Original Article

Diabetic microaneurysms detected by fluorescein angiography spatially correlate with regions of macular ischemia delineated by optical coherence tomography angiography

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Purpose: To characterize the relationship between diabetic macular ischemia (DMI) delineated by optical coherence tomography angiography (OCTA) and microaneurysms (MAs) identified by fundus fluorescein angiography (FFA). **Methods:** Patients with diabetic retinopathy (DR) who underwent OCTA and FFA were retrospectively identified. FFA images were cropped and aligned with their respective OCTA images using i2k Align Retina software (Dual-Align, Clifton Park, NY, USA). Foveal avascular zone (FAZ) and ischemic areas were manually delineated on OCTA images, and MAs were marked on the corresponding FFA images before overlaying paired scans for analysis (ImageJ; National Institutes of Health, Bethesda, MD, USA). **Results:** Twenty-eight eyes of 20 patients were included. The average number of MAs identified in cropped FFA images was 127 ± 42. More DMI was noted in the superficial capillary plexus (SCP; 36 ± 13%) compared to the deep capillary plexus (DCP; 28 ± 14%, $P < 0.001$). Similarly, more MAs were associated with ischemic areas in SCP compared to DCP (92.0 ± 35.0 vs. 76.8 ± 36.5, $P < 0.001$). Most MAs bordered ischemic areas; fewer than 10% localized inside these regions. As DMI area increased, so did associated MAs (SCP: $r = 0.695$, $P < 0.001$; DCP: $r = 0.726$, $P < 0.001$). Density of MAs surrounding FAZ (7.7 ± 6.0 MAs/mm^2) was similar to other DMI areas (SCP: 7.0 ± 4.0 MAs/mm^2, $P = 0.478$; DCP: 9.2 ± 10.9 MAs/mm^2, $P = 0.394$). **Conclusion:** MAs identified in FFA strongly associate with, and border areas of, DMI delineated by OCTA. Although more MAs are localized to SCP ischemia, the concentration of MAs associated with DCP ischemia is greater. By contrast, few MAs are present inside low-flow regions, likely because capillary loss is associated with their regression.

Key words: Automated alignment, diabetic macular ischemia, fluorescein angiography, microaneurysms, optical coherence tomography angiography

Access this article online

Website: https://journals.lww.com/ijo

DOI: 10.4103/IJO.IJO_3155_22

Quick Response Code:

Vision-threatening diabetic retinopathy (DR) can result from macular swelling, known as diabetic macular edema (DME), or complications due to proliferative DR (PDR). These are the leading causes of visual impairment in patients with type 2 and type 1 diabetes mellitus (DM), respectively.[1,2] DR may also affect the macula, leading to the formation of microaneurysms (MAs) and the development of a microangiopathy known as diabetic macular ischemia (DMI), both of which may lead to loss of vision, albeit through different mechanisms. DMI is a more insidious cause of vision loss and can develop in the absence of DME or PDR.[3] DMI has also been linked to the progression of DR. A recent analysis of the RIDE and RISE trials demonstrated that patients who had DMI at baseline progressed to neovascular complications from DR earlier despite intravitreal ranibizumab treatment compared to those who started with normal macular perfusion at baseline.[4] Still, very little is known about the pathophysiology of DMI and its relation to MA formation and vision loss.

In this retrospective study of patients with varying stages of DR, we examined the spatial distribution of MAs and their relationship to areas of capillary dropout (CDO) in the macula. We employed fundus fluorescein angiography (FFA), which is the most effective method for identifying MAs,[5] and optical coherence tomography angiography (OCTA), which is currently the best technique for analyzing areas of CDO within each capillary layer of the macula.[6-8] To precisely compare the relationship of these pathologic changes across imaging modalities, we used image alignment software to automatically register and crop FFA images to their respective OCTA

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Received: 02-Dec-2022 Revision: 20-Mar-2023
Accepted: 01-Jun-2023 Published: 01-Aug-2023

