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Using optical coherence tomography angiography as a biomarker of retinopathy severity and treatment for diabetic retinopathy

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Purpose: The goal was to evaluate optical coherence tomography angiography (OCT-A) as a biomarker to correlate retinal vessel density (VD) with diabetic retinopathy (DR) severity and visual acuity, as well as track antivascular endothelial growth factor (VEGF) treatment efficacy.
Methods: This retrospective cohort study analyzed the automatically quantified VDs of the superficial vascular complex (SVC) and deep vascular complex (DVC), including the whole, foveal, and parafoveal VDs, on quality OCT-A scans in patients diagnosed with DR. A multivariate linear regression and analysis of variance (ANOVA) analysis compared VDs to DR severity, visual acuity, and demographic factors. A linear mixed analysis determined the effects of VD by whether anti-VEGF therapy was given to patients with OCT-A scans at multiple time points.
Results: There was a positive correlation of the VDs in both the SVC whole and parafoveal VD and DVC parafoveal VD with decreased DR severity and increased visual acuity ($p \leq 0.001$). The DVC whole VD was also positively correlated with increased visual acuity ($p < 0.001$). There was no difference in the VDs associated with anti-VEGF treatment over time.
Conclusions: OCT-A VD shows promise for diagnosing and monitoring DR using DR severity and visual acuity. Anti-VEGF treatment had no significant effect ($p = 0.063$) on vascular density in diabetic retinopathy.

Diabetes mellitus (DM), a chronic condition linked to vascular complications, including microvasculature changes caused by diabetic retinopathy, is rapidly growing in global prevalence. Diabetic retinopathy (DR) affects approximately one-third of patients with DM, making it one of the most common and severe ophthalmic complications [1,2]. Vision loss in DR is caused by macular edema and ischemia, as well as retinal neovascularization, which can lead to tractional retinal detachment (RD) and vitreous hemorrhage. Therefore, timely ophthalmological monitoring of diabetes and potential DR complications is needed for patients with DM [2].

To visualize the retinal microvasculature, fluorescein angiography (FA) and optical coherence tomography angiography (OCT-A) are used in the diagnosis and clinical management of DR. FA has been used for several decades as an invasive test to identify the earliest detectable signs of DR, including microaneurysms and enhanced capillary permeability, as well as signs of advanced DR, such as neovascularization, evident from the leakage of FA dye into the vitreous. Relative to the more established FA imaging, the more recent OCT-A technology is advantageous for the management of DR because it produces rapid, high-resolution, non-invasive cross-sectional images of the retina that include both the deep vascular complex (DVC) and superficial vascular complex (SVC), as opposed to FA, which only visualizes the SVC. This allows for the visualization of additional depth in the microvasculature relative to FA [3,4].

Although FA is currently considered the gold standard for retinal angiography, a growing body of literature indicates that OCT-A is a promising biomarker for DR [5,6]. Quantitative measures from OCT-A derived from software such as Optovue (Fremont, CA) allow for the measurement of retinal perfusion, which is impossible with FA. Decreased retinal vessel density (VD) and increased foveal avascular zone (FAZ) have been found to correlate positively with graded increases in DR severity and decreased visual acuity (VA). Both the SVC and DVC have shown correlations, but the DVC correlation has been found to be stronger. This may be because the DVC is more susceptible to ischemia from its location in a watershed zone near the outer plexiform layer, which has high oxygen requirements [7].

Most studies on OCT-A as a DR biomarker have focused on cross-sectional analyses. Studying the correlation of retinal VD with VA and disease severity longitudinally can provide insight into the applicability of OCT-A for monitoring DR progression. The longitudinal relationship between DR treatment and VD has not been thoroughly studied. There are two aims of this study. The first aim is to determine the cross-sectional association of VD in the superficial and deep layers of the retina using OCT-A with DR relative to the clinical

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stage of the disease and VA. The second aim is to determine the longitudinal impact of DR anti-VEGF treatment on VD in the superficial and deep layers of the retina using OCT-A. If VD can be correlated with clinically determined DR severity and treatment, then OCT-A information can be used as a biomarker to guide DR diagnosis and treatment management, as well as to monitor disease progression.

METHODS

This retrospective cohort study examined the OCT-A imaging data and corresponding electronic medical records of patients diagnosed with DR at the Glick Eye Institute in Indianapolis, Indiana, between 2018 and 2020. This study received Institutional Review Board (IRB) approval under the exemption category (IRB 2005759261). This study was IRB approved as exempt under the category of research involving data collection without subject interaction. All data were entered in an Excel spreadsheet (Microsoft Corporation, Redmond, WA).

