The Relationship between Foveal Ischemia and Spectral-Domain Optical Coherence Tomography Findings in Ischemic Diabetic Macular Edema

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Purpose. To investigate the relationship between enlargement of the foveal avascular zone (FAZ) and structural changes on spectral-domain optical coherence tomography (SD-OCT) in patients with ischemic diabetic macular edema (DME).

Methods. This was a retrospective, cross-sectional study including 35 eyes of 33 patients with ischemic DME as determined by irregular margins of the FAZ in fluorescein angiography. We measured the best-corrected visual acuity (BCVA), central subfield thickness (CST), subfield volume, subfoveal choroidal thickness, length of the photoreceptor outer segment (PR-OS), and the lateral extent of inner segment–outer segment (IS-OS) disruption on SD-OCT images, as well as the FAZ to optic nerve head (FAZ/ONH) area ratio by using the ImageJ program.

Results. The mean FAZ/ONH area ratio was 0.28 ± 0.15. The FAZ/ONH area ratio was positively correlated with the logarithm of the minimum angle of resolution (LogMAR) BCVA ($P = 0.001$, $r = 0.529$). The mean CST was 391 ± 110 μm, and the subfield volume was 0.31 ± 0.09 mm^3. The mean length of the PR-OS and the horizontal and vertical extent of IS-OS disruption were 40 ± 8 μm, 169 ± 294 μm, and 114 ± 170 μm, respectively. The mean length of the PR-OS and the horizontal and vertical extent of IS-OS disruption were significantly correlated with FAZ/ONH area ratio ($P = 0.020$, $P = 0.001$, and $P = 0.049$, respectively). The horizontal and vertical extent of IS-OS disruption showed a positive correlation with LogMAR BCVA ($P = 0.027$ and $P = 0.049$, respectively).

Conclusions. Foveal ischemia in DME appears to cause PR-OS shortening and IS-OS disruption resulting in outer retinal layer atrophic changes and subsequent visual loss. (*Invest Ophthalmol Vis Sci.* 2013;54:1080–1085) DOI:10.1167/iovs.12-10503

Diabetic macular edema (DME) is a leading cause of visual loss in diabetes patients.[1] In diabetic retinopathy, enlargement of the foveal avascular zone (FAZ) is often detected by fluorescein angiography (FA).[2] FAZ enlargement is considered an indication of ischemia and may contribute to macular edema.[3] Macular ischemia is also known to be associated with poor visual outcome in diabetic patients regardless of their treatment.[4,5]

Recent technological advances in imaging have made it possible to analyze morphological changes of the retina in various retinal diseases. Optical coherence tomography (OCT) is an important tool being used to evaluate the retinal status and to predict the visual outcome. Several studies have investigated the correlation between structural changes in OCT and the visual prognosis in diabetic patients with macular edema.[6–8] Spectral-domain OCT (SD-OCT) is the most recently developed type of OCT and provides high-resolution images with an axial resolution of <5 μm. SD-OCT therefore provides clearer structural information regarding the retina and helps to identify the pathologic mechanisms in various retinal diseases.[9–10]

The purpose of this study was to investigate the relationship between enlargement of the FAZ and structural changes in SD-OCT and to determine the factors related to visual outcome in patients with ischemic DME.

Methods

Study Subjects

Patients with ischemic DME who underwent FA and SD-OCT (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany) in the Department of Ophthalmology, Asan Medical Center, Seoul, Korea, from March 2011 to December 2011 were included in this study.

Patients with macular edema caused by other diseases, such as age-related macular degeneration or epiretinal membrane or vitreomacular traction, were excluded. Patients who had undergone laser treatment within the past 6 months and/or intravitreal anti-VEGF injection within the past 3 months were also excluded. Patients with significant cataracts graded >NO3 or NC3 were excluded as well.

All patients' medical records were retrospectively reviewed. We then measured the FAZ enlargement area compared to the optic nerve head area ratio (FAZ/ONH area ratio), the central subfield thickness (CST), central subfield volume, length of the photoreceptor outer segment (PR-OS), subfoveal choroidal thickness, lateral extent of inner segment–outer segment (IS-OS) disruption and the best-corrected visual acuity (BCVA).

To compare the length of the PR-OS and the FAZ/ONH area ratio in patients with ischemic macular edema to those seen in our normal study subjects, we also measured the length of the PR-OS as well as the FAZ/ONH area ratio in healthy 30 eyes that were the fellow eyes of patients with a macular hole or epiretinal membrane.