Cite this article as: Abdel-Kader AA, Ramsey DJ, Yussuf WA, Mohalhal AA, Eldaly MA, Elnahry AG. Diabetic microaneurysms detected by fluorescein angiography spatially correlate with regions of macular ischemia delineated by optical coherence tomography angiography. Indian J Ophthalmol 2023;71:3085-90.

scan.[7] In doing so, we further leverage the advantages of both technologies to provide structural and functional information with the precision necessary to make quantification of these changes possible at the capillary level. Although other studies have evaluated DMI and MAs using FFA and OCTA,[7-9] to date no study has specifically analyzed the spatial relationship between MAs detected on FFA imaging and the extent and level of capillary ischemia detected using OCTA. This is important to further understand the relationship between these pathological changes found in patients with DR. Finally, we assessed the impact of other DR biomarkers such as the extent of DME and changes in the size of foveal avascular zone (FAZ) on visual acuity (VA) in the registered and aligned macular images across modalities.

Methods

Study design and population

Patients with DR who underwent FFA and OCTA at Cairo University Hospital were retrospectively identified. The research adhered to the tenets of the Helsinki Declaration and was approved by Cairo University research ethics committee. Exclusion criteria included significant media opacities, myopia greater than 6 D, or history of diseases that could impact the retinal vasculature, including retinal vein occlusion, uveitis, an epiretinal membrane, or glaucoma. No participant had history of intravitreal injections, retinal photocoagulation, or vitreoretinal surgery. Eyes with DME were not excluded; however, OCTA images with significant artifacts, low signal strength, or segmentation errors that could not be corrected were excluded. Images that could not be automatically aligned using i2k Align Retina software (Dual-Align LLC, Clifton Park, NY, USA) were also excluded.

Using medical health records, we extracted the following information: best corrected distance visual acuity (BCVA), intraocular pressure, and examination findings on slit lamp and indirect ophthalmoscopy. Snellen VA was converted to the logarithm of the minimum angle of resolution (LogMAR). Severity of DR was graded using the International Clinical Diabetic Retinopathy Disease Severity Scale.[10]

Image acquisition

FFA was performed using a TRC-50DX retinal camera (480 nm; Topcon Co., Inc., Tokyo, Japan) or a Spectralis HRA + OCT system (488 nm; Heidelberg Engineering, Inc., Heidelberg, Germany). High-quality, mid-phase images obtained after complete arteriovenous filling of the posterior pole were chosen for each eye to allow for the greatest capillary resolution while limiting the tendency of dye leakage to obscure the retinal microvasculature.

Spectral domain (SD)-OCTA was performed using Optovue RTvue XR Avanti (840 nm; Optovue, Inc., Fremont, CA, USA), acquiring a scanning area of 6 × 6 mm centered on the fovea. The superficial capillary plexus (SCP) and the deep capillary plexus (DCP) were automatically segmented using the built-in OCTA software as previously described.[11]

Image alignment and analysis

Each 30° FFA image was automatically cropped and aligned to the corresponding 6 × 6-mm OCTA *en face* total capillary plexus (TCP) image of the retina using i2k Align Retina software as previously described.[7]OCTA images were upsampled to match the native resolution of FFA images to ensure that image alignment did not reduce the quality of information within the FFA images for each eye. To avoid measurement bias, all photos were coded and randomized before grading.

Areas of CDO, defined as areas of flow void, were manually traced in each OCTA image at the SCP and DCP separately using ImageJ. Color-coded OCTA images with vascular density (VD) maps generated by the built-in machine software were used to aid delineation of areas of CDO for measurement of DMI [Fig. 1]. The total area of CDO in each image was determined by dividing the sum of the areas of CDO by the total image area (36 mm^2) and multiplying the result by 100. This percentage reflects the extent of DMI in each capillary layer. Automated ischemia percentage was also calculated from each layer using the automatically generated VD percentages from the built-in OCTA software. It was defined as 100 minus VD in the "Whole Image" section of each capillary layer. FAZ area was manually measured in TCP using the freehand tool of ImageJ (National Institutes of Health, Bethesda, MD, USA) as previously described.[7] MAs were marked after being identified as hyperfluorescent spots visible on mid-phase FFA images, typically 1 min after dye injection to prevent their obscuration by dye leakage [Fig. 2]. For this study, no distinction was made between leaking and nonleaking MAs or telangiectatic capillaries (also known as TelCaps or capillary macroaneurysms) and MAs. All measurements were performed by a single masked investigator (A. G. E.)

