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To cite this article: Mariacristina Parravano, Serena Fragiotta & Giuseppe Querques (2022) Prognostic relevance of optical coherence tomography angiography biomarkers in diabetic macular edema, Expert Review of Ophthalmology, 17:3, 161-163, DOI: [10.1080/17469899.2022.2108406](https://doi.org/10.1080/17469899.2022.2108406)

To link to this article: <https://doi.org/10.1080/17469899.2022.2108406>



Published online: 05 Aug 2022.



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EDITORIAL



Prognostic relevance of optical coherence tomography angiography biomarkers in diabetic macular edema

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ARTICLE HISTORY Received 23 June 2022; Accepted 28 July 2022

KEYWORDS Optical coherence tomography angiography; deep capillary plexus; superficial capillary plexus; diabetic retinopathy; diabetic macular edema

1. Introduction

Optical coherence tomography angiography (OCTA) enables visualization of the retinal capillary plexus structure at various depths, identifying flow density and microaneurysms from the deep capillary plexus (DCP) in diabetic retinopathy (DR) beyond the ability of fluorescein angiography (FA) [1,2]. Diabetic macular edema (DME) is one of the leading causes of vision loss in diabetic patients with a variable and temporary improvement in response to treatment [3].

In this scenario, recognizing particular OCTA features is crucial for identifying the prediction of DME that can be of paramount importance to establishing a better glycometabolic control and thus preventing DME development. Indeed, DME eyes with macular center involvement retaining a good visual acuity of 20/25 letters or better showed no significant differences in vision loss at 2 years in patients managed with aflibercept, laser photocoagulation, or observation [4]. In addition, another important role of OCTA consists in predicting the responsiveness to treatment [5].

2. OCTA features associated with intraretinal fluid accumulation

2.1. Microaneurysms characteristics on OCTA can predict DME development

Microaneurysms (MAs) demonstrated different patterns of blood flow dynamics associated with distinctive OCT and OCTA characteristics [6]. Hyperreflective MAs developed extracellular fluid more frequently than hyporeflective MAs (66% vs. 18%, respectively). Other factors strongly associated with the development of extracellular fluid included the presence of flow on OCTA B-scan within MAs and the location at the level of DCP at baseline. Furthermore, a strong correlation between the higher internal reflectivity of MAs on structural OCT B-scan and the presence of flow on OCTA both associated with the development of intrare-

etinal fluid at 1 year supported the hypothesis of different blood flow dynamics in MAs. In this regard, the presence of hyperreflective MAs represents a prognostic factor for DME development [7]. **The presence of flow within MAs detectable on OCTA has been confirmed to reflect the intraneurysmal turbulence due to the contrast-induced flicker produced by the erythrocytes in motion above the OCTA threshold [8].**

The morphological appearance of MAs on OCTA can also predict FA leakage and thus the retinal thickness. The fusiform appearance increased with DR stage progression passing from 2.7% in mild and moderate non-proliferative DR to 13.9% in the proliferative stage. This type of MA was associated with FA leakage in 82.8% of cases, representing the most relevant leakage-related morphological phenotype with statistical significance [9].

2.2. OCTA metrics predictive of DME development

OCTA metrics can be crucial for assessing the progression risk in DR and DME. In particular, foveal avascular zone (FAZ), FAZ circularity, vessel density (VD), fractal dimension (FD), and vessel diameter index (VDI) can be obtained on both superficial (SCP) and DCP [10].

DME development was associated with a lower VD on SCP, without significant associations in the DCP. In contrast to the OCTA metrics predicting DR progression, which interested DCP with a larger FAZ, a lower VD, and FD of DCP. The evidence of an association between VD of the SCP and DME development was explained by the fact that the fluid production may originate from the SCP, and an increasing leakage at this level may overcome the fluid-removing capabilities carried out by Müller cells and the DCP. Furthermore, eyes with DME had a larger FAZ of DCP and lower VD and FD at the same level, supporting the hypothesis that once the DME has developed, the DCP can be progressively damaged being actively involved in fluid removal [11].

3. OCTA biomarkers as predictors of DME treatment response

3.1. Microvascular changes in DCP predict poor responders DME eyes

The use of OCTA allowed a deep understanding of the role of DCP vascular alterations in DR, as this vascular layer appears more susceptible to diabetic vascular changes occurring primarily at this level [12,13]. This evidence has encouraged a customized analysis of the OCTA metrics considering a differential involvement of the retinal capillary plexuses with the ability to predict more sensitive biomarkers according to microvascular involvement. The microvascular involvement of DCP was also strongly associated with the treatment response of DME to anti-vascular endothelial growth factors (anti-VEGF) [14]. DME eyes poor responders to anti-VEGF agents demonstrated lower mean flow density, a higher number of microaneurysms, and a larger FAZ in DCP compared to those with a good response to treatment. The vascular plexus boundaries were carefully checked and adjusted, if necessary, to minimize the potential bias of cystoid spaces on flow quantification. The total capillary plexus was also calculated to confirm the differences found in the DCP [14].

