Author’s response to reviews

Title: Choroidal Structural Changes Correlate with Severity of Diabetic Retinopathy in Diabetes Mellitus

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Choroidal Structural Changes Correlate with Severity of Diabetic Retinopathy in Diabetes Mellitus” (ID: BOPH-D-19-00132R3). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to us. This is the third revision. I have carefully read the opinions of reviewers and editors and made detailed revisions again. We really hope that you are satisfied with this modification.

We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

− Editor Comments:

In this third revision there are still many flaws and mistakes. Please, read reviewers’ comments carefully and amend the manuscript accordingly and consistently. Four rounds of revisions is a lot, and this might be your last chance. Pay special attention to Table 3. If I calculate the ratio of the luminal to choroidal area, I obtain 0.65, 0.63, 0.61; hence, it seems that the unit for your numbers is %, which would need to be indicated. Same for tables 4 and 5. Even more importantly, the statement "Choroidal thickness and the ratio of the luminal to choroidal area significantly increased with severity of DR eye” is obviously wrong!!! This statement needs to be rectified in several paragraphs of the manuscript.
My answer: I am so sorry that there are still some mistakes in my article. I will carefully correct them.

1) In my original manuscript, we use choroidal vascularity index (CVI) to assess vascular structure choroid microstructure. But the reviewer questioned CVI and suggested us to change it to “ratio of the luminal to choroidal area”. But at that time, I ignored that the unit should be corrected together. This time you pointed out this defect, I am very grateful and I have changed the all the description “65%...” to “0.65, 0.63, 0.61....” in all the Tables (Tables 3, 4 and 5) and the results section. I am very grateful for your suggestion.

2) The statement "Choroidal thickness and the ratio of the luminal to choroidal area significantly increased with severity of DR eye" is obviously wrong!!! I was really careless and made the mistake. I have changed "Choroidal thickness and the ratio of the luminal to choroidal area significantly increased with severity of DR eye" to “SCT increased, but the ratio of the luminal to choroidal area (L/C ratio) significantly decreased···”. I'm sorry about that.

Jee Taek Kim, M.D., Ph.D. (Reviewer 1):

1. In earlier version of revision, you described that "42 patients received laser treatment". And you described treatment history of the patients, as follows: "42 DM patients received fundus laser photocoagulation treatment (22 NPDR eyes and 20 PDR eyes)” in line 41-44, Page 6, according to other reviewer's advice.

This sentence and revised Table 1. can cause misunderstanding to me and other readers, as likely as the included patients were not treatment-naïve state. In general, treatment history of the subjects are previous history before the inclusion. Thus, you should change the sentence appropriately and table 1. The patients included in table 4 or 5 were not shown in table 1. Please edit appropriately.

My answer: I am so sorry that you are confused by the lack of rigor in my description. I will revise it carefully. Thank you for your advice. Because the patients included in table 4 or 5 were not shown in table 1, the description in methodology has been modified. I added some content in the “Method”, “Result” part and changed Table 1 as follows:
“Method” part:

1. Study Population: 42 DM patients received fundus laser photocoagulation treatment (22 NPDR eyes and 20 PDR eyes). 2 patients got local retinal photocoagulation, 40 patients got PRP. I have added the sentences “After the patients were included in the study, 40 patients (20 NPDR patients and 20 PDR patients) underwent PRP treatment, but 3 patients failed to return in time. To investigate the difference before and after PRP treatment, the choroidal parameters of 24 PRP-untreated NPDR, 17 PRP-treated NPDR eyes, 20 PRP-untreated and PRP-treated eyes were also assessed in this study.” to make it more clear.

2. Measurement of Retinal and Choroidal Thickness: I have added the sentences “EDI-OCT scans of the macula were performed for all eyes using spectral-domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) before and after PRP treatment. 38 healthy eyes, 22 DM with no DR eyes, 24 PRP-untreated NPDR eyes, 20 PRP-untreated PDR eyes before fundus laser treatment and 37 eyes (17 NPDR and 20 PDR eyes) after PRP treatment performed OCT examinations.” in the METHOD part.