After alignment and grading, marked OCTA and FFA images were overlaid using Image J and analyzed [Fig. 3]. This was done separately for SCP and DCP. MAs were

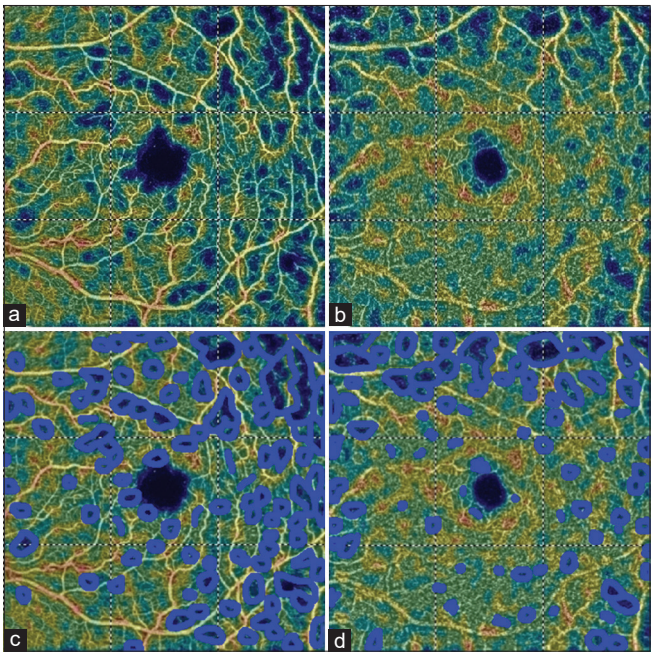

Figure 1: Retina vascular density color-encoded OCTA images of SCP (a) and DCP (b) with flow-void areas, corresponding to capillary dropout, manually delineated in blue (c and d). DCP = deep capillary plexus, OCTA = optical coherence tomography angiography, SCP = superficial capillary plexus

categorized into three groups according to their relationship to areas of CDO in each capillary layer: MAs bordering CDO areas (within ±50 µm of the edge of a CDO area), MAs distant from CDO areas (more than 50 µm from the nearest CDO area), and MAs inside CDO areas (more than 50 µm inside the edge of a CDO area). Finally, the density of MAs surrounding FAZ was specifically calculated by dividing the number of MAs bordering FAZ (within ± 50 µm of the edge of FAZ) by FAZ area.

Statistical analysis

Data were encoded and analyzed using SPSS® Statistics version 22.0 (IBM Corp, Armonk, NY, USA). Data are presented as mean (± standard deviation [SD]), median, minimum, and maximum for continuous variables and as frequency (count) and relative frequency (percentage) for categorical data. We used Student's *t*-test to compare normally distributed quantitative variables, while nonparametric Wilcoxon signed rank test was used for non-normally distributed quantitative variables. Pearson's correlation coefficient and Spearman rank correlation were used to evaluate the linear relationship between continuous and ordinal variables, respectively. All tests were 2-sided, and *P* values below 0.05 were regarded as statistically significant.