The studied outcomes were VA, cross-sectional and longitudinal demographic measurements, and VDs based on the clinical diagnosis of non-proliferative diabetic retinopathy (NPDR), including mild and moderate/severe forms, or proliferative diabetic retinopathy (PDR). VA was clinically determined using a Snellen chart for visual acuity and then converted to a log of minimal angle of resolution (logMAR) measurement to quantify low levels of visual acuity (described as hand motion, counting fingers, and light perception) that were not quantified using the standard Snellen chart [8].

In accordance with the AngioVue System manufacturer guidelines (Optovue, Fremont, CA), only images of a scan quality of six or greater were used in the analysis. Scan quality was determined by the signal strength index, a measure of reflected light brightness during the image scanning process. OCT-A images that were less than six in scan quality were excluded. Quality scans of patients diagnosed with DR were excluded if they were concurrently diagnosed with RD. Patient eyes with panretinal photocoagulation (PRP) were excluded from the longitudinal analyses.

The retinal VDs were quantified using OCT-A imaging of the whole retina and the foveal and parafoveal areas of the retina in both the SVC and DVC using AngioVue (Optovue), as shown in Figure 1A. The OCT-A images acquired measure 6 × 6 mm sections of both the SVC and DVC, centered on the fovea, with the whole image to calculate VD including all these areas. The SVC is defined automatically by the AngioVue software as the plexuses between the vitreous/internal limiting membrane (ILM) segmented line and the inner plexiform layer (IPL)/inner nuclear layer (INL) segmented line. Meanwhile, the DVC is delineated between the IPL/INL segmented line and outer plexiform layer (OPL)/outer nuclear layer (ONL) segmented line (Figure 1B). The foveal VD area is composed of a 1.5 mm diameter area at the center of the fovea. The parafoveal VD area is the area between the 1.5 mm diameter foveal area and a circle, 3 mm in diameter, centered on the fovea.

Cross-sectional: The inclusion criteria included patients diagnosed with DR who had at least one quality OCT-A image of a DR eye taken during the timeframe of the study. The statistical analysis for this portion of the study was completed using Wizard for Mac (version 1.9.42, Evan Miller, Chicago, IL).

A multivariate regression analysis with a post hoc Sidak analysis was completed using the VD measurements of the superficial and deep retinal layers as the dependent variables and DR diagnosis, logMAR, age, gender, and race as the independent variables. An ANOVA was performed to compare the DR diagnosis groups (mild NPDR, moderate/severe NPDR, and PDR) to measure VD. To clarify the protocol used, the Sidak post hoc test was used to better adjust the significance level for multiple comparisons in the multivariate analysis.

Longitudinal: The inclusion criteria for the longitudinal portion of the analysis were the same as those of the cross-sectional analysis, except that only patients with OCT-A images taken at a minimum of two time points during the study window were included. IBM SPSS Statistics for Windows software (version 24.0, IBM Corp., Armonk, NY) was used for the statistical analysis of this part of the study.

A linear, mixed model analysis was performed to examine the longitudinal relationship of anti-VEGF DR treatment compared to no treatment during the study window. To determine the relationship between treatment over time and retinal VD, factors with significance in the cross-sectional analysis were incorporated into the model, including DR diagnosis, age, and logMAR. The VD measurements were the dependent variables in the model, DR diagnosis and treatment were the factors, and months from baseline, age, and logMAR were the covariates. The unique patient identification numbers were the random effects of the model. This model allowed the intrapersonal and interpersonal differences in the time between OCT-A scans, or in other words, the variability between and within subjects, to be accounted for with the retrospective analysis. The model is flexible because of the ability to have missing time datapoints. Unlike a traditional multivariate regression model, which only has fixed effects, this model can account for these effects, as well as random effects associated with each patient's OCT-A scan measurements [9].