This study was approved by the Institutional Review Board and Ethics Committee of Asan Medical Center and conformed to the tenets of the Declaration of Helsinki.

Measurements

Foveal ischemia was defined as enlargement of the FAZ with irregular margins in the FA. The area of FAZ enlargement and ONH were

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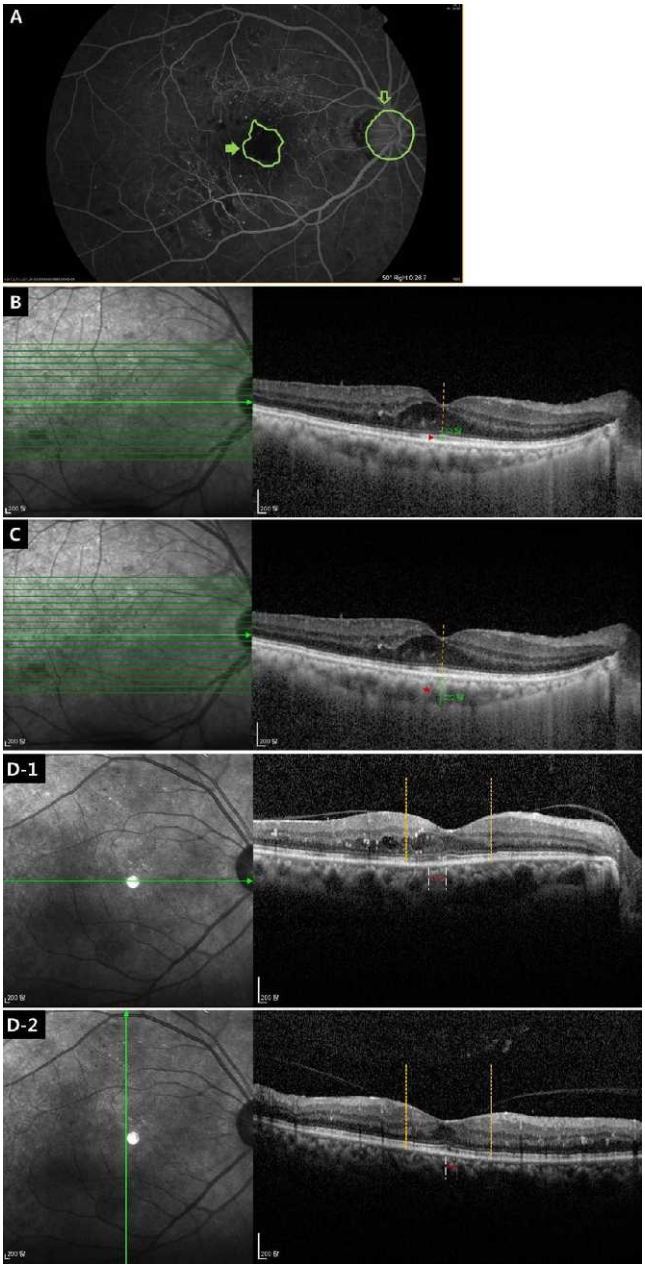

Figure 1. FA and SD-OCT measurements of patients with ischemic diabetic macular edema. (**A**) The area of FAZ enlargement (*solid arrow*) and the disc (*empty arrow*) were measured using ImageJ software. The FAZ/ONH area ratio was 0.7 in this patient. (**B**) The length of the photoreceptor outer segment (*arrow*) was measured according to the distance between the RPE and IS-OS junction at the foveal center. (**C**) Choroidal thickness (*star*) was measured according to the distance between the outer border of the RPE and the scleral border at the foveal center. In this patient, the length of the PR-OS was 52 μm and the subfoveal choroidal thickness was 232 μm. (**D**) Photoreceptor IS-OS disruption in patients with ischemic diabetic macular edema. The lateral extent of IS-OS disruption was measured within 2000 μm of the foveal center (between *yellow lines*) in the horizontal (**D-1**) and vertical (**D-2**) planes. The *red line* indicates IS-OS disruption.

measured using ImageJ software (National Institutes of Health; see http://rsbweb.nih.gov/ij/, in the public domain), and the FAZ/ONH area ratio was measured in each case (Fig. 1A).

The CST and the subfield volume were assessed using automatically measured values. SD-OCT provides an average retinal thickness and volume in the central, 1 mm zone of the fovea as CST and central subfield volume, respectively.

