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OCT Angiography Metrics Predict Progression of Diabetic Retinopathy and Development of Diabetic Macular Edema

A Prospective Study

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Purpose: To prospectively determine the relationship of OCT angiography (OCTA) metrics to diabetic retinopathy (DR) progression and development of diabetic macular edema (DME).

Design: Prospective, observational study.

Participants: A total of 205 eyes from 129 patients with diabetes mellitus followed up for at least 2 years.

Methods: All participants underwent OCTA with a swept-source OCT device (DRI-OCT Triton, Topcon, Inc, Tokyo, Japan). Individual OCTA images of superficial capillary plexus (SCP) and deep capillary plexus (DCP) were generated by IMAGEnet6 (Basic License 10). After a quality check, automated measurements of foveal avascular zone (FAZ) area, FAZ circularity, vessel density (VD), and fractal dimension (FD) of both SCP and DCP were then obtained.

Main Outcome Measures: Progression of DR and development of DME.

Results: Over a median follow-up of 27.14 months (interquartile range, 24.16−30.41 months), 28 of the 205 eyes (13.66%) developed DR progression. Of the 194 eyes without DME at baseline, 17 (8.76%) developed DME. Larger FAZ area (hazard ratio [HR], 1.829 per SD increase; 95% confidence interval [CI], 1.332−2.512), lower VD (HR, 1.908 per SD decrease; 95% CI, 1.303−2.793), and lower FD (HR, 4.464 per SD decrease; 95% CI, 1.337−14.903) of DCP were significantly associated with DR progression after adjusting for established risk factors (DR severity, glycated hemoglobin, duration of diabetes, age, and mean arterial blood pressure at baseline). Lower VD of SCP (HR, 1.789 per SD decrease; 95% CI, 1.027−4.512) was associated with DME development. Compared with the model with established risk factors alone, the addition of OCTA metrics improved the predictive discrimination of DR progression (FAZ area of DCP, C-statistics 0.723 vs. 0.677, $P < 0.001$; VD of DCP, C-statistics 0.727 vs. 0.677, $P = 0.001$; FD of DCP, C-statistics 0.738 vs. 0.677, $P < 0.001$) and DME development (VD of SCP, C-statistics 0.904 vs. 0.875, $P = 0.036$).

Conclusions: The FAZ area, VD, and FD of DCP predict DR progression, whereas VD of SCP predicts DME development. Our findings provide evidence to support that OCTA metrics improve the evaluation of risk of DR progression and DME development beyond traditional risk factors. *Ophthalmology 2019;■:1−10 © 2019 by the American Academy of Ophthalmology*

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Diabetic retinopathy (DR) and diabetic macular edema (DME) are leading causes of visual impairment and blindness in many countries, including in the adult working population and the elderly.[1-3] Timely treatment for eyes at risk of DR progression has been shown to be effective in preventing the onset of visual impairment.[4] In addition, recent results of randomized controlled trials have also shown that intraocular injections of drugs targeting vascular endothelial growth factor or inflammation in DME can result in better visual outcomes.[5,6] Thus, recognition of people at higher risk of DR progression and DME development who could benefit from more intensive interventions is an important course of action for enhancing the management of DR. However, established risk factors, such as duration of diabetes and glycated hemoglobin (HbA_{1c}), are insufficient to determine the retinopathy risk. For example, total glycemic exposure explains only approximately 11% of the variation in DR progression as shown in the Diabetes Control and Complications Trial.[7]

OCT angiography (OCTA) is a functional extension of structural OCT that uses repeated B-scans to detect motion

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contrast and to visualize microvasculature without intravenous dye injection.[8] More importantly, OCTA provides depth-resolved information in a noninvasive fashion that conventional dye-based angiography is not able to, and thereby offers the probability to evaluate microvascular changes in the superficial, intermediate, and deep capillary plexuses individually.[8,9] Previous cross-sectional studies have defined several quantitative OCTA metrics (e.g., vessel density and foveal avascular zone area) and shown that OCTA metrics are associated with the severity of DR and DME.[10-19] Particularly, changes in OCTA metrics can be detected in diabetic patients without clinical retinopathy signs, suggesting that OCTA metrics, reflecting early microvascular alterations in individual capillary plexuses, are potential biomarkers for DR and DME.[18,20] For example, the vessel density of both superficial and deep capillary plexuses is lower in diabetic eyes without clinically detectable DR compared with healthy controls.[20] However, little is known about the prognostic value of OCTA metrics on DR progression and DME development because the study design in most of the current literature is cross-sectional.

In this study, we prospectively examined the relationship of quantitative OCTA metrics to DR progression and DME development in a cohort with diabetes. We also examined whether the OCTA metrics provided incremental predictive value for the risk of DR progression and development of DME beyond established risk factors (e.g., duration of diabetes, DR severity, and glycosylated hemoglobin level). We hypothesize that quantitative OCTA metrics, indicating early and subtle retinal microvascular abnormalities, are independent prognostic factors for DR progression and DME development.

