

Dear Editors and Reviewers:

Thank you for your careful review and insightful comments concerning our manuscript entitled “Continuous glucose monitoring defined Time-in-Range is associated with Sudomotor dysfunction in Type 2 Diabetes.” (58170- World Journal of Diabetes). We have carefully revised the manuscript according to the suggestions and provided detailed responses to the reviewers here. Revised parts are marked with tracked changes in the revised manuscript.

Response to Editors

Question 1: Scientific quality: Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report.

Answer 1: Thank you for your constructive comments. Based on the peer review report, we have made a point-by-point response to the issues raised in the peer review report.

Question 2: Language quality: Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript’s language will meet our direct publishing needs.

Answer 2: Thank you for your suggestion. The paper has been edited by Pu Zang who studied at the University of Washington. The revised parts include grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability.

Question 3: Special requirements for figures: Figures must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, *etc.*). The requirements for the figures and figure legends include: (A) All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes; (B) For line drawings that were automatically generated with software, please provide the labels/values of the ordinate and abscissa in text boxes; (C) Please prepare and arrange the figures using PowerPoint to ensure that all graphs or text portions can be reprocessed by the editor; and (D) In consideration of color-blind readers, please avoid using red and green for contrast in vector graphics or images.

Answer 3: Thank you for your advice. We have re-uploaded Figure 1 as required.

Question 4: Special requirements for tables: Tables must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, *etc.*). Please verify that the tables are referred to in the text by their respective Roman numerals and that the numbering order is correct, and format the tables. Please verify that there are no missing or multiple spaces in the text and tables, e.g. before or after parentheses, between words, or before or after symbols like +, ×, ±, <, >, ≥, and ≤. Please verify that special words or letters in the text and tables are correct, e.g. P (uppercase), n (lowercase), via, vs (lowercase, no punctuation), in vivo, in vitro, and et al (no punctuation) are italicized.

Answer 4: Thank you for your advice. Firstly, we have made sure that Tables are presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3.) And the tables are referred to in the text by their respective Roman numerals and that the numbering order and format of tables is correct. Secondly, there are no missing or multiple spaces in the text and tables, e.g. before or after parentheses, between words, or before or after symbols like +, ×, ±, <, >, ≥, and ≤. Finally, special words or letters in the text and tables are correct, e.g. P (uppercase), p (lowercase), *via*, *vs* (lowercase, no punctuation), *in vivo*, *in vitro*, and *et al* (no punctuation) are italicized.

Question 5: Special requirements for references: Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. NOTE: The PMID is required, and NOT the PMCID; the PMID number can be found at <https://pubmed.ncbi.nlm.nih.gov>. (Please begin with PMID:) The DOI number can be found at <http://www.crossref.org/SimpleTextQuery/>. (Please begin with DOI: 10.**).

Please verify that the references are cited by Arabic numerals in square brackets and superscripted in the text, and that the numbering order is correct. There should be no space between the bracket and the preceding word or the following punctuation. When references in the text and tables are cited with author name, it is necessary to manually verify that the name is consistent with the first author's family (sur)name in the corresponding reference list, e.g. Wang et al[27], Vanhoos et al[53].

Answer 5: Thank you for your suggestion. We have modified the format of the references as required.

Question 6: Special requirements for Article Highlights: If your manuscript is an original study (basic study or clinical study), meta-analysis, or systemic review, the “Article Highlights” section should be provided. Detailed writing requirements for “Article Highlights” can be found in the Guidelines and Requirements for Manuscript Revision.

Answer 6: Thank you for your comment. We have added the “Article Highlights” section in our paper. The added section is marked in red.

Question 7: Ethical documents: Please double check the accuracy of all ethical documents and verify the completeness of the documents according to the type of manuscript.

Answer 7: Thank you for your advice. On the basis of your advice, we have checked the accuracy of all ethical documents, verified the completeness of the documents according to the type of manuscript, and re-uploaded these documents via the F6Publishing system.

Question 8: Approved grant application form(s) or funding agency copy of any approval document(s): If your manuscript has supportive foundations, the approved grant application form(s) or funding agency copy of any approval document(s) must be provided.

Answer 8: Thank you for your advice. We have uploaded funding agency copy of approval documents via the F6Publishing system.

Response to Science Editor:

Question 1: Some syntax/s spelling errors need to be corrected. The questions raised by the reviewers should be answered.

Answer 1: Thank you for your advice. We have revised syntax/s spelling errors in our paper. And we have answered all of the questions raised by the reviewers.

Question 2: The Institutional Review Board Approval Form is not qualified.

Answer 2: Thank you for your advice. We have uploaded the Institutional Review Board Approval Form via the F6Publishing system.

Question 3: The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Answer 3: Thank you for your advice. We have uploaded funding agency copy of approval documents via the F6Publishing system.

Question 4: The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Answer 4: Thank you for your advice. We have re-uploaded Figure 1 as required.