Table 1. Characteristics of Patients

Characteristic	
Age, y	58 ± 11
Sex, *n* (%)	
Male	16 (48%)
Female	17 (52%)
Duration of diabetes, y	15.7 ± 6.8
HbA1c	8.0 ± 1.7
Status of DR, *n* (%)	
Moderate NPDR	3 (8.6%)
Severe NPDR	16 (45.7%)
PDR	16 (45.7%)
Type of edema, *n* = 35 eyes (%)	
Cystoid macular edema	16 (45.7%)
Diffuse retinal thickening	13 (37.1%)
Subretinal detachment	6 (17.1%)

HbA1c, glycosylated hemoglobin.

The length of the PR-OS, subfoveal choroidal thickness, and horizontal and vertical extent of IS-OS disruption were manually measured at the foveal center point using a caliper equipped with SD-OCT; choroidal thickness was measured in the enhanced depth imaging (EDI) mode (Figs. 1B, 1C). The lateral extent of IS-OS disruption was measured within 2000 μm of the foveal center in the horizontal and vertical planes (Figs. 1D-1, 1D-2).

Manual measures of the OCT scans were performed by two blinded authors (DHL, SGJ). Average values of OCT measures were used for all analyses. The length of the PR-OS was defined as the distance between the IS-OS junction and the outer border of the neurosensory retina at the foveal center point. Subfoveal choroidal thickness was measured vertically from the outer border of the retinal pigment epithelium (RPE) to the inner border of the sclera at the foveal center point.

Statistical Analysis

Data were analyzed using SPSS software (version 18.0; SPSS, Inc., Chicago, IL). To assess the intraclass repeatability of the PR-OS length, subfoveal choroidal thickness, and measurements of the extent of IS-OS disruption, the intraclass correlation coefficient (ICC) was calculated. For the ICC calculation, the two-way, mixed-effects model for measure of absolute agreement and the single ratings was used. The Pearson correlation coefficient was used to analyze the relationship between the area of FAZ enlargement and BCVA. Linear regression was performed to analyze the correlation between the OCT findings and the area of FAZ enlargement. Multiple regression was performed to analyze the correlation between the OCT findings and the BCVA. The χ^2 test was used to compare the categorical variables. A P value of <0.05 was considered statistically significant. All values are presented as means with standard deviations.

Results

A total of 33 patients (35 eyes) were included in this study. Of these patients, there were 16 men and 17 women. The mean patient age was 58 ± 11 years (range, 23–70 years). All eyes had diabetic retinopathy (DR): 3 moderate nonproliferative diabetic retinopathy (NPDR), 16 severe NPDR, and 16 proliferative DR (PDR). Among the 35 eyes, 16 presented with cystoid macular edema, 13 with diffuse retinal thickening, and 6 with subretinal detachment with diffuse retinal thickening.

Table 2. Multiple Regression Analysis Comparing the BCVA and OCT Findings

	Mean	SD	β	*P* Value
IS-OS disruption, μm				
Horizontal	169	±294	0.457	0.027*
Vertical	114	±170	0.401	0.049*
PR-OS, μm	40	±8	−0.036	0.800
CST, μm	391	±110	1.277	0.745
Subfoveal volume, mm^3	0.31	±0.09	−1.289	0.743
Choroidal thickness, μm	252	±54	−0.100	0.437

β, beta coefficient.
* $P < 0.05$ was considered statistically significant.

The demographic data of the study participants are shown in Table 1.

The mean FAZ/ONH area ratio in ischemic DME was 0.28 ± 0.15 (range, 0.20–0.63), while the mean FAZ/ONH area ratio in healthy, normal subjects was 0.16 ± 0.4 (range, 0.08–0.25). The FAZ/ONH area ratio showed a statistically significant difference between ischemic DME and healthy eyes ($P < 0.001$). The mean FAZ/ONH area ratio according to DR grading was 0.28 ± 0.15 in NPDR and 0.27 ± 0.15 in PDR, and this difference was not statistically significant. The DR grading did not correlate with the FAZ enlargement ($P = 0.426$).