Methods

Participants

This was a prospective observational study. Patients with diabetes were recruited from CUHK Eye Center, Hong Kong Eye Hospital in Hong Kong, from July 2015 to November 2016 and had been consecutively followed up for at least 2 years. All subjects attended their second visit at month 6 after baseline examinations. Subjects without DR or only mild nonproliferative diabetic retinopathy were followed annually afterward, whereas those with moderate or greater nonproliferative diabetic retinopathy were followed up every 6 months. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by the Hong Kong Kowloon Central Research Ethics Committee with informed consent obtained.

Inclusion criteria were (1) older than 18 years of age; (2) diagnosis of type 1 or type 2 diabetes; and (3) at least 24 months of follow-up. Exclusion criteria were (1) proliferative diabetic retinopathy (PDR) at baseline; (2) eyes with a history of pan-retinal photocoagulation or focal laser treatment within 6 months before recruitment; (3) eyes with a history of cataract surgery or other intraocular surgery within 6 months before recruitment; (4) eyes with ungradable OCTA images, structural OCT images, or color fundus photographs; (5) eyes with ocular condition other than DR (e.g., epiretinal membrane, glaucoma, retinal vein occlusion, or neovascular age-related macular degeneration) at baseline or during follow-ups; (6) eyes that underwent cataract surgery 6 months before development of DME during follow-ups, with the intention to exclude potential cases of Irvine−Gass syndrome. Eyes with DME at baseline were still included to examine the prospective association between OCTA metrics with DR progression, but not with DME development.

All participants underwent a comprehensive ophthalmic investigation at each visit, including measurements of Snellen visual acuity (VA), intraocular pressure, auto refraction, axial length, central corneal thickness, slit-lamp biomicroscopy, and dilated fundus examination. The VA was converted to the logarithm of the minimum angle of resolution for statistical analysis. Baseline DR severity was determined by retinal specialists according to the international clinical diabetic retinopathy disease severity scale on dilated fundus examination.[21]

OCT Angiography Imaging

All participants underwent OCTA using a swept-source OCT (DRI OCT Triton; Topcon Inc, Tokyo, Japan) with a wavelength of 1050 nm, an acquisition speed of 100 000 A-scans per second, and an axial and transversal resolution of 7 and 20 μm in tissue, respectively. We used 3×3-mm volumetric scan centered at the fovea, each consisting of 320 A-scans per B-scan for a total of 320 B-scans, to obtain OCTA images. Slabs of superficial capillary plexus (SCP) and deep capillary plexus (DCP) were automated and segmented by the built-in software (IMAGEnet6, v1.23.15008, Basic License 10); SCP was delineated by 2.6 μm below the internal limiting membrane to 15.6 μm below the junction between the inner plexiform and the inner nuclear layers; DCP was delineated by 15.6 μm below the inner plexiform and the inner nuclear layers to 70.2 μm below them. All of the OCTA images were then sent to the CUHK Ocular Reading Center for further quality control with the following exclusion criteria: (1) quality score less than 40; (2) motion artifacts; (3) inaccurate segmentation of tissue layers or slabs; (4) blurry images (fine capillary networks being not able to distinguish against the background signal); (5) signal loss; (6) poor centration; and (7) projection artifacts on DCP. Included OCTA images were subsequently exported in PNG format and imported into a customized MATLAB (MathWorks, Natick, MA) program. Both SCP and DCP images were processed and measured on the basis of a method described by Tang et al.[10] A series of quantitative OCTA metrics of SCP and DCP, including foveal avascular zone (FAZ) area, FAZ circularity, vessel density (VD), and fractal dimension (FD), were measured by the program automatically (Fig 1). Intra- and inter-session reliability of these measurements have been reported by Tang et al.[10]

Definitions of End Points

DR Progression. Digital retinal fundus photography was taken using a nonmydriatic retinal camera (TRC 50DX, Topcon Inc) after pharmacologic pupil dilation. Two retinal photographs of each eye were obtained in each visit, one centered at the optic disc and the other centered at the fovea. Diabetic retinopathy and its severity were graded by a trained reader (Z.H.S.) from baseline and follow-up retinal photographs using the modified Airlie House classification system with a severity score.[22] This classification provides a 15-step DR severity scale. Diabetic retinopathy progression was defined as an increase in 2 or more steps of severity level compared with baseline (from level 10 to level 20 or more, from level 15 to level 35 or more, from level 20 to level 43 or more, from level 35