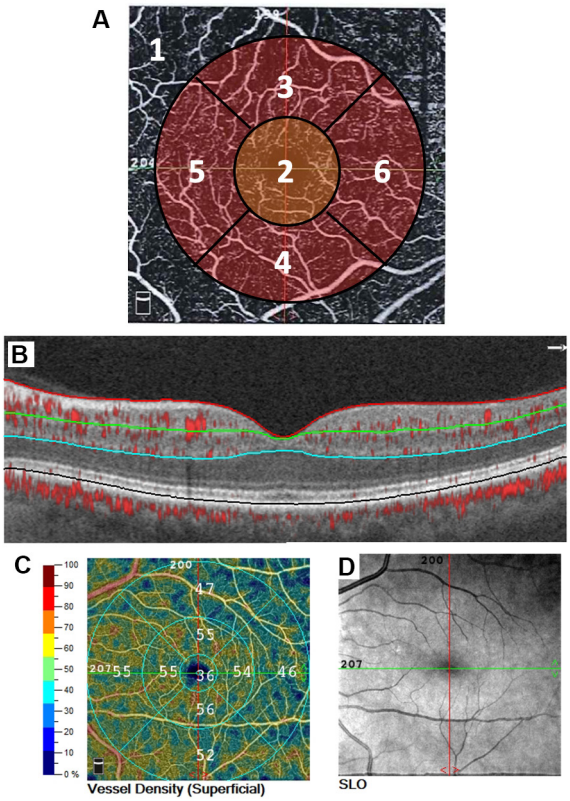

Figure 1. Optical coherence tomography angiography (OCT-A) and segmentation. **A**: 6 × 6 mm OCT-A scan of the whole macula superficial vascular complex (SVC) area (1). Contained within the whole area used to calculate the whole VD, including the fovea (2) and parafovea (3–6). **B**: The B scan indicates the automatic separation of the SVC from the DVC at the inner plexiform layer (IPL)/inner nuclear layer (INL) segmented line in blue. The SVC is defined from the vitreous/ILM segmented line (red) to the IPL/INL segmented line (green), while the deep vascular complex (DVC) is defined from the IPL/INL segmented line (green) to the OPL/ONL segmented line (blue). The VD of the SVC (**D**) and the scanning light ophthalmoscopy (**E**) are shown for reference.

RESULTS

There were no statistically significant differences (p>0.05) between the DR diagnosis groups based on age, gender, race, or DR treatment, as well as medical or surgical history of sleep apnea, cataract surgery, glaucoma, or hypertension once eyes with a history of RD were removed. Patients with a history of RD in the OCT-A image eye (n = 8 for the cross-sectional analysis and n = 6 for the longitudinal analysis) were removed from the analysis because they were unevenly distributed in only the PDR group, which created a confounding bias and a significant difference between the DR diagnosis and treatment groups. If the opposite eye was not affected by RD, those OCT-A scans were included in the analysis. Table 1 summarizes the characteristics of the scans, eyes, and patients included in the cross-sectional and longitudinal analyses.

Cross-sectional: The baseline OCT-A images were from 91 patients who met the eligibility criteria and had a combined total of 151 eye scans taken (33 eyes from 20 patients with mild NPDR, 84 eyes from 51 patients with moderate/severe NPDR, and 34 eyes from 22 patients diagnosed with PDR). There were 319 OCT-A excluded because of low scan quality (<6), and 45 scans were excluded because the patients were not diagnosed with DR. Figure 2 shows representative SVC and DVC OCT-A images, as well as corresponding B scans of maculae. As shown in Table 2, the mean and standard deviation of SVC based on diabetic retinopathy severity was 44.75 ± 1.65 for mild NPDR, 44.36 ± 0.92 for moderate/severe NPDR, and 40.85 ± 1.527 for PDR. The mean and standard deviation of DVC based on diabetic retinopathy severity was 45.18 ± 2.01 for mild NPDR, 43.43±1.21 for moderate/severe NPDR, and 42.35 ± 1.50 for PDR.

In multivariate regression analysis, the whole and parafoveal SVC density positively correlated with lower DR severity (p<0.001). Compared to PDR scans, mild NPDR scans had greater VD in whole and parafoveal SVC areas (p<0.001, β = 3.87, 95% CI = 1.76 to 5.73; p<0.001, β = 5.78, 95% CI = 3.07 to 8.50) and moderate/severe NPDR scans had greater VD in whole and parafoveal SVC areas (p<0.001, β = 3.69, 95% CI = 1.96 to 5.43; p<0.001, β = 4.93, 95% CI = 2.70 to 7.17). The DVC parafoveal VD also correlated positively with lower DR severity (p<0.001) as compared to PDR scans, mild NPDR scans had greater VD in both the whole and parafoveal areas (p = 0.028, β = 2.93, 95% CI = 0.31 to 5.54; p<0.001, β = 4.67, 95% CI = 2.07 to 7.27). Table 2 provides the full details of these multivariate linear regression analysis results.

Table 1. Demographic information on DR patients included in cross-sectional and longitudinal analysis.