3.2. Microaneurysms characteristics exhibit different responses to treatment

Patients with higher hyperreflective MAs could be considered at increased risk for diabetic maculopathy progression. Despite this, hyperreflective MAs indicate a better response to anti-VEGF or steroid treatment because they present active blood flow dynamic pointing through a recent BRB breakdown. Contrariwise, hyporefective MAs may have a poor response to treatment as they denote an indirect sign of advanced nonperfusion in diabetic maculopathy [7].

3.3. Suspended scattering particles in motion (SSPiM)

Suspended scattering particles in motion (SSPiM) is a term coined to describe a decorrelation signal caused by the Brownian motion of particles within intraretinal fluid pockets on OCTA, believed to represent the motion of lipoprotein particles suspended in a liquid compartment or either fibrinogen aggregates within cystoid spaces [15,16]. SSPiM can be visualized on OCTA B-scans as an extravascular OCTA flow signal within intraretinal cysts and as slightly hyperreflective oval areas (i.e. gray) on OCTA vascular slabs [15]. The identification of SSPiM was observed to be associated with poor treatment response using either steroid or anti-VEGF agents. More in detail, the location of SSPiM in the inner nuclear layer affected the treatment response for anti-VEGF agents, while the presence of SSPiM in the outer nuclear layer influenced the response to steroids [17]. Nevertheless, this first evaluation analyzed only the largest cyst at any location for each patient, which may not reflect the status of the entire macular region. Furthermore, the segmentation errors were not estimated and corrected.

SSPiM was identified on both superficial (SCP) and DCP as hyperreflective cystic regions using different OCTA devices. Of note, the segmentation errors were frequent due to vessel displacement induced by the presence of cysts [15]. To better understand the role of SSPiM in treated DME eyes, an evaluation of the entire 3-mm volume was performed by delineating the total cystic area and mean size occupied by SSPiM on OCTA slabs using the B-scans as reference [18]. The response to steroidal treatment evaluated on both superficial and DCP revealed no significant changes in SSPiM total area at 2 and 4 months. SSPiM exhibited a peculiar pyramidal topographic distribution starting from the outer toward the inner retinal layers. This peculiar topographic distribution of SSPiM may reflect the presence of a lipoproteinaceous material denser than fluid sinking toward the outer retinal layers. Therefore, the presence of SSPiM in DME seems to be a consequence of a more severe inner blood–retinal–barrier (BRB) breakdown leading to an increased concentration of a denser material in the absence of an adequate physiologic clearance mechanism. Since the intraretinal fluid demonstrated a rapid and complete resolution after dexamethasone implant, it may be speculated that a denser material may need repeated or long-standing treatments to obtain an optimal response [18].

4. Conclusion

Several OCTA biomarkers have been identified in DME with the potential to predict the treatment response to intravitreal steroids and anti-VEGF agents. Microaneurysms distinction according to their internal reflectivity, the presence of flow, the morphology, and the anatomical location within retinal vascular plexuses help predict the risk of DME at 1 year and the treatment response. The opportunity to segment different anatomical vascular layers provided the advantage of studying DCP in greater detail. This vascular layer is primarily and significantly affected in DR, demonstrating relevant microvascular alterations with prognostic value in forecasting anti-VEGF response. These alterations can be easily recognized in clinical practice, a reduced flow density, an increased number of microaneurysms, and a larger FAZ. Another factor readily identified on both OCTA slabs and B-scans is represented by SSPiM. This OCTA feature accounted for a reduced cystic resolution compared to the intraretinal fluid that can be effectively resolved after a single treatment, suggesting a prominent BRB breakdown and perhaps the need to plan a more intensive treatment in those patients. The optimal interpretation of these OCTA biomarkers could improve the monitoring and management of DME.

Declaration of interest

M Parravano reports personal fees from Allergan, Novartis, Bayer, Zeiss, Omikron, Alfanties, and Sifi outside the submitted work. G Querques has acted as a consultant and/or advisor for Alimera Sciences, Inc., Allegro, Allergan, Apellis, Bausch & Lomb, Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, CenterVue, Heidelberg Engineering, Lumithera, Nevacar, Novartis Pharmaceuticals Corporation, Roche, SIFI, Sooft/Fidia, Topcon, Thea, and Zeiss, none of which are related to the present work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial

conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed receipt of consulting fees from Kowa, as well as travel reimbursements and speaker fees from Novartis, Bayer Pharma, Canon Inc., Santen Pharmaceutical, Kowa, Senju Pharmaceutical, Ono Pharmaceutical and Merck Sharp & Dohme. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

This paper was not funded.

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- This study first reports the response of different cystic components, including SSPiM, to a single dexamethasone implant, suggesting that the presence of SSPiM may indicate a severe BRB breakdown.**