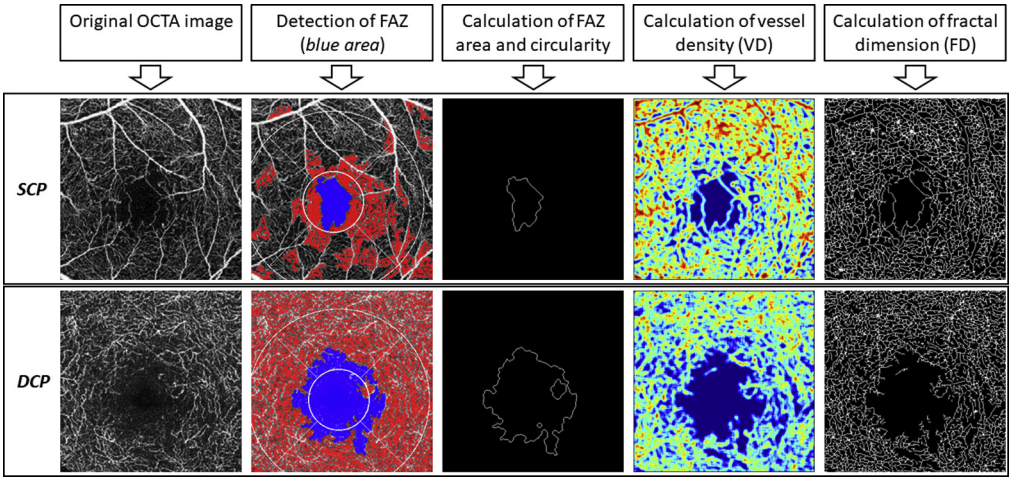

Figure 1. Quantification of retinal microvasculature from OCT angiography (OCTA) images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). A series of OCTA metrics including foveal avascular zone (FAZ) area, FAZ circularity, parafoveal vessel density (VD), and fractal dimension (FD) were automatically calculated by our customized MATLAB (MathWorks, Natick, MA) program.

to level 47 or more, from level 43 to level 53 or more, from level 47 to level 61 or more, from level 53 to level 65 or more) in those who had level 10 to level 53 at baseline.[23]

DME Development. The Cirrus HD-OCT (software version 9.5; Carl Zeiss Meditec, Dublin, CA) measured the retinal thickness from the macular cube scan (512×128 pixels), generating the macular thickness map (6×6 mm^2) centered at the fovea. An Early Treatment Diabetic Retinopathy Study grid was superimposed on the thickness map by a built-in software. Thickness of the central subfield was used for identification of DME. All OCT scans were required to have a signal strength of 5 or more. OCT scans with motion artifacts, poor centration, missing data, or segmentation error were discarded with rescanning performed in the same visit. The development of DME was defined as occurrence of macular edema identified as center-involved macular edema (central subfield thickness ≥305 μm in men or ≥290 μm in women) at the follow-up visits defined by the Diabetic Retinopathy Clinical Research Network (DRCR.net) in those free of DME at baseline.[24]

Assessment of Other Risk Factors

Age was defined as the age at the time of baseline examination. The duration of diabetes was defined as the period between the baseline examination and the date of diagnosis was first recorded by a physician on the patient's chart or in a hospital record system. Each patient's medical record was reviewed at each visit for the most recent fasting blood tests including glycosylated hemoglobin level (HbA_{1c}). History of associated systemic diseases and other diabetic complications were elicited from interview-based questionnaires, and the information was further checked and confirmed from each patient's medical record by physicians. At each visit, systolic and diastolic pressures were measured (model Avant 2120; Nonin Medical, Inc, Plymouth, MN) by the average of the 2 repeated measurements taken according to the protocol of the Hypertension Detection and Follow-Up Program.[25] Mean arterial blood pressure (MABP) estimates were calculated as diastolic pressure plus one third pulse pressure. Body weight and height of all participants were measured at each visit. Body mass index was calculated as body weight (in kilograms) divided by the squared body height (in meters).

Statistical Analysis

In this study, each eligible eye was regarded as the unit of analysis. A generalized estimating equation model was used to examine the differences between included and excluded subjects in baseline characteristics and to compare OCTA metrics between eyes with and without DME at baseline. Cox proportional-hazards model was used to examine the relationship of OCTA metrics at baseline to the risk of DR progression and DME development, adjusting for established risk factors (age, duration of diabetes, HbA_{1c}, MABP, and DR severity) at baseline.[26,27] A shared frailty model following a γ distribution was used to adjust for inter-eye correlation.[28] Schoenfeld's global test was used to confirm the proportional hazards assumption was not violated.[29]

We also examined the incremental value of adding OCTA metrics for prediction of DR progression and DME development. To evaluate the performance of prediction models, we calculated the C-statistic for the Cox regression model proposed by Steyerberg et al[29] in terms of quantifying the predictive discrimination. A C-statistic of 0.5 indicates no discriminative power, and a C-statistic close to 1 indicates perfect discrimination. Likelihood ratio test was used for model comparison. We performed the Hosmer–Lemeshow test to assess the calibration of risk prediction models.[30] In this analysis, P values < 0.05 represent a significant difference between the expected and observed event rates, indicating a model is not well calibrated. To assess overall performance including calibration and to compare the influence of individual components on predictive ability, we also computed the integrated Brier score at 2-year follow-up using the R package "pec."[31] A score of 0 indicates a perfect match of the predicted and observed outcomes, and a score of 1 indicates a total mismatch of the 2 outcomes. All statistical analyses were performed using R (version 3.4.4, R Foundation for Statistical Computing). R package "survival" was applied for Cox proportional hazards regression. A $P < 0.05$ was considered statistically significant.