Demographic Variable	Cross-Sectional	Longitudinal
OCT-A scans, *n*	151	149
Patients, *n*	93	36
Eyes, *n*	151	51
OD, *n* (%)	76 (50.3%)	24 (47.1%)
Mean logMAR of eyes (range)	0.18 (−0.125- 1.301)	0.209 (−0.125–1.301)
Mean age ± SD, *years* (range)	56±13.8 (18–79)	58±12.5 (22–78)
Male, *n* (%)	47 (49.5%)	19 (52.8%)
DR diagnosis, *n of eyes* (%)		
Mild NPDR	33 scans/eyes (21.9%)	11 scans (7.4%) 9 scans with anti-VEGF (7.1%) 6 eyes (11.8%)
Moderate/severe NPDR	84 scans/eyes (55.6%)	97 scans (67.4%) 84 scans with anti-VEGF (76.4%) 31 eyes (60.8%)
PDR	34 scans/eyes (22.5%)	41 scans (27.5%) 34 scans with anti-VEGF (26.8%) 14 eyes (27.5%)
Anti-VEGF, *n* (%)	28 scans/eyes (18.5%)	127 scans (85.2%) 41 eyes (80.4%)
Medical history, *n* (%)		
Cataract surgery	23 eyes (15.2%)	8 eyes (15.7%)
Glaucoma	20 eyes (13.2%)	8 eyes (15.7%)
Hypertension	87 patients (93.5%)	33 patients (91.7%)
Sleep apnea	15 patients (16.1%)	10 patients (27.8%)
Race, *n* (%)		
African American	43 (46%)	15 (41.7%)
Asian	2 (2.2%)	2 (5.6%)
Native Hawaiians and Other Pacific Islanders	2 (2.2%)	0 (0%)
White	46 (49%)	19 (52.8%)

NPDR=non-proliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy; VEGF=vascular endothelial growth factor

Table 3 and Figure 3 show the relationship between retinal VD and DR severity groups. The post hoc Sidak analysis did not change the significance of these findings.

LogMAR was found to be negatively correlated with whole and parafoveal SVC VD ($p<0.001$, $\beta = -5.33$, 95% CI = -8.05 to -2.61; $p<0.001$, $\beta = -7.63$, 95% CI = -11.13 to -4.13) and whole and parafoveal DVC VD ($p<0.001$, $\beta = -7.04$, 95% CI = -10.40 to -3.68; $p<0.001$, $\beta = -8.61$, 95% CI = -11.97 to -5.27). The logMAR increased with decreased VA, so these measures reflected a positive correlation between better VA and increased VD. In contrast to this trend, worse VA was correlated with increased VD in the SVC foveal area (logMAR positively correlated with VD; $p = 0.021$, $\beta = 6.04$, 95% CI = 0.93 to 11.15). The SVC parafoveal VD was found to positively correlate with age ($p = 0.006$, $\beta = 0.094$, 95% CI = 0.03 to 0.16), but no other relationships between VD and age, gender, or race were found to be statistically significant.

Longitudinal: OCT-A images from 35 patients (48 eyes) who met the eligibility criteria had a total of 141 quality OCT-A scans during the study's timeframe (12 scans of six eyes from five patients with mild NPDR, 95 scans of 33 eyes from 22 patients with moderate/severe NPDR, and 34 scans of 11 eyes from eight patients with PDR). Of the included scans, 36 were of patients who received anti-VEGF treatment, including 29

Table 2. Cross-sectional multivariate linear regression analyses of VD by demographic variables.

OCT-A variable	Mild NPDR	Moderate/severe NPDR	PDR	Mild NPDR versus PDR	Mod/severe NPDR versus PDR
SVC					
Whole VD	44.75 +/− 1.65	44.36±0.92	40.85±1.527	p<0.001*, β=3.87	p<0.001*, β=3.69
Foveal VD	17.52±3.26	20.38±1.54	20.04±3.11	p=0.019	p=0.993
Parafoveal VD	45.58±2.27	44.21±1.20	39.11±2.08	p<0.001*, β=5.78	p<0.001*, β=4.93
DVC					
Whole VD	45.18±2.01	43.43±1.21	42.35±1.50	p=0.028*, β=2.93	p=0.378
Foveal VD	34.24±4.01	33.64±1.85	31.12±3.17	p=0.357	p=0.425
Parafoveal VD	50.50±2.08	47.47±1.18	45.91±1.87	p<0.001*, β=4.67	p=0.239

