Optical Coherence Tomography Angiography Avascular Area Association With 1-Year Treatment Requirement and Disease Progression in Diabetic Retinopathy

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• PURPOSE: To assess the association between optical coherence tomography angiography (OCTA)–quantified avascular areas (AAs) and diabetic retinopathy (DR) severity, progression, and treatment requirement in the following year.

• DESIGN: Prospective cohort study.

• METHODS: We recruited patients with diabetes from a tertiary academic retina practice and obtained 3-mm × 3-mm macular OCTA scans with the AngioVue system and standard 7-field color photographs at baseline and at a 1-year follow-up visit. A masked grader determined the severity of DR from the color photographs using the Early Treatment of Diabetic Retinopathy scale. A custom algorithm detected extrafoveal AA (EAA) excluding the central 1-mm circle in projection-resolved superficial vascular complex (SVC), intermediate capillary plexus (ICP), and deep capillary plexus (DCP).

• RESULTS: Of 138 patients, 92 (41 men, ranging in age from 26-84 years [mean 59.4 years]) completed 1 year of follow-up. At baseline, EAAs for SVC, ICP, and DCP were all significantly correlated with retinopathy severity ($P < .0001$). DCP EAA was significantly associated with worse visual acuity ($r = -0.24$, $P = .02$), but SVC and ICP EAA were not. At 1 year, 11 eyes progressed in severity by at least 1 step. Multivariate logistic regression analysis demonstrated the progression was significantly associated with baseline SVC EAA (odds ratio = 8.73, $P = .04$). During the follow-up period, 33 eyes underwent treatment. Multivariate analysis showed that treatment requirement was significantly associated with baseline DCP EAA (odds ratio = 3.39, $P = .002$). No baseline metric was associated with vision loss at 1 year.

• CONCLUSIONS: EAAs detected by OCTA in diabetic eyes are significantly associated with baseline DR severity, disease progression, and treatment requirement over 1 year. (Am J Ophthalmol 2020;217:268–277.

MACULAR ISCHEMIA IS A KEY FINDING IN DIABETIC retinopathy (DR), a leading cause of blindness worldwide in the working age population,[1–3] correlated with visual impairment,[4] treatment response,[5,6] and disease progression.[7,8] Recently, numerous studies have demonstrated the value of optical coherence tomography angiography (OCTA) for quantification of macular vascular changes in DR, correlating it to disease severity and response to treatment.[9–17]

The goal of clinical evaluation of DR is to assess the risk of vision loss and identify the treatment threshold. The Diabetic Retinopathy Study and the Early Treatment of Diabetic Retinopathy Study (ETDRS) evaluated the features of modified Airlie House grading system and fluorescein angiography (FA) features against prospective outcomes.[2,7,18–20] The findings from these studies serve as the fundamentals of standard of care in DR evaluation. We hypothesize that OCTA-quantified macular metrics, beyond being correlated with clinical severity, can predict the risk of progression, vision loss, and treatment requirement.

To test this, we performed a prospective study with rigorous clinical procedures for visual acuity and retinopathy severity assessment.[20] In addition, we have applied advanced OCTA technology that addresses key issues in OCTA evaluation of DR. First, we applied a projection-resolved (PR) OCTA algorithm to remove artifacts that can interfere with the evaluation of the deeper layers of the retinal vasculature.[21] Second, we adopted a 3-layer segmentation scheme instead of the conventional 2 layers, with the understanding from histology that the deep vascular complex consists of 2 distinct laminar capillary plexuses—the intermediate capillary plexus (ICP) and deep capillary plexus (DCP).[22] Our group has previously demonstrated that en face evaluation of these plexuses as individual slabs is more sensitive to vascular changes than overlapping slabs.[11] PR-OCTA is critical in producing distinct 3-layered slabs that are segmented in the

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TABLE 1. Baseline Clinical Characteristics

Parameters	Value
Age (years), mean ± SD (range)	59.4 ± 12.7 (28-84)
Gender (male/female)	41/51
Diabetes type (1/2)	26/66
Diabetes duration (years), mean ± SD (range)	20.1 ± 11.8 (1-55)
HbA1c (%), mean ± SD (range)	7.7 ± 1.6 (5.2-14.0)
Hypertension history (with/without)	70/22
Systolic blood pressure (mmHg), mean ± SD (range)	130.4 ± 20.1 (89-186)
Diastolic blood pressure (mmHg), mean ± SD (range)	70.6 ± 13.1 (46-110)
Body mass index (kg/m^2), mean ± SD (range)	33.3 ± 8.5 (21.1-66.6)
BCVA (ETDRS letters), mean ± SD (range)	79.8 ± 8.5 (40-94)
Intraocular pressure (mmHg), mean ± SD (range)	14.6 ± 3.6 (8-24)
Axial length (mm), mean ± SD (range)	23.7 ± 1.1 (21.2-29.2)
ETDRS severity (scale), n	
No DR (10)	16
Microaneurysms only (20)	3
Mild NPDR (35)	19
Moderate NPDR (43)	4
Moderately severe NPDR (47)	7
Severe NPDR (13)	17
Mild PDR (61)	9
Moderate PDR (65)	11
High-risk PDR (71)	5
High-risk PDR (75)	1
Patients, n	92