Results

There were 266 eligible eyes of 169 patients with diabetes at the baseline examination. We excluded 61 eyes (reasons provided in

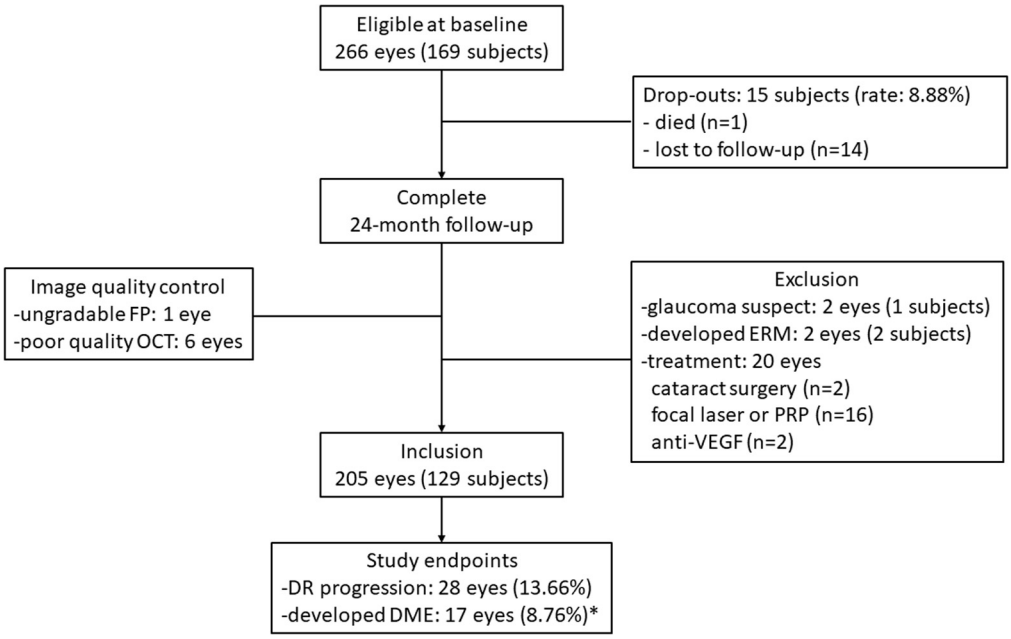

Figure 2. Study flowchart. DME = diabetic macular edema; DR = diabetic retinopathy; ERM = epiretinal membrane; FP = fundus photograph; OCT = optical coherence tomography; PRP = pan-retinal photocoagulation; VEGF = vascular endothelial growth factor. *In assessment of DME development, we further excluded 11 eyes with DME at baseline visit, leaving 194 eyes of 119 subjects being eligible for final analysis.

Fig 2), leaving 205 eyes from 129 patients in the final analysis. Baseline characteristics of included and excluded subjects are summarized in Table 1. Over a mean follow-up period of 27.14 months (interquartile range, 24.16−30.41 months), 28 of the 205 eyes (13.66%) developed DR progression. Eleven eyes were identified as having DME at the baseline visit. Of the 194 eyes (119 patients) without DME at baseline, 17 (8.76%) developed DME. Only 1 eye showed both DR progression and DME development (DME development was detected before progression of DR; lag time was 5.95 months). Survival curves (with life tables) plotting the time to events (DR progression and DME development) in our cohort are shown in Figure S1 (available at www.aaojournal.org).

Univariate and Multivariate Cox Proportional Hazards Models

Table 2 shows the relationships of baseline OCTA metrics to DR progression. In the univariate analysis, FAZ area (hazard ratio [HR], 1.615 per SD increase; 95% confidence interval [CI], 1.280−2.036; P <0.001), VD (HR, 1.896 per SD decrease; 95% CI, 1.330−2.701; P <0.001), and FD (HR, 3.958 per SD decrease; 95% CI, 1.424−11.002; P = 0.01) of the DCP were statistically significantly associated with 2 or more steps of progression of DR. These associations remained significant after adjusting for age, duration of diabetes, HbA_{1c} level, MABP, and severity of DR at baseline (all P values < 0.05) in the multivariate analysis. The FAZ circularity of DCP was not significantly associated with DR progression in both univariate (HR, 0.810 per SD decrease; 95% CI, 0.643−1.019; P = 0.07) and multivariate analyses (HR, 0.779 per SD decrease; 95% CI, 0.585−1.038; P = 0.09). None of the SCP metrics was associated with DR progression in both models.

We then performed a subgroup analysis to examine whether OCTA metrics were associated with incident DR among eyes without clinical detectable DR at baseline (Table S1, available at www.aaojournal.org). Of the 68 eyes (44 subjects) free of DR at baseline visit, 6 eventually developed DR during follow-up. Lower VD (HR, 2.93 per SD decrease; 95% CI, 1.078−7.961; P = 0.04) and lower FD (HR, 5.50×10^2 per SD decrease; 95% CI, $1.98-1.53\times10^5$; P = 0.03) of DCP were significantly associated with DR development after adjusting for covariates. The FAZ area of DCP was no longer significantly associated with risk of DR progression in the subgroup analysis.