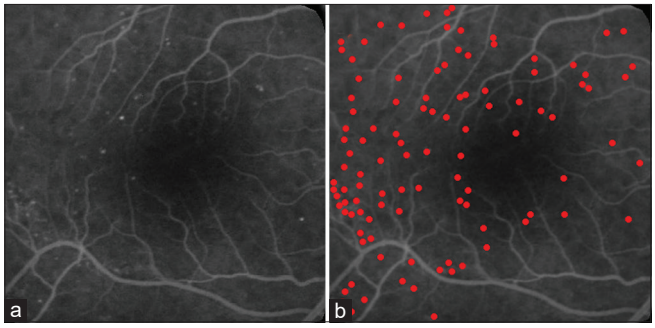

Figure 2: Example mid-phase FFA image (a) and after MAs, identified as hyperfluorescent spots, were manually marked in red (b). FFA = fundus fluorescein angiography, MA = microaneurysms

Results

Patients and image alignment

Thirty-three eyes of 24 patients with DR who underwent imaging met the inclusion criteria for the study. Of these eyes, 21 underwent FFA on a Topcon TRC-50DX retinal camera and 12 on a Spectralis HRA + OCT system. FFA images for 28 eyes (84.8%) from 20 patients were successfully aligned with their corresponding 6 × 6 mm TCP image of the macula obtained by means of OCTA imaging and were included in the subsequent analysis. Images from the remaining eyes could not be registered likely because of imaging artifacts or poor image quality, and therefore, they were excluded. This step effectively ensured that only registered image pairs of sufficiently high quality were included in the study as previously described.[7] Demographic and clinical characteristics of the included patients are provided in Table 1.

Extent of DMI on OCTA

For the study population, the area of CDO was greater in SCP (36% ±13%) compared to DCP (28% ±14%, $P < 0.001$). Not surprisingly, the area of CDO correlated strongly between the plexuses ($r = 0.724$, $P < 0.001$). The area of CDO also correlated with the percent of ischemia automatically generated by the built-in OCTA software for both SCP ($r = 0.680$) and DCP ($r = 0.769$, $Z = 0.765$, $P = 0.445$). FAZ area (0.477 ± 0.221 mm^2) also correlated with CDO area in SCP ($r = 0.488$, $P = 0.009$), as well as with DR severity ($r = -0.574$, $P = 0.001$). No association was identified between CDO and DR severity.

Spatial localization of MAs to areas of DMI

The mean number of MAs on cropped FFA images was 127 (±42). A greater number of MAs were observed to be associated with areas of CDO in SCP compared to DCP (92.0 ± 35.0 vs. 76.8 ± 36.5, $P < 0.001$). The proportion of total MAs associated with areas of CDO was also larger in SCP compared to DCP (72% ±12% vs. 59% ± 17%, $P < 0.001$). As the area of DMI increased, so did the total fraction of MAs associated with each of these plexuses (SCP: $r = 0.695$, $P < 0.001$; DCP: $r = 0.726$, $P < 0.001$). Notably, most of these MAs bordered the ischemic areas (within ± 50 µm) in both SCP (89% ± 13%) and

