Review of: "Differentiating features of OCT angiography in diabetic macular edema"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

In this study, Dr. Mirshahi and associates compared different OCTA metrics in eyes with diabetic retinopathy (DR) with and without diabetic macular edema (DME) to assess the pattern of retinal ischemia in the setting of DME.

The authors used OCT-A, an OCT-derived technique that generates high-resolution angiographic images by using repeated B-scans to detect motion contrast from flowing erythrocytes, to test their hypothesis that ischemia patterns may differ according to the presence of macular edema.

They used different quantitative metrics, such as vessel density (VD), vessel length density (VLD), perfusion density (PD), size and shape of the foveal avascular zone (FAZ), geometric perfusion deficit (GPD), vascular tortuosity index (VTI), and fractal dimension (FD), and they performed the measures for the superficial capillary plexus (SCP) and deep capillary plexus (DCP), separately.

The authors found that eyes with DME:

- 1) have more severe ischemia, as suggested by higher CNP and GPD both in SCP and DCP;
- 2) have lower vascular complexity (as suggested by lower FD).

These findings hold true irrespectively of the stage of DR (NPDR or PDR). Moreover, the authors found that in eyes with DME, the perfusion deficits in the DCP were higher than the SCP (as demonstrated by lower CNP and GPD ratio), while in eyes without DME the extent of non-perfusion was higher in the SCP. Thus, the authors hypothesized a potential causative role of DCP ischemia in the pathogenesis of DME.

This paper contributes to the understanding of vascular changes occurring in DR and leading to the blood-retinal barrier breakdown in patients with DME, showing a possible role for non-perfusion in its development. This research may lead to the discovery of new biomarkers in DR and DME associated with the need for more intensive investigation or treatment.

Strengths of this paper include the use of OCTA, which is superior to traditional angiography in providing depth-resolved information about the superficial, intermediate, and deep retinal perfusion in a non-invasive fashion. Moreover, deep-learning tools, sample size (138 diabetic eyes), and statistical analysis represent additional strength points.

That said, the paper should be interpreted in view of the following potential limitations:

- The small field of view: the authors evaluated only the central macular area (3x3 mm) and no data are provided about the peripheral retina. Peripheral ischemia might induce local vascular endothelial growth

factor production and contribute to the disruption of the blood-retinal barrier in the macula; wider field of view OCTA scan may be more informative in understanding the vascular changes occurring in eyes with DME .

- The poor clinical characterization of the patients' cohort: there are no data about duration of DM, DR or DME, patient' metabolic control (Hb1Ac), previous treatments such as intravitreal injections or panretinal retinal photocoagulation (which may cause modifications in the macular perfusion metrics on OCTA).
- The impossibility to exclude masking artifacts from the cyst from the evaluation of the quantitative OCTA metrics and the absence of data from Intermediate Capillary Plexus: this ambiguity introduces potential confounders to the actual effect of diabetes on the various capillary plexus.
- The absence of a control group: we do not know the normative values in the population selected by the authors.
- The potential for a selection bias: the authors only included eyes with good-quality images. Systematic exclusion of poor-quality images and the single-center design may reduce the generalizability of the results.

In conclusion, this study is well-designed and highlights the possible role of deep capillary non-perfusion in the pathogenesis of DME. The state of the DCP may become a clinical biomarker associated with DME; its significance in forecasting the risk of DME in patients without diabetic macular involvement needs to be addressed by future research.