Peer Review File

Association of systemic cardio-vasculature status with retinal vascular endothelium in diabetes

Reviewer: 1

Page 3 line 14-16: This seems to be a broad summary statement. Which retinal pathological finding do the prevalence numbers refer to? And in all patients regardless of severity grade of cardiovascular disease?

Summary:
The authors review the literature regarding changes in the retinal vasculature in diabetic and non-diabetic retinopathy.

They clearly describe how the retina as an end-organ presents unique vascular challenges that may not be generalisable to capillary bed changes elsewhere in the body. They also describe how diabetes affects the retinal vasculature differently to non-diabetic retinal vascular disease. The authors emphasize the changes in retinal venous endothelium around the area of the lamina cribrosa as a potential cause of eye-specific retinal vascular abnormalities.

Finally, the authors suggest how these pathophysiological findings can be applied to judge clinical risk of disease progression and as an avenue for therapeutic intervention.

I enjoyed reviewing this article. I found it to be well-written and an organized review of the subject matter. The relevance of intracranial pressure remains unclear and although this is not the fault of a review article it is worthwhile acknowledging that we lack data to help us understand the contribution of this variable.

Response:
Thank you very much for your appreciation.

The uploaded manuscript that appears in Manuscript Central does not correspond to the comments of the reviewer regarding page 3, line 14-16. In our uploaded manuscript, the reviewer’s comments refer to this content:

“… venous outflow from the retina. This may result in venous congestion and increased intravascular hydrostatic pressure in the retinal veins of diabetic patients. The clinical signs that predict diabetic retinopathy - venous dilation, as well as the clinical signs of developed diabetic retinopathy - decreased retinal fractal dimension, “

However, this text does not contain any information concerning prevalence. Perhaps the reviewer refers to this citation:

“Retinopathy in the absence of diabetes mellitus (non-diabetic retinopathy) is characterized by the presence of microaneurisms, hemorrhages, hard exudate, cotton wool spots, venous beading, intraretinal microvascular abnormalities, and neovascularisation with a prevalence ranging between 4.8% and 12.5% [7, 28].”

The prevalence numbers refer to a population without diabetes that shows signs of diabetic retinopathy. We have removed the prevalence numbers from the first sentence for clarity and included the age of the examined subject, which was missed earlier. (Page 2, Line 21-22)

We have acknowledged the need for further investigation of this variable and have included an explanation regarding the relevance of increased intracranial pressure in diabetic retinopathy progression and hyperopia. (Page 5, Line 20-26)
Very interesting article and well written.
My main criticism is that there are many great new papers on OCTA, but you never even mentioned it as a tool. I think that this will add much to the article.

Response:
Thank you very much. We have included OCTA studies in our manuscript. (Page 1, last paragraph; Page 5, line 34-37)

1. I am not sure if the title should have the words Literature Review in it
Response:
We apologize for not mentioning the type of our narrative review. Based on our manuscript’s contents, our review should be categorized as a commentary. We have added “Commentary” to the title.

2. Abstract: Line 13 "proximity in the" to "proximity to the"
Response:
We have changed this sentence to “The central retinal artery and vein are in close proximity inside the optic nerve, where they share a common adventitia…” This is because the relationship between the retinal artery and vein is due to their close proximity inside the optic nerve following their penetration through the meningeal sheaths.

3. Intro: 2nd par. Why is there no discussion of FA or OCTA?
Response:
We have included a discussion on “fluorescein angiography” and “optical coherence tomography angiography” in the last paragraph of the introduction.

4. Intro: 3rd par, line 42: change CVD to DR twice
Response:
Thank you for this suggestion. We have revised this line. (Page 1, line 39-41)

5. Page 2 line 5: Coronary heart disease to coronary artery disease
Response:
We have corrected this. (Page 2, Line 17)

6. Following paragraph: what is IMT?
Response:
IMT refers to the intima-media thickness of the carotid artery. We have explained the abbreviation at its first mention. (Page 2, Line 13)

7. Page 2, line 30: No need to start a sentence with However.
Response:
We have excluded “However” from the paragraph. (Page 2 Line 35)

8. Page 3, line 16 endothelia”l"
Response:
We have corrected the omission.

9. Page 4 line 39 "as well as the" to "as well as other"
Response:
We have revised accordingly. (Page 5, Line 5)

10. Page 4: Same as above; why no mention of OCTA or FA?
Response:
We have included a discussion on OCTA. (Page 5, Line 34-37)

11: Conclusion: "microvascular vascular endothelium" to "microvascular endothelium."
Response:
We have revised accordingly. (Page 5, Line 45)

Reviewer: 3
This is a review article regarding association of systemic cardio-vasculature status with retinal vascular endothelium in diabetes.

Concerns:
1) The material and methods section is absent and should contain for example information about: data sources (e.g. bibliographic databases), search terms and search strategies, selection criteria (inclusion/exclusion of studies), the number of studies screened and the number of studies included.

Response:
Thank you for your concern regarding the lack of a materials and methods section. As suggested by Reviewer 3, we have added “commentary” to the manuscript subtitle. We have chosen to present a narrative rather than a systematic review, which requires bibliographic databases, search terms, strategies, and selection criteria. The analysis of our subject included several parameters of endothelium dysfunction and several conditions (cardio-vascular diseases) that may affect the progression of diabetic retinopathy, which makes a systematic review on the subject impossible in a single manuscript. Rather, several systematic reviews are required to analyze the association of these factors with diabetic retinopathy. Due to the nature of the presented material, we chose a commentary style manuscript because we desired to initiate a discussion regarding our presented hypothesis.

2) Page 2, line 13, Cardio-vascular disease and non-diabetic retinopathy section is not related to the article scope and should be deleted.

Response:
We included this section in order to emphasize that a condition similar to diabetic retinopathy occurs in non-diabetic patients who have a cardio-vascular disease. Non-diabetic retinopathy lacks the pathogenic factors associated with metabolic disease, but the similarity of its clinical signs to diabetic retinopathy may indicate that the previously discussed pathogenetic mechanism (central retinal vein congestion) may be present in both conditions. Therefore, we believe this paragraph is relevant to our discussion.

3) All in all it is recommended that this manuscript submitted to one journal in the field of internal medicine because it cannot draw the attention of ophthalmologists.

Response:
We thank the reviewer for his/her recommendation. We agree that this subject may be interesting to internal medicine physicians; however, our question is, do we ophthalmologists have a consensus regarding the pathogenesis of diabetic retinopathy? Many hypotheses have been discussed, many pathogenetic factors have been explored, but still we do not know the exact pathogenesis of diabetic retinopathy.

In this manuscript, we present a hypothesis based on the research from the fields of both internal medicine and ophthalmology that suggests that central retinal vein congestion may be a major factor in the progression of diabetic retinopathy. Although this mechanism has been suggested
before (1-3), to the best of our knowledge, no other literature reviews have discussed this specific mechanism in detail. Therefore, we believe this review is pertinent to ophthalmologists, so that further research into this topic can continue.