BCVA = best-corrected visual acuity; DCP = deep capillary plexus; DR = diabetic retinopathy; EAA = extrafoveal avascular area; ETDRS = Early Treatment Diabetic Retinopathy Study; ICP = intermediate capillary plexus; NPDR = nonproliferative diabetic retinopathy; OR = odds ratio; PDR = proliferative diabetic retinopathy; SVC = superficial vascular complex.

appropriate anatomic layer. Third, we evaluated macular ischemia by measuring avascular areas (AAs) instead of vessel density. Unlike vessel density, AAs are less dependent on signal strength and can be measured by human graders, providing a basis for ground truth validation.[10] Finally, we have used a machine learning algorithm for detection and segmentation of the AA, which we have recently validated across OCTA of a full range of quality and clinical severity and resistant to error caused by defocusing or shadowing from floaters.[23,24]

METHODS

THIS OBSERVATIONAL, PROSPECTIVE, SINGLE-CENTER study was approved by the Institutional Review Board of Oregon Health and Science University, adhered to the tenets of the Declaration of Helsinki, and complied with the Health Insurance Portability and Accountability Act of 1996. Each participant provided written informed consent.

Participants with type I diabetes of >5 years' duration or type II diabetes of any duration who were between 18 and 79 years of age were recruited from the Casey Eye Institute at Oregon Health and Science University. We excluded pregnant or lactating women, those who were unable to consent or cooperate with OCTA scans, or those with the presence of significant nondiabetic ocular diseases or a history of intraocular surgery, except intravitreal injections or cataract surgeries, within 4 months before screening. One eye of each participants was included in the study.

We obtained a medical history, clinical examination, and imaging from each participant at baseline and at a 1-year follow-up visit. Previous intraocular treatments, if any, including focal laser, panretinal photocoagulation, intravitreal injections, cataract surgeries, or vitrectomies were recorded. The clinical examination included ETDRS protocol visual acuity, intraocular pressure, slit-lamp biomicroscopy, and indirect binocular ophthalmoscopy. Imaging procedures included OCTA using a commercially available 70-KHz spectral-domain OCT unit (RTVue-XR; Optovue, Fremont, California, USA) with 840-nm central wavelength and standard 7-field ETDRS color fundus photography. A retinal specialist (T.S.H.) determined the severity of DR based on standard 7-field ETDRS color fundus photographs using the ETDRS severity scale[19,20] masked to other clinical information and

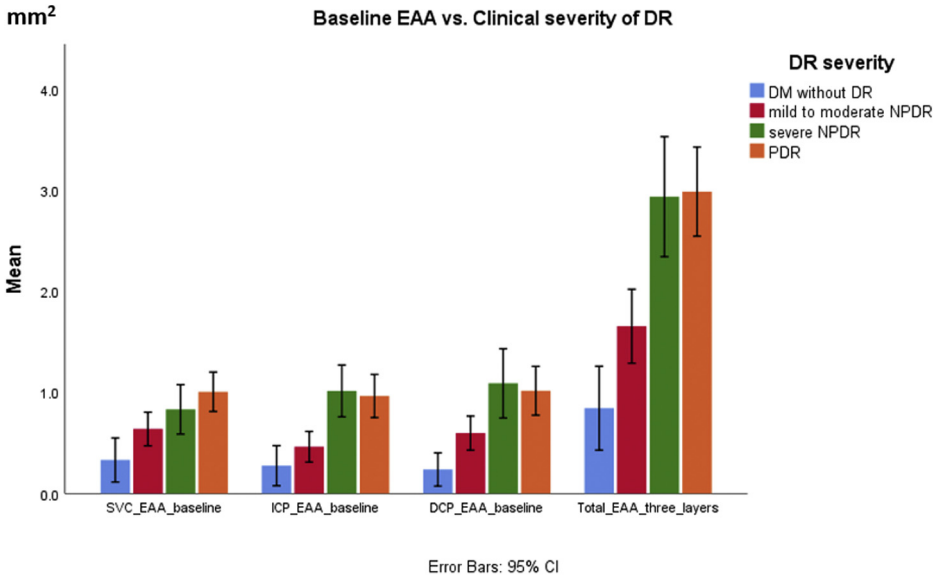

FIGURE 1. Baseline extrafoveal avascular area (EAA) of individual plexuses vs clinical diabetic retinopathy severity. DCP = deep capillary plexus; DM = diabetes mellitus; DR = diabetic retinopathy; ICP = intermediate capillary plexus; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SVC = superficial vascular complex.