Table 3 shows the relationships of baseline OCTA metrics to DME development. Lower VD of SCP was associated with DME development in both univariate (HR, 1.903 per SD decrease; 95% CI, 1.132−3.198; P = 0.02) and multivariate analyses (HR, 1.789 per SD decrease; 95% CI, 1.027−3.115; P = 0.04). Other OCTA metrics did not show significant associations with DME development. Our results were consistent when using subclinical DME as an end point proposed by the DRCR.net (Table S2, available at www.aaojournal.org).[32] In addition, we cross-sectionally compared the OCTA metrics between eyes with and without DME at baseline visit (Table S3, available at www.aaojournal.org). Eyes with DME had a significantly larger FAZ area of DCP and lower VD and FD of DCP compared with those without DME (all P values <0.05). Metrics of SCP did not show a significant difference between the groups.

We further confirmed our primary findings (Tables 2 and 3) by additionally adjusting for axial length and image quality score in multivariate models (Table S4, available at www.aaojournal.org), because these factors may have an influence on OCTA metrics.[33-36] Results with the additional adjustment were similar to the primary findings.

Performance Measures of Prediction Models

Discrimination. Table 4 shows the C-statistic for Cox regression models predicting DR progression and DME development before and after OCTA metrics were added into the model using

Table 1. Baseline Characteristics of Included and Excluded Participants

Characteristics	Unit	Included (n = 205)		Excluded (n = 61)		P Value
		No.	*Mean (SD) or %*	*No.*	*Mean (SD) or %*	
Age	Year	129	62.92 (9.88)	40	65.16 (11.76)	0.42
Gender	Female	68	52.71	16	40.00	0.16
	Male	61	47.29	24	60.00	
Age at diagnosis of diabetes	Year	129	50.51 (10.63)	40	53.57 (14.88)	0.52
Duration of diabetes	Year	129	12.41 (8.19)	40	11.59 (9.84)	0.99
Type of diabetes	Type 1	4	3.10	2	5.00	0.57
	Type 2	125	96.90	38	95.00	
HbA_{1c}	%	129	7.44 (1.38)	36	7.71 (1.99)	0.42
Systolic blood pressure	mmHg	129	143.30 (17.87)	40	146.40 (22.67)	0.55
Diastolic blood pressure	mmHg	129	78.95 (9.95)	40	78.43 (12.14)	0.55
Mean arterial blood pressure	mmHg	129	100.39 (10.56)	40	101.08 (14.11)	0.97
Body mass index	kg/m^2	129	25.84 (4.60)	40	26.79 (6.22)	0.47
Self-reported comorbidities						
Cardiovascular disease		24	18.60	7	17.50	0.88
Stroke		11	8.53	2	5.00	0.54
Diabetic nephropathy		12	9.30	2	5.00	0.39
Axial length	mm	205	23.75 (1.30)	60	23.93 (1.12)	0.47
Spherical equivalent	Diopter	205	−1.08 (2.67)	60	−1.00 (2.99)	0.77
logMAR		205	0.18 (0.16)	61	0.34 (0.28)	0.01
Severity of retinopathy	No DR	68	33.17	19	31.66	0.02*
	Mild	48	23.42	7	11.67	
	Moderate	73	35.61	22	36.67	
	Severe	16	7.80	12	20.00	
Central subfield thickness	µm	205	254.80 (32.35)	55	279.30 (59.09)	0.16
OCTA Metrics						
Superficial Capillary Plexus						
FAZ area	mm^2	205	0.40 (0.13)	61	0.40 (0.27)	0.70
FAZ circularity		205	0.61 (0.11)	61	0.50 (0.12)	<0.001
Vessel density	%	205	76.29 (7.00)	61	75.50 (8.32)	0.51
Fractal dimension		205	1.68 (0.05)	61	1.69 (0.05)	0.12
Deep Capillary Plexus						
FAZ area	mm^2	205	1.09 (0.43)	61	2.01 (1.01)	<0.001
FAZ circularity		205	0.39 (0.15)	61	0.37 (0.14)	0.09
Vessel density	%	205	33.99 (3.57)	61	28.17 (9.14)	<0.001
Fractal dimension		205	1.67 (0.05)	61	1.65 (0.05)	0.02

DR = diabetic retinopathy; FAZ = foveal avascular zone; HbA_{1c} = glycated hemoglobin; logMAR = logarithm of the minimum angle of resolution; OCTA = OCT angiography; SD = standard deviation.
*P trend.

established risk factors alone. On the basis of the findings from Table 2, FAZ area, VD, and FD of DCP were added in the calculation of C-statistic for the Cox regression models of DR progression. Models with the inclusion of FAZ area of DCP (C-statistic, 0.723 vs. 0.677; P <0.001), VD of DCP (C-statistic, 0.727 vs. 0.677; P = 0.001), and FD of DCP (C-statistic, 0.738 vs. 0.677; P <0.001) significantly improved the predictive discrimination for DR progression compared with models using established risk factors alone. On the basis of the findings shown in Table 3, we selected VD of SCP and added it the model for DME development. Addition of VD of SCP significantly improved predictive discrimination (C-statistic from 0.875 to 0.904, P = 0.036) for DME development.