The mean CST and subfield volume were 391 ± 110 μm and 0.31 ± 0.09 mm^3, respectively. The mean length of the PR-OS and the subfoveal choroidal thickness were 40 ± 8 μm and 252 ± 54 μm, respectively (Table 2). The mean length of the PR-OS in healthy eyes was 53 ± 4 μm, which represented a significant difference compared with that for ischemic DME ($P < 0.001$). Of the 35 eyes, 21 (60%) had no IS-OS disruption; 14 eyes (40%) did have IS-OS disruption. The mean extent of IS-OS disruption in the horizontal and vertical planes was 169 ± 294 μm and 114 ± 170 μm, respectively. The ICC values for length of the PR-OS, subfoveal choroidal thickness, horizontal IS-OS disruption, and vertical IS-OS disruption were 0.97 (95% confidence interval [CI] 0.95–0.98), 0.93 (95% CI 0.84–0.97), 0.97 (95% CI 0.95–0.98), and 0.94 (95% CI 0.88–0.97), respectively, which showed strong reliability (Table 3).

The correlation between the FAZ/ONH area ratio and the SD-OCT findings showed a tendency toward a reduction in the CST, subfield volume, and PR-OS as the FAZ/ONH area ratio increased. The extent of IS-OS disruption also showed a positive relationship with the FAZ/ONH area ratio (Fig. 2). The mean FAZ/ONH area ratio, according to the type of edema, was 0.26 ± 0.15 in cystoid macular edema, 0.32 ± 0.17 in diffuse retinal thickening, and 0.24 ± 0.08 in subretinal detachment; and the CST was thickest in the subretinal detachment type ($P = 0.01$). However, there was no significant correlation between the type of edema and the FAZ/ONH area ratio ($P = 0.458$).

Among these OCT findings, the length of the PR-OS and the horizontal and vertical extent of IS-OS disruption were statistically correlated with FAZ enlargement in ischemic DME patients ($P = 0.020$, $P = 0.001$, and $P = 0.049$ respectively).

The FAZ/ONH area ratio showed a negative correlation with the BCVA ($P = 0.001$, $r = 0.529$) (Fig. 3). Among the OCT parameters, horizontal IS-OS disruption showing a strong correlation with poor visual acuity ($P = 0.027$) (Table 2).

Discussion

Diabetes is associated with a loss of pericytes as well as their autoregulatory function, thus resulting in destruction or weakening of vessel walls. As the blood supply to the inner retina in the FAZ is provided by small capillaries and through simple diffusion, hypoxia may not only induce but may also be exacerbated by macular edema. Therefore, hypoxia may have an important role in the development of DME as it increases capillary permeability and fluid leakage.[11] Foveal ischemia can cause visual field defects, reduction in contrast sensitivity, and poor response to intravitreal triamcinolone and anti-VEGF injections.[5,12–14]

Table 3. Intraclass Repeatability Index for PR-OS Length, Subfoveal Choroidal Thickness, and IS-OS Disruption Length in Ischemic Macular Edema Obtained Using SD-OCT

	ICC	95% CI
PR-OS	0.97	0.95–0.98
Subfoveal choroidal thickness	0.93	0.84–0.97
IS-OS disruption, horizontal	0.97	0.95–0.98
IS-OS disruption, vertical	0.94	0.88–0.97

FAZ enlargement is known to occur in patients with diabetic retinopathy, although the FAZ area varies considerably in normal study subjects.[2] Despite this variability, FA remains the gold standard for evaluating the retinal perfusion status and for detecting macular ischemia in patients with diabetic retinopathy.[15,16]

Technological advancements have made possible the direct correlation of pathologic lesions detected on FA and the structural changes seen on OCT. This makes it possible for clinicians to visualize histologic changes of the retina according to its hemodynamic status, and thereby assists researchers in their understanding of the pathophysiologic mechanisms underlying DME and in their ability to determine the prognostic factors related to the visual outcome. Previous studies have reported that foveal ganglion cell layer damage and loss of the inner retinal layers seen on SD-OCT correlated well with the macular ischemic damage detected on FA in patients with diabetic retinopathy.[7,17]

Ischemic maculopathy is an important predictor of poor visual outcome in diabetic retinopathy patients.[18] Macular ischemia may cause not only macular edema but also loss of the retinal layer, namely atrophy of the retina. To predict the functional outcome and a patient's response to treatment, analysis of retinal structural changes according to the macular perfusion status is important. Therefore, considering the variability of the FAZ size and the changes in FAZ size according to refractive error, we used the FAZ/ONH area ratio, calculated by dividing the enlarged FAZ area by the disc area, both measured using ImageJ software. Using this value, we evaluated the correlation of the SD-OCT findings with the extent of foveal ischemia. CST, subfield volume, length of the PR-OS, lateral extent of IS-OS disruption, and subfoveal choroidal thickness were included as SD-OCT parameters.