OCTA images. The DR severity at baseline and at the 1-year follow-up were assessed separately in a masked fashion. Progression of DR severity was defined as a ≥1 level increase within the ETDRS severity scale.[19,20] The treating clinician determined the treatment requirement according to the standard of care without reviewing OCTA images.

We obtained 3-mm × 3-mm central macular OCTA scans with 304 × 304 A-scan density. Orthogonal registration and merging of 2 consecutive scans were used to obtain macula volume scans.[25] We excluded scans with a signal strength index <55 or scan quality index <6 or obvious motion artifacts.[10] Remaining scans were exported for a custom imaging processing and analysis, the details of which have been reported previously.[9,10,26–29] Briefly, a semiautomated algorithm based on directional graph search segmented the volumes into the superficial vascular complex (SVC), ICP, and DCP. The SVC layer was defined from the internal limiting membrane to the inner plexiform layer/inner nuclear layer interface, which included the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer, approximately 80% of the ganglion cell complex (GCC). The ICP was defined as the outer 20% of the GCC plus the inner 50% of the inner nuclear layer. The DCP was defined as the outer 50% of the inner nuclear layer to the outer plexiform layer. A senior retina fellow reviewed the segmentations and adjusted manually where necessary. In cases where significant diabetic macular edema (DME) or exudates caused incorrect segmentation, we manually corrected the boundaries using the adjacent B-scans without edema as reference. A custom deep-learning algorithm detected extrafoveal AA (EAA) excluding the central 1-mm circle in PR-OCTA as described previously.[9,10,24] The convolutional neural network–based algorithm used OCTA and en face reflectance map to determine whether a low flow signal area represents a true nonperfusion area or a low signal or motion artifact.[24]

Statistical analysis was performed using SPSS for Windows (v 25.0; IBM Corp, Armonk, New York, USA). Descriptive statistics included mean, standard deviation (SD), range, and percentages where appropriate. Analysis of variance was used to compare the EAAs of different groups. Pearson correlation was used to analyze the associations between EAA in different plexus and visual acuity. The association between DR severity and EAA at baseline was analyzed using Spearman correlation. Logistic regression analyzed the association between baseline EAA and the retinopathy progression, treatment for DME or DR, and vision loss during the 1-year follow up. All P values were 2-sided, and $P < .05$ was considered statistically significant. Bonferroni correction was applied when performing multiple comparisons.

RESULTS

NINETY-FIVE OF 138 (69%) PATIENTS WITH DIABETES WERE enrolled and followed for 1 year, 3 of whom were excluded because of poor image quality. The specific reasons for non–follow-up, when they could be identified, were a change in insurance (n = 1), death (n = 2), and moving out of the area (n = 5). Table 1 summarizes the baseline clinical characteristics of the participants. There were no significant