Question 5: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Answer 5: Thank you for your comment. We have added the “Article Highlights” section in our paper. The added section is marked in red.

Response to Editorial Office Director:

Question 1: I have checked the comments written by the science editor. There are some issues should be addressed. This is a retrospective study, unmeasured bias cannot be ruled out. There was no priory hypothesis or sample size calculations provided.

Answer 1: We definitely agree with your suggestion. According to the advice, we clearly addressed these weaknesses in last paragraph of discussion. The details are as follows: “Nevertheless, our study had some limitations. First of all, all subjects in this study underwent 3 days of CGM, therefore, the results of this study may not be generalizable. Secondly, the study was cross-sectionally designed, thus it is difficult to observe the relationship between 5-10 years of A1c and sudomotor functions longitudinally. Thirdly, this is a retrospective study and hospital-based study therefore, unmeasured bias cannot be ruled out. Therefore, based on these limitations, carrying out large-sample, multi-center research is something we are about to put on the agenda.” And in the future research, we will pay more attention to the calculation of the sample size.

Response to Company Editor-in-Chief:

Question 1: 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, and the manuscript is conditionally accepted with major revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors.

Before final acceptance, the authors need to meet publishing requirement by submitting correct documents which listed by the editors. Re-Review: Required.

Answer 1: Thank you for your comment. We have submitted correct documents via the F6Publishing system.

Response to Reviewer 1#

Thank you for your constructive comments, the following is my point-by-point responses.

Question 1: As stated above, international consensus recommends use of at least 2 weeks of CGM data for research and clinical purpose as 2 weeks correlates well with A1c. Use of 72 hours of CGM data is too short duration and I am not sure that will convey meaningful results.

Answer 1: Thank you for your comment. According to the international consensus, the ideal time for CGM is 2 weeks ^[1]. And 12-15 days of CGM may be needed to optimally evaluate glycemic control ^[2]. However, based on the research of others and due to the limitation of hospitalization time^[3, 4], we used the 3 days data for the preliminary analysis. So according to your valuable advice, we have written this weakness very clearly in our paper. The details are as follows: “All subjects in this study underwent 3 days of CGM, therefore, results of this study may not be generalizable” So in future studies, we will focus on exploring the relationship between long-term CGM wearing time and diabetic complications.

[1] Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care*, 2017,40:1631-1640

[2] Riddlesworth T D, Beck R W, Gal R L, et al. Optimal Sampling Duration for Continuous Glucose Monitoring to Determine Long-Term Glycemic Control. *Diabetes Technol Ther*, 2018,20:314-316

[3] Lu J, Ma X, Zhou J, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care*, 2018,41:2370-2376

[4] Lu J, Ma X, Shen Y, et al. Time in Range Is Associated with Carotid Intima-Media Thickness in Type 2 Diabetes. *Diabetes Technol Ther*, 2020,22:72-78.

Question 2: Diabetes complications depends on diabetes control and duration and therefore, this cross-sectional nature of study would not provide definitive conclusion. Rather, this is a hypothesis generating. Results of this study may not be generalizable. I suggest extracting last 5-10 years of A1c of these patients and reanalyze the data as I am sure average A1c would correlate with sudomotor functions.

Answer2: We definitely agree with the reviewer's suggestion. Due to the cross-sectional design of the study, our findings may only provide the basis for future longitudinal studies. Therefore, with your valuable advice, we revised the penultimate paragraph of discussion as follows: “Besides, the difference of HbA1c between patients with sudomotor dysfunction and without sudomotor dysfunction was not significant and the regression analysis revealed there was no relevance between HbA1c and sudomotor dysfunction, these may because, as a cross-sectional study, we could only get the preliminary correlation between HbA1c level and sudomotor function, so the data from our study may only provide the basis for future longitudinal

studies.” Besides, in the last paragraph of discussion, we emphasized this limitation. In the future study, we will focus on the relationship between the long-term variation of HbA1c and sudomotor function.

Question 3: Authors (last paragraph of discussion) mentioned that there are few limitations. However, these few limitations are major limitations and downplaying limitations would not help. I would suggest acknowledging these major limitations

Answer 3: We agree completely with the reviewer and would to correct this. we corrected last paragraph of discussion according to your valuable advice. The details are as follows: “Nevertheless, our study had some major limitations. First of all, all subjects in this study underwent 3 days of CGM, therefore, the results of this study may not be generalizable. Secondly, the study was cross-sectionally designed, thus we could only get the preliminary correlation between HbA1c level and sudomotor function. Thirdly, this is a retrospective study and hospital-based study therefore, unmeasured bias cannot be ruled out. Therefore, based on these limitations, carrying out large-sample, multi-center research is something we are about to put on the agenda.”

Question 4: Also, this is a retrospective study and hospital based study therefore, unmeasured bias cannot be ruled out.

