, Table 1, and Table 2.

6. The reviewer's comment: Did the authors seek the assistance of an English consultant? There are awkward sentence structures. For examples: line 3 abstract: "low hypoglycemia incidence"; hypoglycemia is a noun as is incidence; it should either read low incidence of hypoglycemia or low hypoglycemic incidence. In the Introduction: "with the same HbA1c" consider "with similar or identical HbA1C results"; "which is a reliable" consider "because it is a more reliable"; "Besides, the safety" consider "In addition, the safety"; "In this study, we observed the" consider "As the aims of this study, the clinical and therapeutic effect of combined EXQW and metformin treatment in type 2 diabetes patients are evaluated by using dynamic glucose monitoring and metabolic indicators".

Response: The manuscript has been edited and polished by a professional English editing organization. We are so sorry for some grammatical errors in the manuscript. The sentences mentioned above have been corrected and marked in red (Line 140, 143 and 159 in Page 7, Line 178 in Page 8). In addition, we change the indispensable to indispensable in introduction section of third line (Line 138 in Page 7); In materials and methods, we change the approval number is K007 Ethics [2018] to (2018K007) (Line 187 in Page 8). In the endpoint section, we switch the order HOMA- $\beta$  and HOMA-IR to correspond to the islets function and insulin resistance described earlier (Line 245 in Page 10). Other modifications have been highlighted in red.

7. The reviewer's comment: The sentence in the Introduction that starts with "A recent study has revealed that exenatide twice daily" should be in the Discussion and should be followed by a sentence that states "This present study has extended this prior research by demonstrating that ...".

Response: we appreciate the reviewer's positive and constructive comments and suggestions. The above mentioned content has been added in the third line of the Discussion section (Line 350-354 in Page 14), as follows: A recent study has revealed that exenatide twice daily and metformin could jointly improve GV profile. This present study has extended this prior research by demonstrating that the combination of EXQW and metformin could significantly improve GV and blood glucose control. Additionally, the therapeutic effects on weight loss, waist circumference reduction, and improvement of islet function were also evident.

8. The reviewer's comment: The paragraph in the Introduction that starts with "Flash glucose monitoring system" should be moved in the Introduction to before the authors'

#### hypothesis.

Response: We have made correction according to the reviewer's comments (Line 148-154 in Page 7). We have moved the paragraph that starts with "Flash glucose monitoring system (FGMS)" to the second paragraph of the introduction, and introduced FGMS after the introduction of glucose variability (GV), which is more damaging to tissues and blood vessels compared to persistent hyperglycemia.

9. The reviewer's comment: In Material and Methods Endpoint, there should be a reference provided for assessment of pancreatic islets function and insulin resistance. In Material and Methods FGM system Data, FGM should not be abbreviated (abbreviations should not be used in a Section Header) and the authors do not state in this section whether the "parameters for blood glucose control" were determined using a statistical package.

Response: For the assessment of pancreatic islets function and insulin resistance in Materials and Methods Endpoint, we have provided a reference (reference 8). Abbreviations suggested by reviewer should not be used in a section header has been corrected (Line 249 in Page 11). In the results section, change the GV alterations to Glycemic variability alterations (Line 311 in Page 13). The parameters of GV and blood glucose control were obtained by SigmaPlot 12.5 version for Windows and SPSS version 23.0 software, except that some of them were provided by AGP. See Materials and Methods Flash glucose monitoring system data (Line 274-277 in Page 11).

10. The reviewer's comment: In the Results section, the authors provide mean values but need to add standard deviations.

Response: Thank you very much for your suggestion. The mean values and standard deviations of the Results section have been added and shown in red (Line 341 and 342 in Page 14).

11. The reviewer's comment: The references need to be carefully completed. Several are now incomplete and many are not in proper format.

Response: Considering the Reviewer's suggestion, we went through the guidelines for editing original article and carefully revised them one by one according to the format and requirements of the references mentioned.

Special thanks to you for your insightful comments.

#### Reviewer #2:

We thank the reviewers for their careful consideration. We greatly appreciate the positive comments and address major concerns below.

1. The reviewer's comment: Appropriate captions and legends should be provided in tables and figures. In Figure 2, what the vertical bar represents?

Response: Thanks for your comments, we have provided appropriate captions and legends in figures and tables. In Figure 2, the vertical bar represents a standard error.

2. The reviewer's comment: The patients' characteristics is poorly written in Table 1. Age and sex are necessary data, which should be described in the Abstract. Data of, for instance, body mass index, smoking, pre-existing diseases, and complications are also

informative.

Response: I'm so sorry that the characteristics information of the patient in the manuscript is incomplete. We gladly accept the reviewer's opinion to describe age and gender in the abstract (Line 99 in Page 5). In addition, we have rearranged the table for other necessary basic information, including age, body mass index, smoking, pre-existing diseases, complications, etc., as shown in Table 1.

3. The reviewer's comment: **During the treatment with EXQW and metformin, how did the authors advise to diet and physical activity?**

Response: It is recommended that all subjects have meals at 8:00, 13:00 and 18:00 each day. According to the Dietary Guidelines for Type 2 diabetes in China and Guidelines for the prevention and control of type 2 diabetes in China, patients were instructed to eat 50%-65% carbohydrate, 20%-30% fat and 15%-20% protein every day, and they were given 150min of moderate-intensity aerobic exercise every week (Line 219-225 in Page 10).

Thanks for the helpful comments!

### **Reviewer #3:**

1.The reviewer's comment: **Relatively small number of patients**

Response: Thank you for the feedback and suggestions. The population of diabetic patients was large, but the patients included in this study were treated with oral metformin only, others who were taking other oral hypoglycemic agents or insulin were not qualified to participate this study. In addition, flash glucose monitoring system devices were relatively expensive for the general public, so the number of participants was limited. Of course, it cannot be denied that the relatively small number of subjects is one of limitations of this study, so further researches with large sample are promising.

We thank all the reviewers for helpful comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper and the manuscript with track changes was uploaded in this revision.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Yunfeng Liu

First Hospital of Shanxi Medical University, China.