“Result” part:

1. Demographic and clinical characteristics: 42 DM patients received fundus laser photocoagulation treatment (22 NPDR eyes and 20 PDR eyes). 2 patients got local retinal photocoagulation, 40 patients got PRP. I have deleted the sentence “After the patients were enrolled in the study, 42 DM patients received….”.
On the one hand, we want to describe the history of laser treatment of all the DR patients, on the other hand, we don't want the reader mistakenly think that the included patients in Table 1 were not treatment-naïve state, and I don't want the reader to feel that the patients in the form are treated after treatment. So it’s really difficult to make changes in Table 1. So we decided to describe its treatment history in the “Method” part—“After the patients were included in the study, 40 patients (20 NPDR patients and 20 PDR patients) underwent PRP treatment, but 3 patients failed to return in time. To investigate the difference before and after PRP treatment, the choroidal parameters of 24 PRP-untreated NPDR, 17 PRP-treated NPDR eyes, 20 PRP-untreated and PRP-treated eyes were also assessed in this study”, and deleted the description of laser treatment in Table 1 and “Result” part, avoiding misunderstanding.

“The patients included in table 4 or 5 were not shown in table 1. Please edit appropriately.” It is difficult to add the PRP-treated information (Tables 4 and 5) in Table 1, but I have made some supplementary descriptive statements in both the Method and Results sections.

I have added the sentences “After the patients were included in the study, 40 patients (20 NPDR patients and 20 PDR patients) underwent PRP treatment, but 3 patients failed to return in time. To investigate the difference before and after PRP treatment, the choroidal parameters of 24 PRP-untreated NPDR, 17 PRP-treated NPDR eyes, 20 PRP-untreated and PRP-treated eyes were also assessed in this study” in “Method” part and “I have added the sentences “NPDR and PDR eyes were performed OCT examinations before and after PRP treatment.” to make it more clear.

Although this description is somewhat tedious, it can clearly describe the situation. Thank you for all the suggestions you gave us for several times, which were helpful to my article.
Siqing Yu (Reviewer 4):

1. Abstract. Line 28. The authors probably mean RNFL thickness, but "thickness" is missing.

2. Abstract. Line 48. According to the result and table 3, the ratio of the luminal to choroidal area decreased with DR progression. However, the authors made a statement "Choroidal thickness and the ratio of the luminal to choroidal area significantly increased with severity of DR eye". Please verify the research data. This lead to entirely different conclusions.

3. Abstract. Line 53. This report is mostly about DR development but not recurrence. I recommend deleting "predict DR recurrence" in the conclusion for it is overstated.

My answer: Thank you for your advice. According to your suggestion, I make the following modifications:

1) Abstract. Line 28. I've changed “retinal nerve fiber layer (RNFL)” to “retinal nerve fiber layer (RNFL) thickness”.

2) Abstract. Line 48. This is my description error. Thank you for your advice. I have corrected it in “Abstract” part. I've changed “Choroidal thickness and the ratio of the luminal to choroidal area significantly increased…” to “Choroidal thickness increased, but the ratio of the luminal to choroidal area significantly decreased…”.

3) Abstract. Line 53. I have deleted the description "predict DR recurrence" in “Abstract” part, and change it to “Changes in the ratio of the luminal to choroidal area may predict DR development …”.
4. Page 3. Line 49. The authors took the advice of the Reviewer 2 to replace the term "CVI" with "ratio of the luminal to choroidal area". However, the authors used "CVI" in the background, but "ratio of the luminal to choroidal area" is used in the method, and both of them in the discussion. This leads to some confusion. Could you combine these two terms in the introduction or methods part? I suggest to use abbreviation "L/C ratio" for "ratio of the luminal to choroidal area" and replacing all the "CVI" with "L/C ratio".

My answer: Thank you for your advice. According to your suggestion, I've changed “ratio of the luminal to choroidal area” to the abbreviation “L/C ratio” in the methods and result part. But no same changes have been made in the introduction section this time, because it's really hard for the following reasons:

Actually, it's hard to make this change, because in their articles (Sonoda et al and Agrawal et al.), they did use the new term “choroidal vascularity index, CVI” in their study, not the one I used in my paper (ratio of the luminal to choroidal area). If I change “CVI” to “ratio of the luminal to choroidal area or L/C ratio” in the quote section (Introduction part), it would be inconsistent with the article description of Sonoda et al and Agrawal et al.