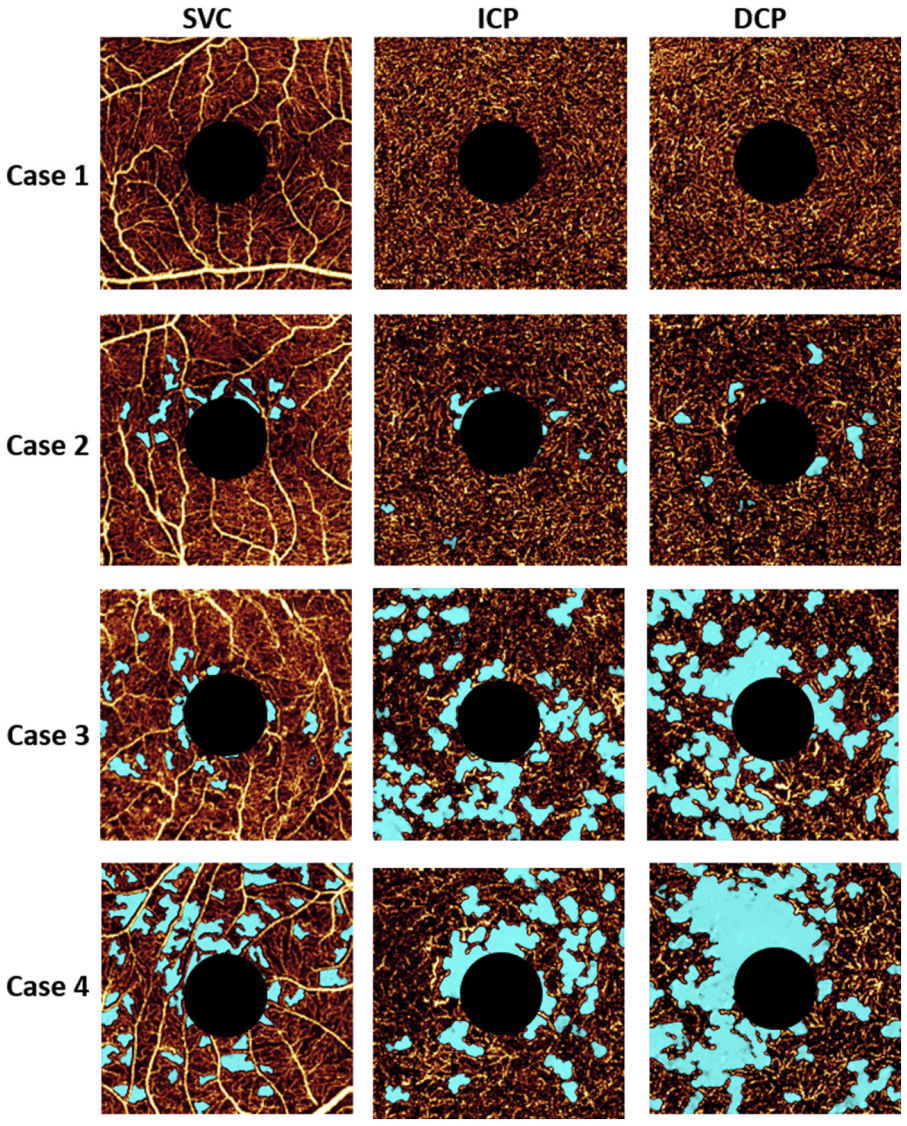

FIGURE 2. Optical coherence tomography angiography of a diabetic eye without retinopathy (case 1), mild nonproliferative diabetic retinopathy (case 2), severe nonproliferative diabetic retinopathy (case 3), and proliferative diabetic retinopathy (case 4). Light blue indicates avascular area. Superficial vascular complex (SVC), intermediate capillary plexus (ICP) and deep capillary plexus (DCP) are presented in separate en face angiograms.

differences between the follow-up and non–follow-up groups in terms of mean age (59.4 ± 12.7 vs 55.1 ± 12.9 years, $P = .15$), gender proportion (54% vs 50% female, $P = .59$), DR severity (severe nonproliferative diabetic retinopathy [NPDR]/proliferative diabetic retinopathy [PDR] proportion 46.7% vs 48.5%, $P = .86$), SVC EAA (0.72 ± 0.51 vs 0.60 ± 0.52 mm^2, $P = .24$), ICP EAA (0.67 ± 0.55 vs 0.60 ± 0.68 mm^2, $P = .55$), and DCP EAA (0.74 ± 0.61 vs 0.68 ± 0.71 mm^2, $P = .61$) at baseline.

The EAA of SVC, ICP, DCP, and the sum of all plexuses were significantly correlated ($P < .001$) with retinopathy severity with Spearman coefficients of 0.42, 0.53, 0.48, and 0.62, respectively (Figures 1 and 2). For DM without DR, mild to moderate NPDR, severe NPDR, and the PDR groups, the mean SVC EAA was 0.33 mm^2, 0.64 mm^2, 0.83 mm^2, and 1.01 mm^2 ($P < .001$), respectively; ICP EAA was 0.28 mm^2, 0.46 mm^2, 1.01 mm^2, and 0.96 mm^2 ($P < .001$), respectively; DCP EAA was 0.24 mm^2, 0.60 mm^2, 1.09 mm^2, and 1.02 mm^2 ($P < .001$), respectively; the sum of EAA of all the 3 layers was 0.84 mm^2, 1.65 mm^2, 2.94 mm^2, and 2.99 mm^2 ($P < .001$), respectively. At baseline, the DCP EAA was associated with worse visual acuity (Pearson correlation coefficient = −0.24, $P = .02$) (Figure 3), but the SVC EAA (correlation coefficient = −0.05, $P = .70$) and ICP EAA (correlation coefficient = −0.01, $P = .79$) were not.

At 1 year, 11 eyes progressed in severity by at least 1 step. The baseline severity for these 11 eyes were mild to