Performance Measures of Prediction Models

Calibration. Figure 3 illustrates the prediction error curves of Cox regression models predicting DR progression and DME development during the study period. Table S5 (available at www.aaojournal.org) shows the integrated Brier scores at 2-year follow-up of these models. Cox regression models for DR progression with inclusion of FAZ area of DCP (Brier score = 0.047), VD of DCP (Brier score = 0.050), FD (Brier score = 0.048) of DCP had lower Brier scores, indicating better calibration compared with the model with established risk factors alone (Brier score = 0.052). Likewise, addition of VD of SCP into the model with established risk factors alone for DME development decreased the Brier score (from 0.026 to 0.024). In addition, all P values in the Hosmer−Lemeshow test were larger than 0.05 (Table S5, available at www.aaojournal.org), suggesting that none of these models had a significant lack of fit, or in other words, all these models were well calibrated.

Discussion

In this prospective study, we have identified several OCTA-derived biomarkers that are predictive of DR progression and DME development over 2 years of follow-up. To summarize, eyes with larger FAZ area, lower VD, and lower FD on DCP are associated with a higher risk of DR

Table 2. Relationships of OCTA Metrics to Risk of DR Progression

OCTA Metrics	Univariate		Multivariate*	
	HR (95% CI)	*P Value*	*HR (95% CI)*	*P Value*
Superficial Capillary Plexus				
FAZ area per SD increase	1.329 (0.918–1.922)	0.13	1.364 (0.927–2.008)	0.12
FAZ circularity per SD decrease	1.260 (0.837–1.897)	0.27	1.180 (0.768–1.812)	0.45
Vessel density per SD decrease	1.273 (0.829–1.885)	0.23	1.228 (0.808–1.866)	0.34
Fractal dimension per SD decrease	1.318 (0.787–2.207)	0.29	1.232 (0.734–2.067)	0.43
Deep Capillary Plexus				
FAZ area per SD increase	1.615 (1.280–2.036)	<0.001	1.829 (1.332–2.512)	<0.001
FAZ circularity per SD decrease	0.810 (0.643–1.019)	0.07	0.779 (0.585–1.038)	0.09
Vessel density per SD decrease	1.896 (1.330–2.701)	<0.001	1.908 (1.303–2.793)	<0.001
Fractal dimension per SD decrease	3.958 (1.424–11.002)	0.01	4.464 (1.337–14.903)	0.02

CI = confidence interval; DR = diabetic retinopathy; FAZ = foveal avascular zone; HR = hazard ratio; OCTA = OCT angiography; SD = standard deviation.
*Multivariate model adjusted for age, duration of diabetes, glycated hemoglobin, mean arterial blood pressure, and baseline DR severity.

progression, whereas eyes with lower VD on SCP are more likely to develop DME. Such associations are independent of established risk factors including age, duration of diabetes, HbA_{1c}, MABP, and severity of DR at baseline. Furthermore, addition of OCTA metrics significantly improves the discrimination and calibration for DR progression and DME development when compared with the models using established risk factors alone.

This study provides new longitudinal evidence to demonstrate the predictive value of OCTA metrics, indicative of diabetic macular ischemia (DMI), for progression of DR and DME. Our findings are in line with prior fluorescein angiography studies and support previous cross-sectional OCTA studies.[10,37-42] Diabetic macular ischemia, clinically defined as enlargement or disruption of the FAZ and capillary dropout in parafoveal area, was first established by using fluorescein angiography decades ago. Previous studies have shown fluorescein angiographic risk factors are associated with progression of DR and DME.[38] Although fluorescein angiography remains the gold standard for evaluation of DMI, its invasiveness and 2-dimensional nature have limited its clinical utility. Because of the advent of OCTA, DMI can be assessed noninvasively and, more importantly, in distinct retinal capillary plexuses. Human retinal capillary beds are arranged in series, parallel, and spatial specialized.[43] Being able to explore distinct capillary beds in vivo will enhance our understanding of both vascular physiology and pathophysiology of DR in depth.

It is noteworthy that FAZ area, VD, and FD of DCP were significantly associated with DR progression, whereas none of these metrics of SCP conferred similar prognostic value. One possible explanation is that microvascular changes related to DR progression occur at DCP earlier than SCP. A growing body of evidence supports the differential involvement of distinct retinal capillary layers in diabetic eyes. Onishi et al[44] observed a relative preservation in flow in the SCP compared with a steep decline at the intermediate and deep plexuses. Chen et al[45] reported a higher discriminative ability of FD of DCP in distinguishing diabetic eyes without minimal DR from control eyes than that of SCP. Previous histologic studies also indicated that the DCP is more vulnerable to injury and preferentially

Table 3. Relationships of OCTA Metrics to Risk of DME Development

OCTA Metrics	Univariate		Multivariate*	
	HR (95% CI)	*P Value*	*HR (95% CI)*	*P Value*
Superficial Capillary Plexus				
FAZ area per SD increase	0.983 (0.582–1.633)	0.81	0.581 (0.287–1.174)	0.13
FAZ circularity per SD decrease	1.031 (0.606–1.755)	0.34	0.964 (0.578–1.610)	0.89
Vessel density per SD decrease	1.903 (1.132–3.198)	0.02	1.789 (1.027–3.115)	0.04
Fractal dimension per SD decrease	1.675 (0.694–4.043)	0.25	1.875 (0.779–4.512)	0.16
Deep Capillary Plexus				
FAZ area per SD increase	1.044 (0.618–1.765)	0.77	0.956 (0.527–1.733)	0.88
FAZ circularity per SD decrease	1.285 (0.574–2.877)	0.49	1.651 (0.703–3.878)	0.25
Vessel density per SD decrease	1.230 (0.762–1.985)	0.40	1.056 (0.624–1.785)	0.84
Fractal dimension per SD decrease	0.971 (0.613–1.538)	0.90	1.103 (0.619–1.963)	0.74