At present, there are many researches on CVI, and some ophthalmologists have accepted this novel term “CVI”. I used “CVI” in my original manuscript, but I followed the advices of Reviewer 2 and used “ratio of the luminal to choroidal area” instead of “CVI”. But I don't think it's appropriate to change the noun “CVI” in the studies of Sonoda et al. and Agrawal et al. in “Introduction” section, since their articles have already been published, which they use the term “CVI”.

At the beginning of the study on choroid microstructure, some scholars used “ratio of the luminal to choroidal area” to describe the choroid microstructure change, but as research increased, Agrawal et al. put forward this new term—CVI, which was accepted by others. In this case, it is not very appropriate if I still use the old noun “ratio of the luminal to choroidal area” or replace “CVI” to “ratio of the luminal to choroidal area” in the citation.

Actually, I prefer to unify the description to “CVI” in the whole text, including abstract, introduction, method, results, and discussion parts. If my explanation does not satisfy you, or you have other suggestions, please inform me, and I will make corresponding modifications.
5. Page 6. "SCT" appeared for the first in the result. Please indicate this abbreviation in the method.

My answer: Thank you for your advice. According to your suggestion, I've added this abbreviation “the subfoveal choroidal thickness (SCT)”.

6. Page 9. Line 3. Are OCT acquired on the same day after PRP treatment? If not, could you give the interval between OCT acquisition and PRP treatment?

My answer: OCT were not acquired on the same day after PRP treatment. On the day after PRP treatment, most patients suffered from ocular pain and mild corneal edema, which made OCT examination inconvenient, at the same time, the patients themselves were not willing to continue any other examination. Therefore, we asked the patients to come to the hospital for follow-up consultation 3-7 days after the PRP treatment to conduct OCT examinations again. So the interval between OCT acquisition and PRP treatment was 3~7 days.

7. Page 9. Line 44. Please rewrite the sentence "Agrawal et al.[32] have demonstrated...." There is obvious grammatical mistake.

My answer: Thank you for your advice. I've changed “Agrawal et al.[32] have demonstrated...” to “Agrawal et al.[32] demonstrated....”.

8. Page 10. Line 55. Please check the grammar in sentence "But LA were…."

My answer: Thank you for your advice. I've changed “But LA were….“ to “But LA was….“.

9. Figure legend 1. Please change the abbreviation to SCT, since it is used elsewhere in the manuscript.

My answer: Thank you for your advice. I've changed “subfoveal choroidal thickness (CT) measurements…” to “SCT measurements…”.
10. Table 1. 1) Could you also present the percentages of the categorical data in the table? 2) Please state which statistical test was used in the last footnote. Fisher's exact test and Chi-squared test are two different tests.

My answer: Thank you for your advice.

1) I've added “the percentages of the categorical data” in the Table 1 and other Tables.
2) I've changed “···using the Fisher’s exact test of Chi-Square test” to “···using the Fisher’s exact test”.

11. Table 2. 1) RNFL data in table 2 are not well presented. Please indicated what the numbers in/out of the brackets stand for. 2) I did not find how retinal thickness was measured in the method. Are they measured at 3 points or in average? Please add this information in the method. 3) Abbreviations can be used in the table since they are clarified in the footnotes.

My answer: Thank you for your advice.

1) Since the RNFL thickness data did not conform to the normal distribution, it is expressed in median (interquartile range, IQR). I've changed “RNFL” to “RNFL thickness” in Table2. I expressed it not clearly in the tables, I have re-described it in all the 5 Tables.

2) In the “Measurement of CT” part: I have changed the title name from “Measurement of CT” to “Measurement of Retinal and Choroidal Thickness” and added some description of retinal thickness measurement in this part. I've described “The retinal thickness, CT and RNFL thicknesses were measured using the in-built callipers tool at three points (subfoveal, 0.5 mm temporal and nasal to the fovea)”. But in the statistical analysis, we only choose 0.5 mm nasal to the fovea RNFL and retinal thicknesses for statistical analysis. In order to make the description more clear, I added the description “Only 0.5 mm nasal to the fovea retinal thickness and RNFL thickness were included in statistical analysis”.
3) Abbreviations can be used in the table since they are clarified in the footnotes.

I have made corresponding modifications in Tables.

Thank you for all the 11 suggestions you gave us, which were helpful to my article.

Thank you and all the reviewers for the kind advice.

Sincerely,

Hui Wang