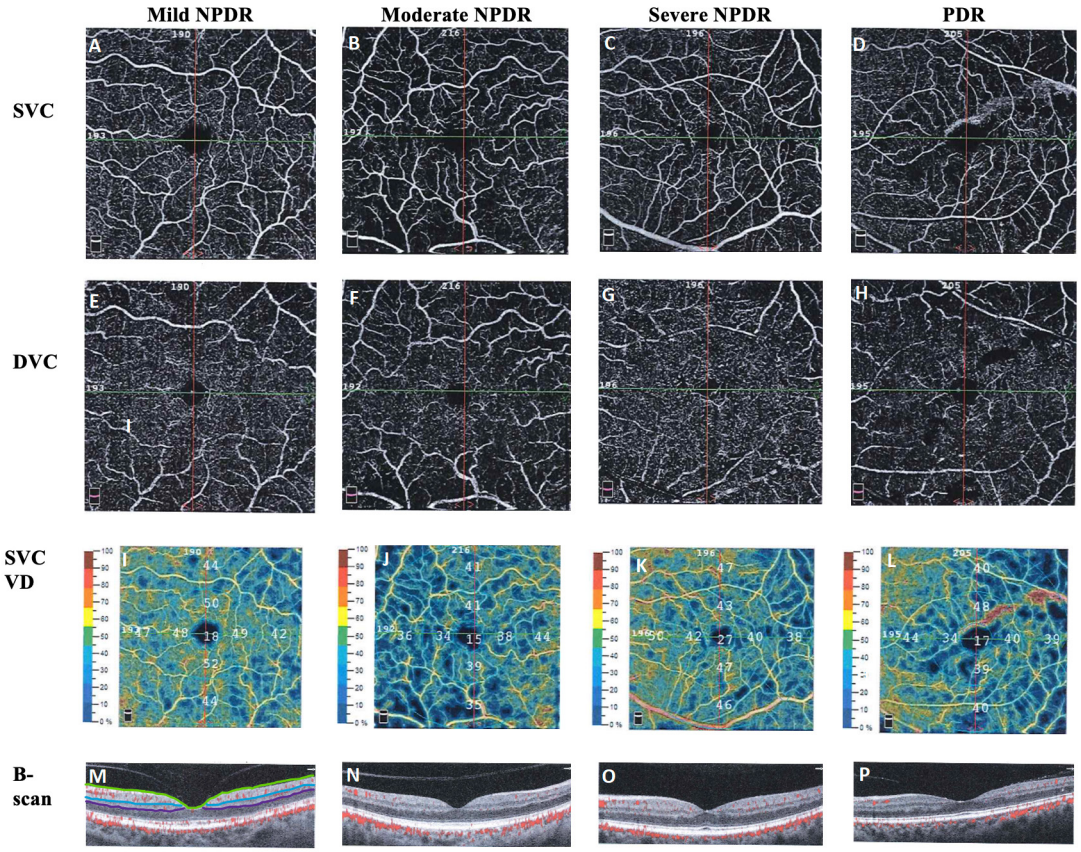

Figure 2. Superficial vascular complex (SVC) and deep vascular complex (DVC) of optical coherence tomography angiography (OCT-A) with corresponding B scan by diabetic retinopathy (DR) diagnosis. A-D: Indicate the SVC using 6 × 6 mm OCT-A images centered on the fovea in representative patients with increasing levels of DR severity. E-H: Show the DVC of the same eye with the same dimensions and DR. I-L: The color-coated map of the SVC area illustrates the study finding that the whole and parafoveal VD of the SVC decreased with increasing DR severity. M-P: Show the corresponding B scans for each level of DR severity with no evidence of macular edema.

Table 3. Cross-sectional ANOVA of VD by DR diagnosis.

OCT-A variable	Mild NPDR	Moderate/severe NPDR	PDR	P value	Adjusted p value
SVC					
Whole VD	44.75 +/− 1.65	44.36±0.92	40.85±1.527	<0.001*	<0.003*
Foveal VD	17.52±3.26	20.38±1.54	20.04±3.11	0.214	0.514
Parafoveal VD	45.58±2.27	44.21±1.20	39.11±2.08	<0.001*	<0.003*
DVC					
Whole VD	45.18±2.01	43.43±1.21	42.35±1.50	0.098	0.266
Foveal VD	34.24±4.01	33.64±1.85	31.12±3.17	0.328	0.697
Parafoveal VD	50.50±2.08	47.47±1.18	45.91±1.87	0.003*	0.009*

scans of eight eyes from five patients with moderate/severe NPDR that had a mean of 7.75 months of follow-up per eye and eight scans of two eyes from two patients with PDR that had a mean of eight months of follow-up per eye. Overall, the mean follow-up time per patient was 7.65 months, with a mean total of three OCT-A scans of each eye. The range in follow-up time was from one to 17 months with a mode of four months and a median of 6.50 months. The standard deviation of follow-up time was 4.06 months.