CI = confidence interval; DME = diabetic macular edema; FAZ = foveal avascular zone; HR = hazard ratio; OCTA = OCT angiography; SD = standard deviation.
*Multivariate model adjusted for age, duration of diabetes, glycated hemoglobin, mean arterial blood pressure, and baseline DR severity.

Table 4. Predictive Discrimination for DR Progression and DME Development with and without OCTA Metrics in the Cox Regression Models Based on Established Risk Factors*

Outcome	Addition of OCTA Metrics	C-statistic		Change in C-statistic (%)	*P* Value
		Without OCTA Metric	*With OCTA Metric*		
DR progression	FAZ area of DCP	0.677	0.723	0.046 (6.79)	<0.001
DR progression	Vessel density of DCP	0.677	0.727	0.050 (7.39)	<0.001
DR progression	Fractal dimension of DCP	0.677	0.738	0.061 (9.01)	<0.001
DME development	Vessel density of SCP	0.875	0.904	0.029 (3.31)	0.036

DCP = deep capillary plexus; DME = diabetic macular edema; DR = diabetic retinopathy; FAZ = foveal avascular zone; OCTA = OCT angiography; SCP = superficial capillary plexus.
*Model with established risk factors consisted of age, duration of diabetes, glycated hemoglobin, mean arterial blood pressure, and baseline DR severity.

affected.[46,47] In concordance with previous studies, our findings support the clinical relevance of OCTA-derived parameters in detection of disease progression, especially those of DCP that are informative of early DMI. Nevertheless, the speed of OCTA-detected DMI progression and the clinical relevance of these progressive changes remain to be elucidated.

It is noteworthy that only VD and FD of DCP remain significantly associated with the incidence of DR, whereas the FAZ area of DCP was no longer a significant risk factor, as shown in the subgroup analysis (Table S1, available at www.aaojournal.org). Although we do not have a definitive explanation for this observation, it is possible that the sample size was smaller in the subgroup analysis,