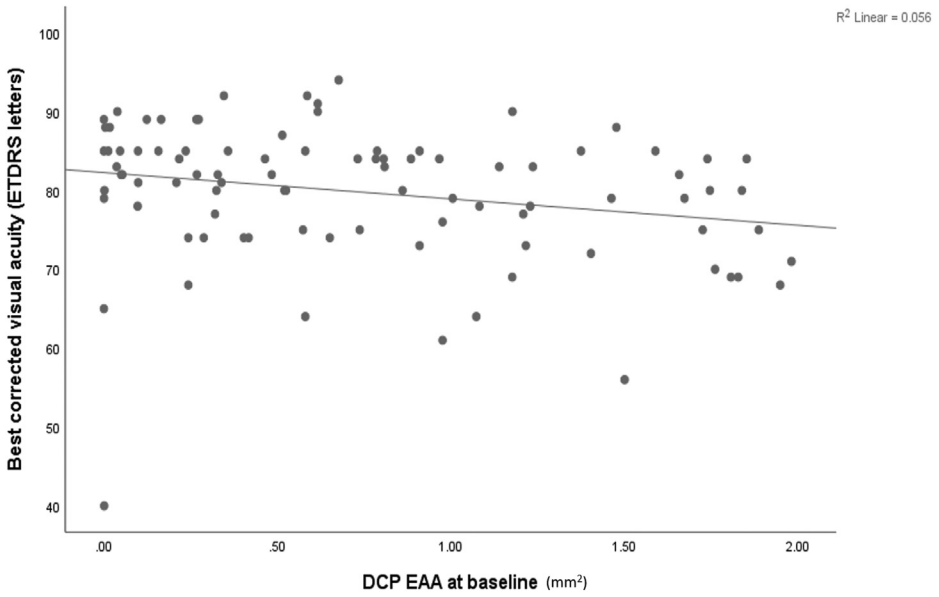

FIGURE 3. Correlation plot of the deep capillary plexus extrafoveal avascular area (DCP EAA) and best-corrected visual acuity in Early Treatment of Diabetic Retinopathy Study letters.

moderate NPDR in 4 eyes, severe NPDR in 3 eyes, and PDR in 4 eyes. The baseline EAA for the eyes that progressed vs those that did not were 1.08 ± 0.36 mm^2 and 0.67 ± 0.51 mm^2 ($P = .01$) for SVC, 1.01 ± 0.64 mm^2 and 0.64 ± 0.53 mm^2 ($P = .04$) for ICP, and 0.99 ± 0.73 mm^2 and 0.73 ± 0.59 mm^2 ($P = .19$) for DCP, respectively. In univariate logistic regression analysis, the progression was significantly associated with SVC EAA (OR = 6.10, $P = .02$), ICP EAA (OR = 2.26, $P = .04$), but not with DCP EAA ($P = .19$). The progression was borderline associated with axial length ($P = .07$) and HbA1C level ($P = .09$) but was not associated with age ($P = .44$), gender ($P = .57$), diabetes mellitus type ($P = .22$), hypertension history ($P = .64$), or baseline DR severity ($P = .20$) (Table 2). A multivariate logistic regression model with the progression as the dependent variable, and the variables with Ps < .10, including SVC EAA, ICP EAA, axial length, and HbA1C level as covariates showed that progression was significantly associated with SVC EAA only (OR = 8.73, β = 2.17, $P = .04$), with the estimated probability of progression = $(e^{2.17x - 4.09})/(1 - e^{2.17x - 4.09})$, where x is SVC EAA in millimeters squared.

At baseline, 46 eyes were treatment naïve. The other 46 eyes had undergone treatments including focal laser in 22 eyes, panretinal photocoagulation in 17 eyes, intravitreal anti–vascular endothelial growth factor (VEGF) injections in 29 eyes, intravitreal steroids in 2 eyes, and cataract surgeries in 22 eyes. During follow-up, 33 eyes (including 6 baseline treatment-naïve eyes and 27 previously treated eyes) underwent treatment for diabetic macular edema or vitreous hemorrhage, including intravitreal injection of anti-VEGF agents (n = 28), intravitreal steroids (n = 3), focal laser (n = 2), panretinal photocoagulation (n = 5), and vitrectomy (n = 2). The baseline EAA was significantly larger in the eyes that required treatment during the 1-year follow-up than in those that did not in SVC (0.90 ± 0.49 vs 0.63 ± 0.50 mm^2, $P = .02$), ICP (0.90 ± 0.57 vs 0.54 ± 0.49 mm^2, $P = .002$), and DCP (1.02 ± 0.67 vs 0.59 ± 0.51 mm^2, $P = .001$). In the univariate logistic regression model, treatment requirement was significantly associated with the presence of DME (OR = 6.99, $P < .001$); clinical DR severity (OR = 2.82, $P < .001$); DCP EAA (OR = 3.39, $P = .002$); ICP EAA (OR = 3.54, $P = .002$); and SVC EAA (OR = 2.95, $P = .017$). The treatment requirement was not significantly associated with age, gender, body mass index, HbA1C level, or axial length (Table 3). The multivariate model demonstrated that the treatment requirement was significantly associated with DCP EAA (OR = 3.39, β = 1.22, $P = .002$), but not with SVC EAA ($P = .13$) or ICP EAA ($P = .19$), with the probability of treatment = $(e^{1.22x - 1.55})/(1 - e^{1.22x - 1.55})$, where x is DCP EAA in millimeters squared. Separate analysis on the treatment-naïve eyes demonstrated that treatment requirement was significantly associated with ICP EAA (OR = 6.58, $P = .039$) and borderline associated with DCP EAA (OR = 5.14, $P = .065$) but was not associated with SVC EAA ($P = .21$).

