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To,

Dr. Jin-Lei Wang,

Editor-in-Chief,

World Journal of Clinical Cases

December 18, 2021

Subject: Revision and resubmission of manuscript ID: 71495

Dear Editor-in-Chief

Thank you for allowing us to revise our paper on "Changes in corneal nerve morphology and function in patients with dry eyes having type 2 diabetes." The comments offered by reviewers have helped revise the paper.

We have carefully considered the reviewers' comments and responded point-by-point to each reviewer, indicating exactly how we addressed each point. All authors have approved the revisions. We have highlighted the changes made to our revised manuscript using track changes in MS word and marked yellow for specific change(s).

Most of the revisions prompted by the reviewer's comments require no further explanation than what appears in our responses below. We hope the revised manuscript will better suit the *World Journal of Clinical Cases* but are happy to consider further revisions (if any).

Sincerely,
Dr. Fang

Responses to reviewers

We sincerely thank the reviewers for their constructive criticisms and valuable comments, which helped revise the manuscript.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Authors of the manuscript investigated dry eye syndrome in patients with or without diabetes. The article is well presented, however, control selection raises question.

Major issues:

1. Selection of controls raises questions, as authors did not conduct proper tests to exclude prediabetes or not-diagnosed diabetes. Fingertip glucose measurement for diagnostic purposes is unacceptable. As per latest guidelines of ADA, oral glucose tolerance test or HBA1C is the gold standard to diagnose glucose metastasis related diseases. <https://doi.org/10.2337/dc21-S002>

Reply: Thank you for allowing us to clarify it. Indeed, there are flaws in blood glucose testing in the non-diabetic patients' group. At that time, these patients were enrolled in this way. Initially, they were asked about their diabetes history, and none of them had diabetes. Then, they were further asked whether they had undergone biochemical blood tests within one year. If their blood sugar levels were normal, they were considered non-diabetic. Finally, they were given a fingertip blood test to check their fasting blood

glucose one year prior to enrollment. The blood glucose of the dry eye non-diabetic group was 5.07 ± 0.76 mmol/L, and the control group was 5.08 ± 0.62 mmol/L.

We also understand that the American diabetes association recommended OGTT, or HBA1C, as the gold standard test. Therefore, we have added this as part of the limitation of this current study and plan to use these in future studies on this topic.

2. No information was given about the nDEnDM group. Were those study participants totally healthy volunteers, or did they have any symptoms just not meeting the DE criteria? If the second, can they be called truly as controls?

Reply: Thank you for allowing us to clarify it. The nDEnDM group included patients who visited the ophthalmology department for non-dry eye reasons such as cataracts and myopia. Some patients complained of dry eyes but did not diagnose with dry eyes after examination and volunteers such as colleagues. They all went through an eye examination and did not meet the exclusion criteria.

3. Did exclusion criteria included diabetic retinopathy / neuropathy as well?

Reply: Yes, diabetic retinopathy and diabetic optic neuropathy were excluded in the non-diabetic group. A few patients in the diabetic group had diabetic fundus disease; however, the degree of fundus disease is not included in the data analysis.

Discussion's first paragraph is strange. In the first part authors talk about DE in general, then the second half of the paragraph reflects to results, which are not in line with the first half.

Reply: Thank you for this constructive comment. We have modified the first paragraph of the discussion section to make it more logical.

Minor questions:

1. The cut-off for short- and long-duration of diabetes should be moved to Methods. Please indicate mean \pm SD duration for both groups. Furthermore, did those patients with long-time diabetes have diabetic retinopathy, neuropathy or any other diabetes-related complications?

Reply: We sincerely appreciate this constructive comment. As suggested, the cut-off for short- and long-duration diabetes had been moved to Methods. Also, we have indicated the mean \pm SD duration for both groups in the revised manuscript. Some diabetic patients have diabetic fundus disease, but the degree of fundus disease is not included in the data in the diabetic group.

2. Author contribution is missing.

Reply: In the revised manuscript, we have added the author's contribution statement accordingly.

3. Abstract contains several abbreviations that are not resolved.

Reply: We have resolved the abbreviations issue in the abstract in the revised manuscript.

4. Second part of Core tip cannot be understood without reading the article. The purpose of Core tip is to gain attraction without any technical detail, and must remain comprehensible, even to a researcher who does not work as an ophthalmologist / diabetologist. Please, update Core Tip accordingly.

Reply: Thank you for this valuable suggestion. We have updated the Core tip accordingly.

5. "Introduction Dry eye syndrome (DES) is a common..." Correct abbreviation, in the whole manuscript DE is used, not DES.

Reply: We have resolved the abbreviations issue in the revised manuscript.

6. Introduction contains abbreviations that are only resolved later in Methods. Please, correct.

Reply: We have resolved the abbreviations issue in the revised manuscript.