The parafoveal DVC (p = 0.030, β = -3.277) VD was negatively correlated with no treatment compared to anti-VEGF treatment. However, this relationship did not remain significant when treatment combined with diagnosis or months from baseline were accounted for in the analysis. Increased VA was positively correlated with SVC whole (p = 0.004, β = -4.222) and parafoveal VD (p = 0.004, β = -5.564) and DVC whole (p = 0.022, β = -4.017) VD as measured by logMAR, which is inversely related to VA. Lower DR diagnosis severity was positively correlated with SVC parafoveal VD (p = 0.009, β = 6.126) and DVC parafoveal VD (p = 0.005, β = 5.633) when comparing mild NPDR to higher levels of severity. Increased age was positively correlated with SVC

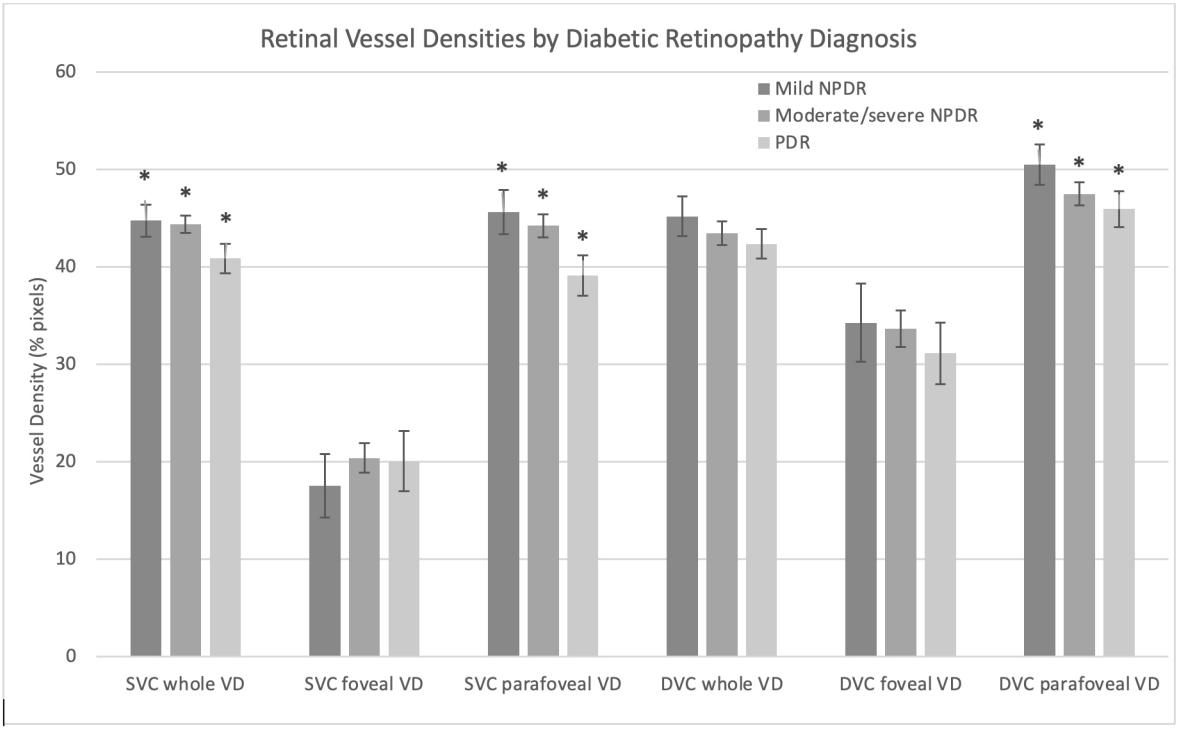

Figure 3. Retinal vessel densities by diabetic retinopathy (DR) diagnosis. Mean vessel densities are shown for each retinal area for each DR severity diagnosis. Error bars depict the standard deviations of the vessel densities. Asterisks indicate which retinal areas showed significant differences in vessel densities between DR severity diagnosis groups in multivariate regression analysis.

parafoveal VD (p = 0.031, β = 0.138), as well as both the DVC whole VD (p = 0.007, β = 0.120) and parafoveal VD (p = 0.002, β = 0.154). The time from the baseline scan was not independently correlated with VD. Table 4 indicates the complete details of these mixed linear model results. The standard error by level of diabetic retinopathy severity was 1.88 for mild NPDR and 0.92 for moderate/severe NPDR with PDR as the comparison group.

Table 4. Longitudinal linear mixed model of SVC and DVC VD by DR diagnosis and treatment.