Considering the potential impact of DME on EAA quantification, we did a separate analysis on those eyes without DME (n = 69) after excluding eyes with DME (n = 23) at baseline. The results were similar to those described above. At baseline, the EAA of SVC, ICP, and DCP increased significantly with severity of DR. For DM without DR, mild to moderate NPDR, severe NPDR, and the PDR

TABLE 2. Logistic Regression Analysis (Univariate) of the Baseline Predictors of Diabetic Retinopathy Progression at the 1-Year Visit

Parameters	B	*P* Value	OR (95% CI)
SVC EAA (mm^2)	1.807	.02	6.10 (1.29-28.80)
ICP EAA (mm^2)	1.181	.04	2.26 (1.04-10.24)
DCP EAA (mm^2)	0.680	.19	1.97 (0.72-5.44)
Axial length (mm)	−0.659	.07	0.52 (0.25-1.06)
HbA1C (%)	−0.722	.09	0.49 (0.21-1.12)
DR severity	0.411	.20	1.51 (0.81-2.82)
Body mass index (kg/m^2)	−0.100	.11	0.91 (0.80-1.02)
Diabetes type (1 or 2)	−0.799	.22	0.45 (0.12-1.63)
Age (years)	−0.019	.44	0.98 (0.94-1.03)
Sex	0.377	.57	1.46 (0.39-5.39)
Hypertension history	−0.388	.64	0.68 (0.14-3.42)
Diastolic blood pressure (mmHg)	0.010	.69	1.01 (0.96-1.06)
Systolic blood pressure (mmHg)	−0.005	.78	1.00 (0.96-1.03)
Intraocular pressure (mmHg)	0.016	.86	1.02 (0.85-1.21)

CI = confidence interval; DCP = deep capillary plexus; DR = diabetic retinopathy; EAA = extrafoveal avascular area; ICP = intermediate capillary plexus; OR = odds ratio; SVC = superficial vascular complex.

groups, the mean SVC EAA was 0.29 mm^2, 0.74 mm^2, 0.67 mm^2, and 0.99 mm^2 ($P = .001$), respectively; ICP EAA was 0.29 mm^2, 0.44 mm^2, 0.98 mm^2, and 0.98 mm^2 ($P < .001$), respectively; and DCP EAA was 0.25 mm^2, 0.56 mm^2, 0.82 mm^2, and 0.94 mm^2 ($P = .001$), respectively. Compared with eyes without progression at the 1-year follow-up visit, those progressed had a significant larger baseline SVC EAA (1.21 vs 0.66 mm^2, $P = .025$), larger but not statistically significant ICP EAA (1.03 vs 0.64 mm^2, $P = .13$), and DCP EAA (0.88 vs 0.64 mm^2, $P = .39$). Eyes that required treatment during the 1-year follow-up, compared with those that did not require treatment, had a significantly larger baseline EAA in SVC (0.96 vs 0.62 mm^2, $P = .02$), ICP (0.95 vs 0.56 mm^2, $P = .01$), and DCP (0.87 vs 0.57 mm^2, $P = .02$). In eyes without DME, there was no significant association between visual acuity and SVC EAA ($r = -0.02$, $P = .88$), ICP EAA ($r = -0.09$, $P = .48$), and DCP EAA ($r = -0.19$, $P = .18$) at baseline.

At the 1-year visit, there were 4 eyes that lost ≥15 ETDRS letters of vision. The cause of vision loss was diabetic macular edema in 3 eyes and cataract in 1 eye. No baseline OCTA metric was associated with a vision loss of ≥15 ETDRS letters at 1 year (all $P > .05$).

DISCUSSION

PHOTOGRAPHIC GRADING OF DR SEVERITY, PARTICULARLY 7-field grading using the ETDRS scale, has been the gold standard in the management of DR. It has been the standard way of reporting retinopathy severity in virtually all major clinical trials. Although it has the singular advantage of being backed by prospective data on the risk of progression of disease and vision loss on a large cohort of patients, its place in everyday practice has been challenged.[30] In 2003, Wilkinson and associates[31] proposed the International Clinical Diabetic Retinopathy Scale (ICDRS) as a more practical alternative to the ETDRS scale, which many clinicians find cumbersome and impractical. While the ICDRS has gained some acceptance, it still relies on qualitative interpretation of subtle clinical findings, such as venous beading or intraretinal microvascular abnormalities. In addition, clinical trials for diabetic macular edema using anti-VEGF treatments have found that the clinical features used for clinical grading are altered by anti-VEGF medications, while noting that macular ischemia may be useful in predicting progression to proliferative disease.[8] This study explored the potential of OCTA avascular areas as an objective alternative to photographic grading scale to assess the risk of progression and treatment requirement.