7. Some abbreviation were never resolved (e.g. ICVM).

Reply: We have resolved the abbreviations issue in the revised manuscript.

8. "Bland–Altman analysis in SPSS16.0 statistical software was used to analyze the consistency of data from the two researchers. If the data were consistent, the mean value of the two was taken as the inspection result." This should be in Statistical Analysis.

Reply: As suggested, we have moved the sentences to the Statistical analysis section.

9. "No differences in NFD and NFD were also observed between patients with different durations of diabetes in the DMnDE group..." Please, revise.

Reply: Thank you for bringing this up for us. This has been corrected in the revised manuscript.

10. "diabetes neuropathy" -> diabetic neuropathy.

Reply: This has been corrected in the revised manuscript.

11. Tables 3 and 4 are hard to read. Please, correct the column widths.

Reply: The column widths of Tables have been modified for readability as suggested.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript was well written although I have penned down my comment on the script

Abstract:

#Is there any reason why 131 was chosen ?

Reply: Thank you for allowing us to clarify it. There was no particular reason for choosing an exact number of 131. The 131 enrollees were mainly those who visited the ophthalmology department with complaints of dry eye, non-dry eye reasons such as cataracts and myopia, and volunteers such as colleagues between January 2019-August 2020. To avoid confusion to the readers, we have modified the sentences in the revised manuscript.

#Why so much difference in the number of patients in each group ?

Reply: The large difference in sample size between groups is mainly because this observation involves ophthalmology, neurology, and laboratory examinations. The examination cannot be completed at one time. It requires patients to come to the hospital multiple times to perform various examinations separately, challenging to complete. Therefore, the number of patients with the non-dry eye is relatively small, which is a deficiency of this study. Therefore, we have included this as part of the limitation of this study and discussed it at the end of the discussion section.

Correlation analysis:

Was there any correlation with HbA1c ?

Reply: The statistical analysis of HbA1c was performed on all diabetic patients (dry eye and non-dry eye), dry eye-diabetes group, and diabetic non-dry eye group. The three HbA1c were normal distributions, and no correlation was found with each observation index. Please see table 5 in the revised manuscript.

Discussion:

#A mention of one or two these proteins will be convincing, even though it was not measured in this study.

Reply: We sincerely appreciate this constructive comment. We have added a few names of such proteins in the revised manuscript.

Yes I have this notion too

Reply: Please see the reply above and explain as part of the limitation (iii).

Responses to Editorial Office's comments

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The study analyzed several groups of patients with diabetes and dry eye, and observed that patients with both type 2 diabetes and dry eye had impaired corneal neuromorphology and function, while patients with diabetes alone or dry eye only had abnormal corneal neuromorphology and no impaired neurological function. These results are of great significance to patients with dry eyes having type 2 diabetes.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Reply: We appreciate these sincere comments. We have revised the English language with a professional editing service to improve the language quality further.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, 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. 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. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Reply: Thank you for this advice. We have followed this advice while revising the manuscript accordingly.

Dear Dr. Fang,

Thank you for submitting your manuscript (NO.: 71495) to the World Journal of Clinical Cases.

I am pleased to inform you that I have added an additional comment regarding your manuscript. The comment is as follows:

There are some issues need to be addressed.

-----1. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. For example, "Diabet Med" and "Ocul Surf".

Reply: Thank you for bringing this up for us. We have checked and revised the reference list accordingly in the revised manuscript.

-----2. Your revised manuscript has been 2nd reviewed by original reviewers. There are some points need to be addressed in your manuscript. Please revise the manuscript according to the reviewer's comments and send me Q&A responses from the reviewer in Word format.

Reply: We have carefully addressed the second review comment by the original reviewer and replied point-by-point below in Q&A word format.

-----3. Please complete all the revisions based on the version of "4290-71495-v1", and upload above mentioned files in a ".zip" file.

Reply: We have followed this suggestion accordingly.

Responses to Reviewer Comments

REVIEWER: The following small issues should be fixed prior publication:

Q1. Resolve abbreviations of table 5.

A: Thank you for this suggestion. We have resolved the abbreviations of table 5 as suggested. [see revised table 5]

Q2. "In the non-diabetic group, diabetic retinopathy and diabetic optic neuropathy were excluded." -> Shouldn't it be: "In the diabetic group, diabetic retinopathy and diabetic optic neuropathy were excluded."

A: Thank you for allowing us to clarify it. Please note that diabetic fundus lesions should not appear in non-diabetic patients. All non-diabetic patients in the experiment had no such lesions. Although this is not the exclusion criterion of this group, it can be used as supplementary proof that they do not have diabetes. We would be happy to consider observations of diabetic fundus lesions in our future studies.