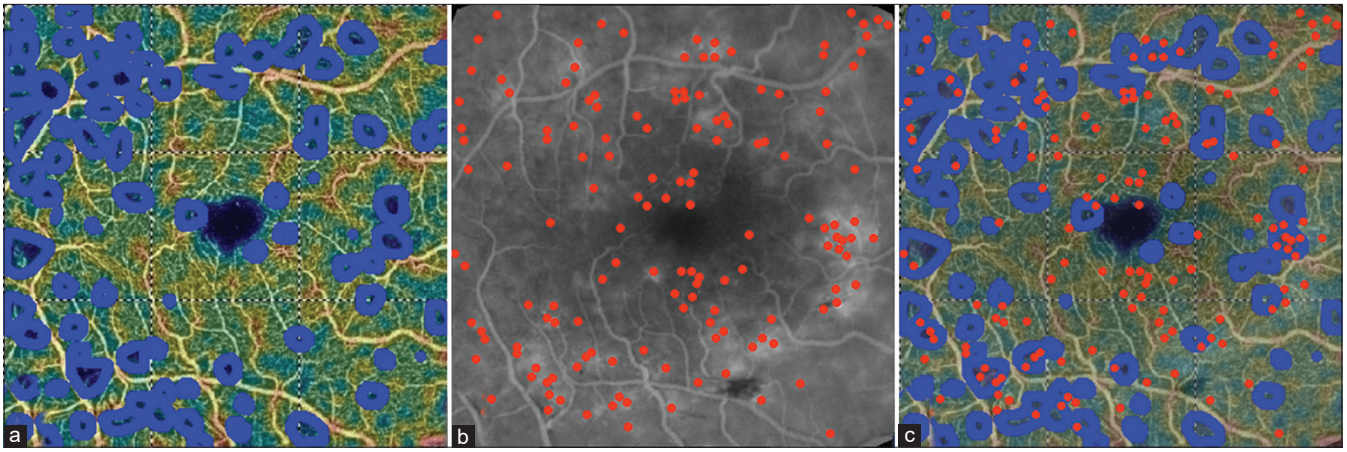

Figure 3: After alignment and grading, the OCTA (a) and FFA (b) images were overlaid using ImageJ (c) and the spatial relationship between MAs and CDOs was assessed. An MA was defined as (i) bordering an area of CDO if their markings touched, (ii) distant from an area of CDO if it was identified to be outside of any area of CDO, and (iii) inside an area of CDO if was inside a CDO area without their markings overlapping. Marking thickness was set at approximately 50 µm using the Pencil Tool in Image J. CDO = capillary dropout, FFA = fundus fluorescein angiography, MA = microaneurysms, OCTA = optical coherence tomography angiography

Table 1: Demographic and clinical characteristics of included patients

Characteristics	Value
Age, years (±SD)	53.6 (±7.2)
Female gender, *n* (%)	14 (70%)
Diabetes type 2, *n* (%)	15 (75%)
Duration of diabetes, years (±SD)	12.5 (±5.5)
Hemoglobin A1c, % (±SD)	8.1 (±1.7)
Hypertension, *n* (%)	13 (65%)
Best corrected distance visual acuity, LogMAR (±SD)	0.68 (±0.43)
Central macular thickness, μm (±SD), [range]	328.6 (±151.5), [225–828]
Lens Status	
Clear, *n* (%)	7 (25%)
Nuclear sclerosis, *n* (%)	13 (46.4%)
Cortical cataract, *n* (%)	8 (28.6%)
Severity of diabetic retinopathy	
Mild, *n* (%)	2 (7.1%)
Moderate, *n* (%)	5 (17.9%)
Severe, *n* (%)	15 (53.6%)
Proliferative, *n* (%)	6 (21.4%)
Fluorescein angiography type	
Topcon (TRC-50DX), *n* (%)	18 (64.3%)
Spectralis (HRA + OCT), *n* (%)	10 (35.7%)

SD=standard deviation

DCP (93% ± 8.8%); only a minority of them was localized within the ischemic regions (13% ± 23% and 8.7% ± 13% in SCP and DCP, respectively). Finally, the density of MAs surrounding FAZ (7.7 ± 6.0 MAs/mm^2) was similar to other areas of macular ischemia (7.0 ± 4.0 MAs/mm^2 for SCP, $P = 0.478$ and 9.2 ± 10.9 MAs/mm^2 for DCP, $P = 0.394$). No association was identified between the total number of MAs and the size of FAZ, BCVA, central macular thickness (CMT), or DR severity, likely because no distinction was made between leaking and nonleaking MAs.

Impact of DMI on VA

Across all study eyes, CMT (329 ± 152 μm) moderately correlated with BCVA (LogMAR 0.606 ± 0.301, $r = 0.689$, $P < 0.001$). Interestingly, only the extent of CDO in SCP correlated with BCVA ($r = -0.618$, $P < 0.001$). By contrast, no association was identified between BCVA and age, gender, number of MAs, FAZ size, or severity of DR. Next, we determined whether CDO yielded any additional utility in predicting BCVA for the eyes in our study. Adding area of CDO in SCP to a regression of multiple variables increased the prediction of BCVA to adjusted $R^2 = 0.719$ ($\Delta R^2 = 0.266$, $P < 0.001$).