In this prospective longitudinal study, we found that OCTA-quantified AAs are significantly associated with clinical DR severity grading and treatment requirement and disease progression at 1 year, showing the potential prognostic value of OCTA in DR management. This confirms previous studies based on FA suggesting that macular ischemia is associated with disease progression.[7,8] This finding suggests that eyes with larger macular avascular area on PR OCTA may need closer monitoring for disease progression and treatment requirement.

The association between EAAs and DR severity was consistent with our previous studies, which found that segmented EAA is closely associated with DR severity.[9–11] Our study has shown the strongest association between SVC EAA and DR severity,[10] but the literature is divergent on which vascular plexus and which parameter is the most closely associated with DR severity.[12–15,17] Durbin and associates[17] demonstrated that the superficial retinal layer vessel density had the highest area under the receiver operating characteristic curve for differentiating DR from healthy eyes compared with the foveal avascular zone (FAZ) area and vessel density in the deep retinal layer.[17] Bhanushali and associates[13] found that spacing between the large vessels in the deep retinal layers had the highest diagnostic power for differentiating DR from normal control subjects compared with other parameters, including spacing between large and small vessels in the superficial plexus, FAZ area, and vessel density.[13] Comparing the vessel density and FAZ area of superficial and deep layer in 3-mm × 3-mm and 6-mm × 6-mm scans for differentiating DR severity, Binotti and Romano[14] reported that vessel density on deep plexus in 3-mm × 3-mm scans has the highest area under the receiver operating characteristic curve for detecting high-risk DR. Ashraf and associates[12]

TABLE 3. Logistic Regression (Univariate) Analysis of Baseline Predictors of Treatment Requirement in 1 Year

Parameters	B	*P* Value	OR (95% CI)
Clinical diabetic retinopathy severity	1.037	<.001	2.82 (1.72-4.68)
Diabetic macular edema or not	1.945	<.001	6.99 (2.46-19.85)
DCP EAA (mm^2)	1.221	.002	3.39 (1.58-7.29)
ICP EAA(mm^2)	1.263	.003	3.54 (1.52-8.22)
SVC EAA(mm^2)	1.081	.017	2.95 (1.21-7.16)
Axial length (mm)	−0.359	.104	0.70 (0.45-1.08)
HbA1C (%)	0.202	.218	1.22 (0.89-1.69)
Age (year)	−0.015	.368	0.99 (0.95-1.02)
Body mass index (kg/m^2)	−0.018	.507	0.98 (0.93-1.04)
Sex	−0.247	.572	0.78 (0.33-1.84)

CI = confidence interval; DCP = deep capillary plexus; EAA = extrafoveal avascular area; ICP = intermediate capillary plexus; OR = odds ratio; SVC = superficial vascular complex.

reported that FAZ area in superficial plexus, vessel density in deep layer, and FAZ acircularity were the best parameters for distinguishing DR severity. There may be important methodologic differences leading to these discrepancies. One is the segmentation scheme. Many studies, while reporting that they are segmenting SVC from DVC, included the ICP along with the SVC in the segmentation scheme, creating an overlapping slab, which may decrease the sensitivity of detecting capillary loss in the SVC. Another problem is projection artifacts, which may influence not only the measured vessel density but also the segmentation scheme.[32]

In addition to carefully dealing with projection artifacts and using anatomically correct boundaries for segmentation, we chose to use AAs instead of vessel densities (skeletonized or binarized) to assess macular ischemia. Studies have shown the dependence of vessel density on OCTA signal strength and age,[10,33] while AAs are less dependent on those potential confounders.[10,24] In addition, vascular metrics in OCTA are subject to artifacts caused by vitreous opacities and vignetting, which can cause false capillary dropouts. Using a deep learning algorithm that can distinguish false low perfusion areas caused by low signal artifacts[24] we excluded these false capillary dropouts, improving the performance of the metric.

We found that a larger DCP EAA was significantly associated with worse baseline BCVA, but not SVC or ICP. The DCP is located at the outer border of the inner nuclear layer.[22,34] Experimental studies found that the DCP contributes 10%-15% of photoreceptor inner segment oxygen requirement.[35] In hypoxia, the retinal vascular contribution to the metabolic needs of the outer retina becomes more significant because the choroidal vasculature fails to autoregulate its blood supply in the setting of hypoxia.[36] Recent studies with OCTA demonstrated colocalization of photoreceptor disruption and DCP nonperfusion, highlighting the importance of the DCP to the oxygen requirement of the photoreceptor in DR.[37–39] Previous structural OCT studies have demonstrated the impact of disruption of photoreceptors on visual acuity in DR.[40,41] Our findings further support the role of DCP ischemia in photoreceptor loss in DR. After excluding DME eyes, in eyes without DME, the association between a larger DCP EAA and worse visual acuity was not significant ($r = -0.19$, $P = .18$). Although this may be related to the relatively small sample size (not powerful enough to reach statistical significance), this result suggests that DME may play a more important role than DCP ischemia in vision loss.