OCT-A variable	**SVC whole VD**			**SVC foveal VD**			**SVC parafoveal VD**		
	F-test	**β (95% CI)**	***P value***	***F-test***	**β (95% CI)**	***P value***	***F-test***	**β (95% CI)**	***P value***
Age	0.41	0.04 (−0.1, 0.1)	0.527	0.03	−0.019 (−0.222, 0.184)	0.850	5.084	0.138 (0.013, 0.264)	0.031*
Diagnosis	2.49		0.088	0.07		0.928	3.712		0.028*
Mild NPDR		3.9 (0.1, 7.5)	0.043*		−1.487 (−9.250, 6.276)	0.703		6.126 (1.595, 10.657)	0.009*
Mod/sev NPDR		1.3 (−0.6, 3.1)	0.174		−0.38 (−4.5, 3.7)	0.857		1.4 (−0.9,3.7)	0.236
PDR		0	-		0	-		0	-
LogMAR	8.69	−4.2 (−7, −1.4)	0.004*	0.01	0.11 (−6.6, 6.8)	0.975	8.801	−5.5 (−9.3, −1.9)	0.004*
Time (months)	0.66	0.04 (−0.1, 0.1)	0.420	2.47	0.2 (−0.1, 0.5)	0.119	1.101	0.08 (−0.06, 0.2)	0.296
Treatment	0.01		0.971	0.73		0.399	0.235		0.631
Anti-VEGF		−0.06 (−3.6, 3.5)	0.971		2.7 (−3.7, 9.1)	0.399		−0.93 (−4.8, 3)	0.631
No treatment		0	-		0	-		0	-
OCT-A variable	DVC whole VD DVC foveal VD parafoveal VD			DVC foveal VD			DVC parafoveal VD		
	F-test	**β (95% CI)**	***P value***	***F-test***	**β (95% CI)**	***P value***	***F-test***	**β (95% CI)**	***P value***
Age	8.26	0.12 (0.03, 0.2)	0.007*	0.961	0.095 (−0.1,0.29)	0.335	11.551	0.154 (0.06, 0.25)	0.002*
Diagnosis	1.24		0.297	0.132		0.877	4.283		0.017*
Mild NPDR		2.82 (−0.8, 6.5)	0.126		−0.10 (−8.0, 7.8)	0.980		5.63 (1.79, 9.47)	0.005*
Mod/sev NPDR		0.82 (−1.2, 2.8)	0.420		1.02 (−3.28, 5.3)	0.637		0.60 (−1.02, 3.19)	0.310
PDR		0	-		0	-		0	-
LogMAR	5.38	−4.01 (−7.45, −0.58)	0.022*	3.284	6.5 (−0.6, 13.6)	0.072	1.823	−2.40 (−5.9, 1.1)	0.180
Time (months)	1.780	0.103 (−0.05, 0.25)	0.185	2.148	0.22 (−0.08, 0.51)	0.145	0.593	0.06 (−0.09, 0.2)	0.443
Treatment	3.662		0.063	0.061		0.807	5.060		0.030*
Anti-VEGF		−2.58 (−5.30, 0.15)	0.063		−0.76 (−7.02, 5.50)	0.807	0	−3.28 (−6.2, −0.33)	0.030*
No treatment		0	-		0	-		0	-

CI=confidence interval; NPDR=non-proliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy; VEGF=vascular endothelial growth factor; OCT-A=optical coherence tomography angiography. Values with statistical significance are indicated with an asterisk (*).

DISCUSSION

In this study, the VD data from OCT-A scans in patients diagnosed with DR were examined to ascertain the relationship between VA and DR severity at baseline, as well as their relationship with anti-VEGF treatment over time, to determine the utility of OCT-A as a biomarker in patients with DR. VD was found to be positively correlated with better VA for the SVC and DVC whole and parafoveal VD as well as less severe DR for the whole and parafoveal SVC VD and parafoveal DVC VD. When adjusted for age, DR diagnosis, logMAR, time, and random individual effects, patients without treatment had lower SVC and DVC foveal VD. Table 4 indicates this finding and others are consistent with the cross-sectional analysis for the longitudinal analysis. However, this relationship was not significant when the effects of time or treatment were concurrently examined with treatment.

VD, which is measured by the percentage of the area containing vessels compared to the total section of the image of interest, has been shown to have potential as an OCT-A biomarker using automated quantification. VD has the ability to quantify macular capillary nonperfusion as an indicator of ischemia [10], decrease with increasing DR severity [11], and decrease with reduced VA [12,13]. The VD of the DVC is a predictor of DR progression, while the VD of the SVC predicts diabetic macular edema (DME) development, although this was not the subject of this study [14]. Measurements of the SVC and DVC parafoveal VD, specifically, were found to correlate well with DR severity, with the DVC showing reduced VD earlier in the disease course than the SVC [15]. The findings of this study are consistent with the relationship between VD, VA, and DR severity established in the literature.

Anti-VEGF treatment in patients with DR has not been shown to worsen or affect macular capillary nonperfusion or VD. In the short term, after one month of follow-up, one injection of anti-VEGF did not impact VD in patients with DME or retinal vein occlusion [16]. When accounting for the number of injections of anti-VEGF, up to three, as well as the injection type and previous treatment, there was no associated change in VD in patients with PDR and DME [17]. The findings of this study are consistent with the literature, as there was no change in VD indicated in the treatment group over time after anti-VEGF treatment for more than seven months of follow-up. However, the foveal VD in both retinal layers was lower in the group that did not receive anti-VEGF treatment relative to the treatment group, although this was not significant when combined with time or diagnosis.