Discussion

The number of people affected by DR is rapidly growing as the prevalence of DM is increasing worldwide.[12] DM damages the retinal microvasculature, resulting in DR.[13] The most prominent pathologic changes in DR include the development of MAs and progressive loss of capillaries.[14] FFA was the first imaging method used to diagnose DMI by allowing the detection of retinal capillary loss in the macula, as well as FAZ enlargement.[15,16] However, the interpretation of FFA is mainly qualitative, limited largely to characterizing the superficial retinal vasculature, and not easily standardized between clinics. The technique is also relatively invasive, and at times produces unpleasant side effects,[17] which limits its utility for diagnosing and monitoring DMI. The recent introduction of OCTA represents a paradigm shift because it is noninvasive, depth resolved, and allows for serial, high-resolution imaging of both SCP and DCP, providing registered scans which facilitate quantitative analysis in three dimensions. It also outperforms FFA in localizing areas of retinal capillary ischemia by readily detecting flow voids, and its ability to resolve these regions is not limited by dye leakage or macular xanthophyll pigment.[6,7] Nevertheless, FFA is superior for detecting MAs because FFA is based on blood flow rather than red blood cell motion and can, therefore, better identify both low-flow MAs and leakage.[7-9]

To our knowledge, our study is the first to combine the ability of OCTA to identify DMI in separate capillary layers with the superior ability of FFA to identify MAs. By doing so, we leverage the advantages of each imaging modality and, for the first time, report the relationship between DMI at each capillary level and MAs using the gold standard for each pathology. As we expected based on findings from previous histologic and clinical studies,[14] MAs were found to be more concentrated near ischemic areas, with a significant positive correlation. This was noticeable across both SCP and DCP. Only SCP ischemia, however, showed a significant positive correlation with the overall number of MAs seen on FFA, indicating that SCP ischemia could be a stronger driver of MA formation compared to DCP ischemia. The distribution of MAs and CDO observed using FFA has been previously investigated in relation to DME using the OCT Early Treatment Diabetic Retinopathy Study (ETDRS) macular thickness map in a study of 115 eyes.[18] Although OCTA was not used, the results of this study showed that MAs were significantly more prevalent in less-edematous macular areas and the total length of circumference of CDOs was significantly correlated with the number of MAs.

A recent study that examined 18 diabetic eyes using OCTA and colored fundus photographs discovered that at least a quarter of MAs that were not detected by OCTA could be attributed to low flow, as they tended to be found in areas with lower capillary density.[19] Based on our OCTA findings, DMI can be compared to a flower bouquet with ischemia

more severe in SCP and MAs clustered around it the drive being excessive vascular endothelial growth factor (VEGF) production. Interestingly, previous studies have suggested that MAs are more prevalent in DCP in DR.[7,20-23] This could be because DCP is often relatively more intact compared to SCP in DR, allowing for more MAs to form or persist in DCP. This is also supported by our finding that few MAs are present inside the flow void regions, which were more prevalent in SCP, likely because capillary loss would be associated with their regression. It is also important to note that areas of CDO in DR do not commonly reverse with the available treatments and their development may be impacted by treatment with anti-VEGF.[24] This stresses the importance of accurate quantification of these regions to optimize their follow-up and assess the effects of different present and future treatments.

Our study confirms that in DR, SCP has more ischemia compared to DCP. A similar study that compared 54 eyes from patients with moderate nonproliferative diabetic retinopathy (NPDR) to age-matched healthy eyes reported a significant decrease in SCP VD, but only minor alterations in DCP.[25] Similar to our study, a retrospective cross-sectional study that compared 137 eyes of 86 patients with different stages of DR to healthy age-matched eyes reported a linear correlation between SCP and DCP VD, as well as increase in FAZ diameter.[26] Finally, a study that compared 75 eyes from patients with DR to healthy control eyes found the number and area/perimeter ratio of intercapillary spaces increased considerably with increasing DR severity.[27]