The association of AAs and 1-year disease progression is in agreement with previous studies based on FA. ETDRS report 13[7] found that FA-graded macular capillary nonperfusion is a risk factor for progression to proliferative DR. The 1-year risk of developing PDR was 18.2% in eyes without macular ischemia and 41.3% in eyes with severe macular ischemia.[7] Sim and associates[4] reported that a greater macular ischemia grade on FA was independently predictive of 27-month progression, and diabetic macular ischemia progression itself was predictive of the loss of visual function. The results of the RISE and RIDE trials also showed that patients with diabetic macular ischemia progressed to neovascular complications of DR earlier than those without macular ischemia.[8] Interestingly, DCP EAA, which is not visualized with FA,[42] is not associated with 1-year disease progression in the current study.

In the current study, we did not find a significant association between systemic factors, such as HbA1C level, duration of diabetes, hypertension, and DR progression, although these were reportedly associated with development and progression of DR in other studies.[43,44] We speculate that in our relatively small group of patients the macular ischemia contributes more to DR worsening than systemic factors, particularly over a relatively short period of 1 year. It is noteworthy that in all the parameters we tested (Table 3), SVC and ICP EAA were the only parameters predictive of ≥1-step DR progression. Similar findings were noted in the RIDE and RISE studies; the presence of macular capillary nonperfusion on FA was the only parameter predicting progression to PDR.[8]

About one third of the participants underwent treatment for DME or PDR, with the majority receiving intraocular injections of anti-VEGF agents. In addition to presence of DME and higher DR severity, larger SVC, ICP, and DCP EAAs increased the possibility of treatment requirement. In our multivariate model, after adjustment of DME, every increase of 1-mm DCP EAA increased 2.6-fold the possibility of the 1-year treatment requirement. This finding may be of practical significance for clinicians when scheduling follow-up visits and treatment plans.

Clinicians make treatment decisions in DR based on multiple factors, such as the severity of DR, DME, and visual acuity. Because DCP EAA is significantly associated with disease severity and worse visual acuity, it is not surprising that we find a significant association between DCP EAA and treatment requirement for the overall study population. For treatment-naïve eyes, the treatment requirement is significantly associated with ICP EAA. Other than the fact that ICP EAA is associated with DR severity, it is unclear why the strongest relationship with treatment requirement was seen in the ICP.

In this study, OCTA-quantified AAs were not associated with vision loss of ≥15 ETDRS letters at 1 year. This may be because vision loss in DR can occur over a longer timeline than 1 year. In addition, only 4 eyes lost ≥15 ETDRS letters in our cohort, limiting the power to detect a significant result. Furthermore, as the patients received sight-saving treatments according to standard of care, we did not observe the natural history of these eyes.

Limitations of the study included a relatively small cohort with a relatively low follow-up rate of 69%. However, the non–follow-up group had similar baseline demographic characteristics, DR severity, and AAs compared with the group that completed follow-up. The 1-year follow-up period is short, especially considering the time course of DR. The patients received standard of care treatments but the specific strategy in delivering the standard of care treatment was inconsistent. Another limitation of the study is the small field of view of the OCTA scans (3-mm × 3-mm). The currently available OCTA technology obtains the most reliable capillary-level resolution images with 3-mm × 3-mm field of view.[45] However, a good correlation between central macular ischemia and peripheral ischemia has been reported,[46] and numerous studies showed excellent correlation between OCTA metrics from 3-mm × 3-mm scans and DR clinical severity.[9–15,17] It is, then, a reasonable hypothesis that the OCTA-derived metric from the central macula can predict DR progression and treatment requirement. The strengths of the study include rigorous clinical evaluation including ETDRS vision, masked photographic grading, advanced image processing with PR OCTA and 3-layer segmentation, and machine learning–aided AA detection that is robust over a wide range of image quality.[24] A study with a larger cohort and a longer follow-up period may further validate the predictive value of OCTA-measured metrics in the clinical management of DR.

In conclusion, AAs detected by projection-resolved OCTA in diabetic eyes are significantly associated with baseline DR severity, disease progression, and treatment requirement over 1 year, providing clinically useful information based on objective metrics. A larger prospective study with a longer follow-up period is necessary to further validate the potential of OCTA AAs as a practical and objective biomarker in the management of DR.

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