Thickening of the ischemic retina, particularly in the middle retinal layers, has already been reported.[7] One study showed that ischemic diabetic macular edema was correlated with ganglion cell layer damage, namely with thinning of the ganglion cell layer.[17] Another study reported that loss of the inner retinal layer corresponded to the area of capillary nonperfusion.[8] This discordance appears to be related to the duration of ischemia, which may induce macular edema, especially with inner retinal layer thickening, by increasing capillary permeability in earlier periods of ischemia. However, longstanding ischemia seems to cause atrophy of retinal tissue and reduction of the foveal volume in later disease, which can lead to severe visual loss.

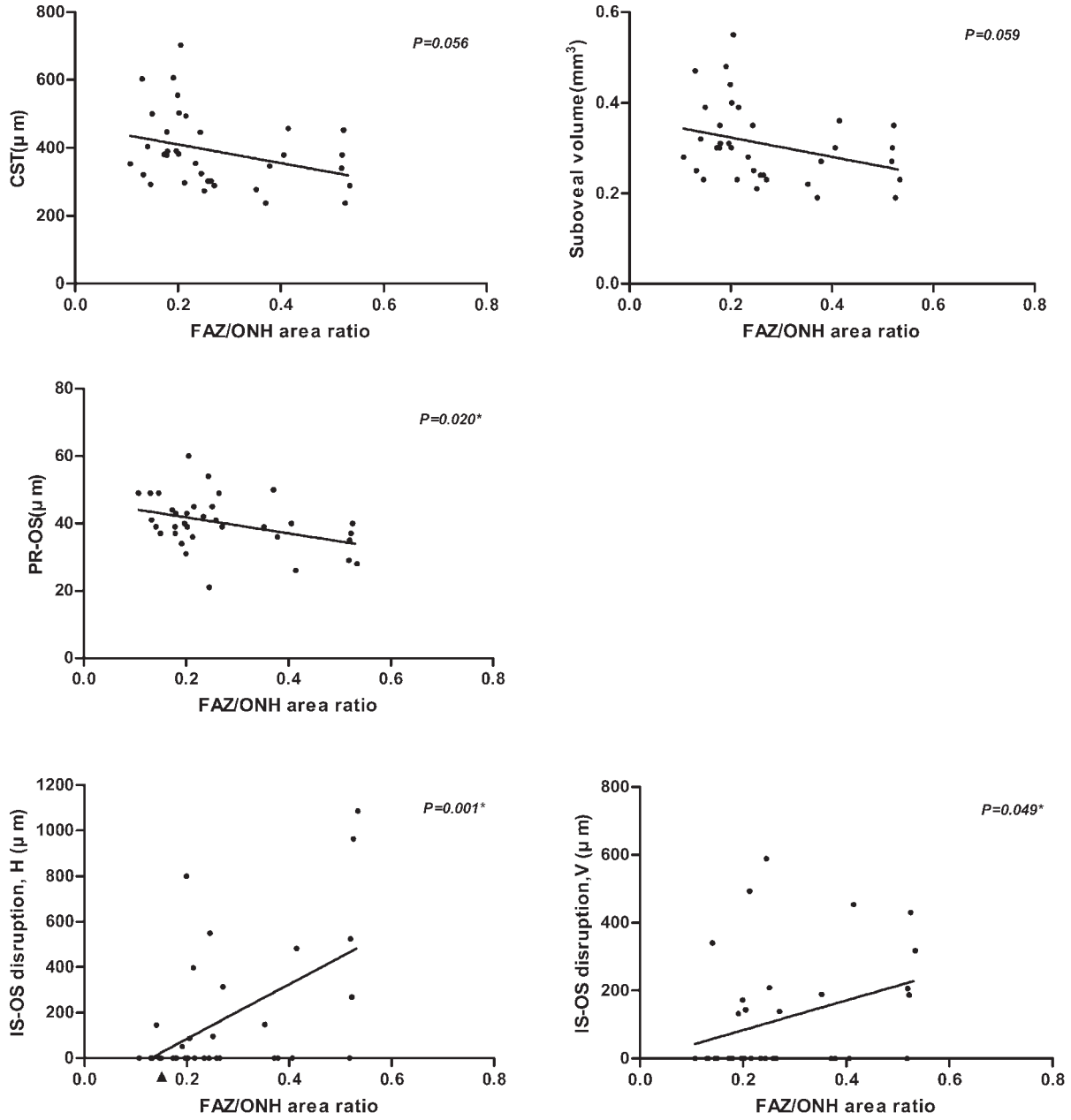

Figure 2. Correlation between the FAZ/ONH area ratio and the SD-OCT parameters. *$P < 0.05$ was considered statistically significant. H, horizontal; V, vertical.