Answer 4: We definitely agree with the reviewer’s suggestion. According to the advice, we clearly stated that unmeasured bias cannot be ruled out for it was a retrospective study and hospital based study.

Question 5: There was no priory hypothesis or sample size calculations provided. This may be due to unplanned cross-sectional study.

Answer 5: Thank you for your careful comment. In the future research, we will pay more attention to the calculation of the sample size.

Question 6: Sample size is large and p of 0.01 may be better than 0.05.

Answer 6: We definitely agree with the reviewer’s advice. And based on the advice, we modified a value of $P < 0.01$ was considered statistically significant. This revised statistical results are marked in red.

Question 7: Please provide information on other diabetes microvascular complications in Table 1.

Answer 7: Thank you for your suggestion. According to the advice, the information on other diabetes microvascular complications including diabetic nephropathy (DN) and diabetic retinopathy (DR) has been added in Table 1. The detailed statistical results are as follows:

	sudomotor dysfunction (-)	sudomotor dysfunction (+)	$\chi^2/t/z$	P
Microvascular complications				
DN (n, %)	51(15.41)	53(39.26)	31.465	<0.001
DR (n, %)	69(20.85)	62(45.93)	29.846	<0.001

DN, diabetic nephropathy, DR, diabetic retinopathy

Question 8: Table 2 can be moved as supplemental.

Answer 8: Thank you for your advice. According to the advice, Table 2 has been moved as supplemental.

Response to Reviewer 2#

Thank you for your constructive comments, the following is my point-by-point responses.

Question 1: The Materials and Methods section provides insufficient information. Information about other complications of diabetes mellitus, as well as treatment must be added. TBR among two groups was 0, so it raises the question about sugar lowering drugs used by patients. As duration of diabetes was 7 (2.11) in sudomotor dysfunction (-) and 10 (6.15) years in sudomotor dysfunction (+) group, it is clear that insulin was prescribed. Please add and check the information.

Answer 1: Thank you for your suggestion. And based on your valuable suggestion, we added Information about other complications of diabetes mellitus, as well as treatment in our materials and methods section. This added portion was: Diabetic nephropathy (DN) was defined on the basis of persistent microalbuminuria detected during at least two examinations with a high urine albumin-to-creatinine ratio (ACR >30 mg/g). Diabetic retinopathy (DR) was diagnosed when non-proliferative or proliferative retinopathy was observed during fundus examination and stereofundus photography after pupillary dilation by the same ophthalmologist. The treatment of diabetes was recorded from the medical record system. Besides, we also made a further statistical analysis on the complications of diabetes mellitus and treatment. The detailed results are as follows:

	sudomotor dysfunction (-)	sudomotor dysfunction (+)	$\chi^2/t/z$	<i>P</i>
Microvascular complications				
DN (n, %)	51(15.41)	53(39.26)	31.465	<0.001
DR (n, %)	69(20.85)	62(45.93)	29.846	<0.001
Treatment (n, %)				
No treatment	27(8.16)	7(5.19)	7.107	0.069
OHA	104(31.42)	29(21.48)		
Insulin	44(13.29)	20(14.81)		
OHA & Insulin	156(47.13)	79(58.52)		

DN, diabetic nephropathy, DR, diabetic retinopathy, OHA, oral hypoglycemic agents.

Question 2: CGM was performed for 72 hours, but it stays that TIR, TBR, TAR are presented during 1 day period. Please confirm.

Answer 2: Thank you for your question. According to the international consensus, TIR is defined as the percentage of time when blood glucose is between 3.9 -10 mmol /L during 1 day period. TBR refers to the percentage of time when blood glucose is below 3.9 mmol /L during 1 day period. Otherwise, TAR refers to the percentage of time when blood glucose is above 10 mmol /L during 1 day period^[1]. In our study, all subjects underwent 3-days CGM, and we used the average time percentage of blood glucose within the target range over three days as the final value of TIR、TBR、TAR. In order to avoid misleading, we added this sentence to the method section.

[1] Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose

Monitoring. *Diabetes Care*, 2017,40:1631-1640

Question 3: Major suggestion: it is recommended by international consensus to use of at least 2 weeks of CGM data for research and clinical purpose as 2 weeks correlates well with HbA1c. Authors have used only 72 hours of CGM data, but it was stated as limitation of this study. It should clearly be written that it is a major limitation, so obtained results may not be generalizable and further studies are be needed.

Answer 3: We agree completely with the reviewer and would to correct this. On the basis of valuable advice, we corrected last paragraph of discussion. The details are as follows: “Nevertheless, our study had some limitations. First of all, all subjects in this study underwent 3 days of CGM, therefore, the results of this study may not be generalizable.”

Question 4: There are some syntax errors and misspelling throughout the paper. Please check the paper carefully to exclude them.

Answer 4: Thank you very much for your careful review, we examined the full text carefully and corrected syntax and spelling errors.