Currently, it is still unclear if retinal capillary ischemia is the cause of MA formation, or vice versa,[28,29] although both conditions often coexist and are a major cause of vision loss in DR.[14,30,31] Knowledge of the specific sequence of events that lead to these manifestations of DR could, therefore, have important prognostic and management implications. Importantly, for the eyes in our study, CDO in SCP was an independent predictor of BCVA, even after accounting for CMT. Our study adds to a growing body of evidence that CDOs correlate with VA changes.[32,33] This is important because DMI is an important cause of vision loss[3] and may also account for why some eyes fail to gain vision or even lose vision despite treatment.[34] Similar to other studies,[3] our study did not find a connection between FAZ and BCVA, though other studies have found conflicting results.[32]

Our study is limited by its retrospective nature and the small number of eyes with varying DR levels. Our study also lacked racial and ethnic diversity, which limits the generalization of findings. Future studies should address these gaps because it is known from studies that examined patients who identified as members of racial or ethnic minority groups in the USA that they face a disproportionately high burden from DR[1,2] and at the same time are less likely to access eye care.[35] Another limitation is that we used two FFA systems, which differ in contrast, resolution, and other machine-based variables; however, our study lacks the power to evaluate these differences. The platform-independent nature of our image alignment method likely moderates some of the impact from these differences. Furthermore, several of our findings have been validated by previous studies that compared DR findings on FFA to OCTA, albeit on a qualitative level.[8,9] We also did not distinguish between leaking and nonleaking MAs or between MAs and TelCaps, which are best imaged using indocyanine green angiography.[36] Future studies should examine in detail these additional features that may serve as functional biomarkers. Our study also used a 6 × 6 mm scanning area centered on the fovea to encompass the entire macula, rather than the smaller 3 × 3 higher-density scan, which could have improved the precision of certain measurements, especially in relation to the fovea. However, we believe that the clinical advantages of a larger scanning area outweigh these other considerations because the macula is an anatomical region with important implications for treatment and vision.[1,37] Finally, although the alignment software allowed us to precisely retrieve the same retinal area in both FFA and OCTA images, and objectively eliminate images of poor quality or those with excessive imaging artifacts, the process of registering FFA images to their corresponding OCTA itself could also introduce artifacts. However, this method has been shown to introduce less than 2% image distortion in practice.[38]

Conclusion

DMI is a vision-threatening consequence of DR that is best assessed using OCTA. By contrast, MAs are most effectively visualized by FFA and have a strong association with vision loss.[1-2,37] Our study allowed for the first time the characterization and validation of the spatial relationship between MAs identified on FFA and the areas of CDO in each capillary layer detected by OCTA, the gold standard imaging modality for each of these pathologies. In addition to being more ischemic, a greater number of MAs were observed to be associated with, and border, areas of CDO in SCP compared to DCP; yet, the concentration of MAs was greatest in relation to DCP ischemia. Importantly, few MAs were present inside low-flow regions, likely because capillary loss is associated with their regression. By combining the techniques of FFA and OCTA, future prospective studies could effectively examine the longitudinal implications of both superficial and deep retinal ischemia and its relationship to MA formation in DR.

Acknowledgements

The authors thank Dr. Paul R. Cotran, Dr. Jeffrey L. Marx, Dr. Gregory R. Blaha, as well as Carol Spencer, Lahey Hospital Librarian, for research support. The manuscript is based on a presentation from the Association for Research in Vision and Ophthalmology Imaging in the Eye Conference, April 27, 2019, in Vancouver, Canada.

Ethical approval

This report was approved by the Cairo University research ethics committee (approval number: MD-39-2021) and followed the tenets of the Declaration of Helsinki.

Financial support and sponsorship

D. J. R. was supported by the Harry N. Lee Family Chair in Innovation at the Lahey Hospital and Medical Center, Beth Israel Lahey Health.

Conflicts of interest

There are no conflicts of interest.

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