In a previous study, ischemic retina was correlated with outer retinal thinning.[7] Photoreceptor integrity and thickness are also good predictors of the visual outcome in patients with DME,[6,19,20] although the mechanism of photoreceptor damage in DME is still not clearly understood. A recent study suggested several possible mechanisms: extravasated blood constituents and inflammatory cells, which might exacerbate the macular structure; subretinal fluid, which might decrease the metabolism of photoreceptor cells; and extended cystoid spaces, which might lead to retrograde degeneration of photoreceptor cells.[20] Our study showed that the lateral extent of IS-OS disruption was significantly correlated with FAZ enlargement as well as with visual acuity. The extent of IS-OS disruption was widely used as the parameter of photoreceptor integrity in numerous previous studies, even though the reflective band on SD-OCT termed "IS-OS junction" could be the ellipsoid portion of the inner segments instead of the actual boundary between photoreceptor inner and outer segments.[21] We also measured the length of the PR-OS in ischemic DME patients. Previous histologic studies demonstrated a PR-OS length of 25 to 63 μm[22,23]; and in another study of the Cirrus OCT-based PR-OS length in healthy subjects, the mean cone outer segment length was 40.6 μm.[24] Our study revealed a mean PR-OS length of 40 ± 8 μm in ischemic DME compared to 53 ± 5 μm in healthy eyes, seen using Spectralis OCT. We speculated that this difference was due to the use of a different OCT device. A previous study reported that the central retinal thickness (CRT) was significantly greater for the Spectralis than for the Cirrus in DME; the mean difference of the measured CRT value between the two devices was 12 μm.[25] In our study, PR-OS shortening showed a correlation with a high FAZ/ONH area ratio in ischemic DME. A possible explanation is that long-

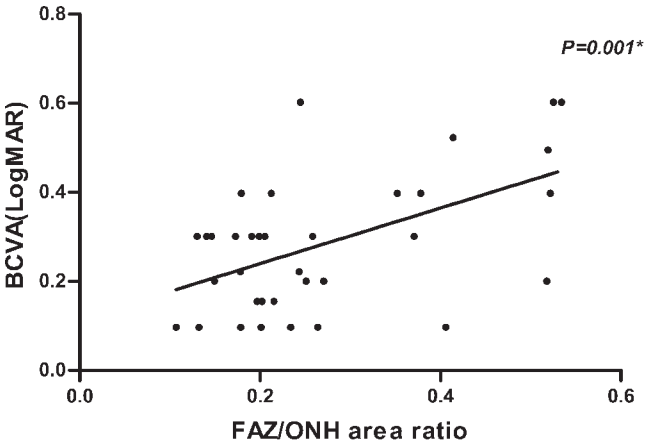

Figure 3. Correlation between the FAZ/ONH area ratio and the BCVA. The slope is 0.529. $^*P < 0.05$ was considered statistically significant.

standing or more severe ischemic DME might cause photoreceptor damage resulting in PR-OS shortening.

Caio et al. reported that choroidal thickness decreases in patients with DME.[26] However, in our study there was no significant correlation between choroidal thickness and FAZ enlargement. We believe that this result was due to important confounding factors regarding choroidal thickness, such as refractive error, grading of retinopathy, and patient age, none of which was controlled in our study.

Several published studies have reported histologic findings for retinal edema. Intracytoplasmic swelling of Müller cells corresponds to retinal swelling, and liquefaction necrosis of Müller cells leads to cystoid macular edema.[27–29] In our study, approximately 50% of the patients with ischemic macular edema showed a cystoid macular edema pattern. However, there was no significant correlation between the type of edema and FAZ enlargement.

In conclusion, despite much variability in the FAZ area, the FAZ/ONH area ratio was significantly correlated with both the length of the PR-OS and the lateral extent of IS-OS disruption. In addition, among these SD-OCT parameters, IS-OS disruption was correlated with visual acuity in ischemic DME.

Our study has several limitations, including its small sample size and its retrospective nature. There are also confounding factors that contribute to the ischemic status, such as previous laser treatment, anti-VEGF injection, and the duration of the edema. Further studies in which these confounding variables are considered will be required.

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