

Cluj-Napoca, Feb. 21st 2021

Dear Editor,

We are very grateful for the reviewers' comments, since they helped us improve the quality of our manuscript.

We addressed all the issues that were raised and hope that our manuscript will get the acceptance for being published in this prestigious journal.

Below are the responses to the raised comments:

Comment 1. A review focusing on the role of the outer retinal barrier in diabetic macular edema is of utmost importance. However, the paper does not focus just on this topic but rather on retinal and choroidal biomarkers in diabetic retinopathy. Either the content or the title and purpose should be changed.

- Response: we modified the title of the manuscript as follows: **“The Malfunction of Outer Retinal Barrier and Choroid in the Occurrence and Progression of Diabetic Macular Edema”**

Comment 2. It features the most biomarkers on this topic, but some specifications show be addressed and some changes are necessary: RPE-PR complex: the findings of a thickened RPE in diabetic patients may also be a consequence of impaired glycogen metabolism and its accumulation inside the RPE in diabetic patients as show in this paper (<https://pubmed.ncbi.nlm.nih.gov/24458975/>)

- Response: we introduced the above mentioned title in the Discussion section – page 9

Comment 3. Choroidal thickness (CT) in patients with DR is a highly unreliable variable and multiple studies show different results. Better studies should be cited. The conclusion of this section shows that CT does not seem to be a good biomarker. There is a thorough review about this (<https://pubmed.ncbi.nlm.nih.gov/27545332/>)

- Response: we cited the above mentioned review in the Discussion section of the manuscript – page 11.

Comment 4. In patients Choroidal vascular index (CVI) in patients with DM There are more important references regarding CVI in DR, namely <https://pubmed.ncbi.nlm.nih.gov/28988899/> that performed a volumetric analysis.

- Response: we discussed the above mentioned reference at page 12.

Comment 5. There are also studies analyzing CVI after treatment with antiVEGF, like <https://pubmed.ncbi.nlm.nih.gov/29492689/>.

- Response: we discussed the above mentioned reference at page 12.

Comment 6. I would recommend adding this paper using indocyanine angiography showing early areas of choroidal hypoperfusion in DR, years before the recent studies with OCT

<https://pubmed.ncbi.nlm.nih.gov/9727518/>

- Response: we added a paragraph on ICGA citing the above mentioned reference - page 12.

Comment 7. A section about the use of OCT-A to evaluate the outer RBB is important.

<https://pubmed.ncbi.nlm.nih.gov/30810284/>

- Response: we added a paragraph on OCT-A citing the above mentioned reference - page 12.

Comment 8. Laboratory studies that studied the outer BRB should be included.

- Reponse: we included laboratory studies on the outer BRB – page 5

Comment 9. Several times along the text it is stated that the outer BRB separates the neural retina from the underlying choriocapillaris. In fact, the outer BRB separates the retinal pigmented epithelium (which is not considered part of the neural retina) from the underlying choriocapillaris.

- Reponse: we corrected the above mentioned statement- pages 2, 3 and 4.

Sincerely yours,

Prof. Dr. Simona Nicoara