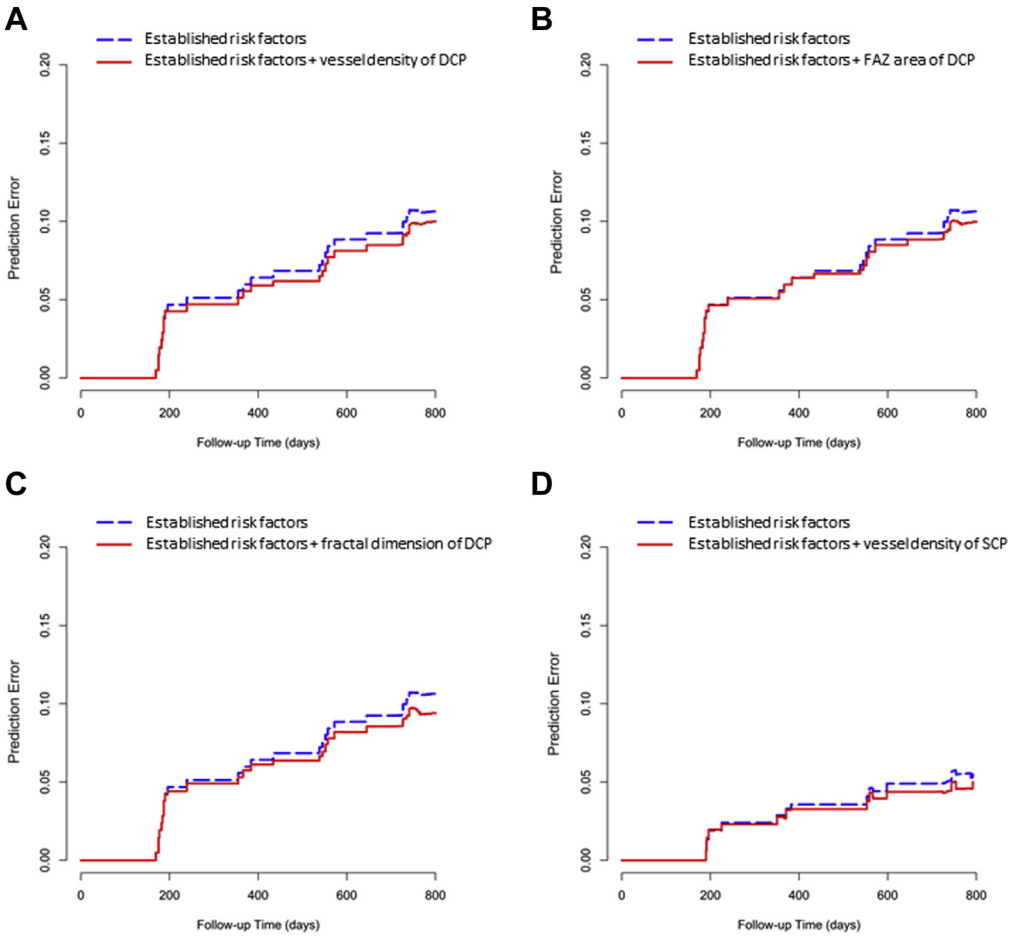

Figure 3. Prediction error curves for prediction models of developing diabetic macular edema (DME) and diabetic retinopathy (DR) progression. **A,** Model with established risk factors alone versus model with established risk factors and foveal avascular zone (FAZ) area of deep capillary plexus (DCP) to predict DR progression. **B,** Model with established risk factors alone versus model with established risk factors and vessel density of DCP to predict DR progression. **C,** Model with established risk factors alone versus model with established risk factors and vessel density of DCP to predict DR progression. **D,** Model with established risk factors alone versus model with established risk factors and vessel density of superficial capillary plexus (SCP) to predict DME development.

and thus the power was inadequate. Park et al[48] showed that FAZ is to be best distinguished at the middle capillary plexus (MCP), whereas the DCP does not extend as close to the FAZ border as the MCP. Consequently, the FAZ is larger and less well defined in the DCP compared with the MCP.[48] The border of FAZ is not well demarcated in the DCP, and thus measurement of FAZ area of DCP was less robust, leading to increased variability of measurement compared with VD and FD of DCP.[49,50] Further studies are required to evaluate which of the OCTA metrics has the highest predictive value to be useful in clinical practice.

As opposed to DR progression, DME development was associated with VD of the SCP, but not with DCP metrics. Theoretically, an imbalance in fluid entry versus fluid exit would lead to formation of DME. It is believed that, under normal circumstances, fluid production may originate from the SCP that courses through the interstitial tissue of the retina to be absorbed by the actions of Müller cells and the DCP.[51] Breakdown of the inner blood−retinal barrier and consequent increased leakage from the SCP could reach a level that the fluid-removing capabilities would be overwhelmed.[51] Recent cross-sectional studies suggested that DCP may be involved in the removal of fluid from the retina as potentially mediated by the DCP.[51-55] In addition, disruption or damage to the DCP may lead to DME development because DCP is the principle venous outflow system for retinal capillary plexuses.[56,57] Consistent with previous cross-sectional studies, our cross-sectional results also showed that eyes with DME had decreased perfusion of DCP (e.g., larger FAZ area and decreased VD as shown in Table S3, available at www.aaojournal.org).[58] Nonetheless, our prospective and longitudinal findings suggested that VD of SCP, rather than DCP metrics, was related to the development of DME (Table 3). Whether SCP is the major source of fluid production remains largely unknown. Future studies with larger sample sizes are needed to replicate our findings and to uncover the complexity of mechanisms involved in this process.

It is well known that traditional risk factors (e.g., HbA_{1c}, duration of diabetes) do not fully explain the risk of an individual developing DR progression and DME. We further showed that the addition of OCTA metrics, which provides independent risk information on microvasculature, improve predictive discrimination for both DR progression and DME development compared with the models using only established risk factors. Nevertheless, it is noted that the overall improvement of C-statistic is only approximately 3% to 9% beyond that of using established risk factors alone. Further studies are needed to determine whether measurement of OCTA metrics can identify a more specific subgroup of patients who could benefit from more intensive investigations or even start treatment. This also includes work to optimize the risk-prediction algorithm to determine how it may influence clinical decision-making and to estimate the cost-effectiveness and acceptability of such an investigation.

Study Strengths and Limitations

The strengths of our study were the prospective study design, longitudinal follow-up, and an objective, automated quantification method for measurement of OCTA metrics.[10] We acknowledge several limitations in this study. First, we only evaluated the parafoveal SCP and DCP with a 3×3-mm field of view, and we did not evaluate the peripheral retina. Second, we only included eyes with good-quality images, which may have introduced selection bias and limited the generalizability of results. Selective survival participation might also affect the generalizability of our findings. Third, the follow-up period of this study is relatively short. Fourth, we used the manufacturer-recommended default settings for SCP and DCP, and the inherent errors in segmentation is unknown.[59]

In conclusion, the OCTA metrics on DCP were associated with DR progression, whereas VD of SCP was related to DME development. These OCTA metrics further improved predictive discrimination of DR progression and DME development. Our findings offer new insights into the management of DR and support the role of OCTA metrics as a factor to be considered in the assessment of DR and DME in individuals with diabetes.

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Abbreviations and Acronyms:
CI = confidence interval; **DCP** = deep capillary plexus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **FAZ** = foveal avascular zone; **FD** = fractal dimension; **HbA_{1c}** = glycated hemoglobin; **HR** = hazard ratio; **MABP** = mean arterial blood pressure; **MCP** = middle capillary plexus; **OCTA** = OCT angiography; **PDR** = proliferative diabetic retinopathy; **SCP** = superficial capillary plexus; **VA** = visual acuity; **VD** = vessel density.

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