Increased age correlated positively with parafoveal SVC VD, which was unexpected, as healthy control patients show decreased VD with aging [18-20]. In the longitudinal analysis of this study, this relationship was significant for both the SVC and DVC parafoveal VD. In diabetic patients, fractal dimension (FD), a measure of vascular complexity, has been shown to decrease with aging, and increased DR has been associated with FD decreasing with VD [12]. This could reflect the thinning of the superficial nerve fiber layer as patients age [21]. Alternatively, it might indicate increased vascular perfusion of the remaining vessels from the loss of pericytes for autoregulation of capillary perfusion following progressive diabetic damage to vasculature, a process that would be more pronounced in older diabetic patients [22]. Thus, VD may appear higher in older patients with diabetes, given less autoregulation or increased collateral formation of the remaining vessels.

Although FAZ is known to correlate with DR severity and VA [15], this relationship was not examined in this study because the AngioVue software was unable to quantify the large area for a significant number of baseline scans (n = 30). Patients undergoing PRP treatment were not included in the longitudinal analysis due to a possible confounding effect (n = 5). The effects of PRP on VD merit future studies, as there have been conflicting findings, including no change and increased VD over time [23,24]. Additionally, this study did not differentiate between patients with DME and those without DME, although these differences are indicated by the patients with NPDR who received anti-VEGF treatment.

Conclusion: This study indicated the efficacy of the use of OCT-A scans as a biomarker for DR VD by disease severity and VA. Anti-VEGF treatment did not show a significant change in VD over time compared to DR patients without treatment during the study timeframe. Longer follow-up periods may be needed to elaborate on the long-term effects of anti-VEGF on VD.

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REFERENCES

1. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia 2019; 62:3-16. [PMID: 30171279].

2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010; 376:124-36. [PMID: 20580421].

3. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous 2015; 1:5-[PMID: 27847598].

4. Tey KY, Teo K, Tan ACS, Devarajan K, Tan B, Tan J, Schmetterer L, Ang M. Optical coherence tomography angiography in diabetic retinopathy: a review of current applications. Eye Vis (Lond) 2019; 6:37-[PMID: 31832448].

5. Choi EY, Park SE, Lee SC, Koh HJ, Kim SS, Byeon SH, Kim M. Association Between Clinical Biomarkers and Optical Coherence Tomography Angiography Parameters in Type 2 Diabetes Mellitus. Invest Ophthalmol Vis Sci 2020; 61:4-[PMID: 32150245].

6. Sandhu HS, Elmogy M, El-Adawy N, Eltanboly A, Shalaby A, Keynton R, El-Baz A. Automated diagnosis of diabetic retinopathy using clinical biomarkers, optical coherence tomography (OCT), and OCT angiography. Am J Ophthalmol 2020; 216:201-206. .

7. Chua J, Sim R, Tan B, Wong D, Yao X, Liu X, Ting DSW, Schmidl D, Ang M, Garhöfer G, Schmetterer L. Optical Coherence Tomography Angiography in Diabetes and Diabetic Retinopathy. J Clin Med 2020; 9:[PMID: 32503234].

8. Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the freiburg visual acuity test. Invest Ophthalmol Vis Sci 2006; 47:1236-40. [PMID: 16505064].

9. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med 1997; 16:2349-80. [PMID: 9351170].

10. Hwang TS, Gao SS, Liu L, Lauer AK, Bailey ST, Flaxel CJ, Wilson DJ, Huang D, Jia Y. Automated Quantification of Capillary Nonperfusion Using Optical Coherence Tomography Angiography in Diabetic Retinopathy. JAMA Ophthalmol 2016; 134:367-73. [PMID: 26795548].

11. Bhanushali D, Anegondi N, Gadde SG, Srinivasan P, Chidambara L, Yadav NK, Sinha Roy A. Linking Retinal Microvasculature Features With Severity of Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Invest Ophthalmol Vis Sci 2016; 57:OCT519-25. [PMID: 27472275].

12. Tang FY, Chan EO, Sun Z, Wong R, Lok J, Szeto S, Chan JC, Lam A, Tham CC, Ng DS, Cheung CY. Clinically relevant factors associated with quantitative optical coherence tomography angiography metrics in deep capillary plexus in patients with diabetes. Eye Vis (Lond) 2020; 7:7-[PMID: 32025523].

13. Abdelshafy M, Abdelshafy A. Correlations Between Optical Coherence Tomography Angiography Parameters and the Visual Acuity in Patients with Diabetic Retinopathy. Clin Ophthalmol 2020; 14:1107-15. [PMID: 32425497].

14. Sun Z, Tang F, Wong R, Lok J, Szeto SKH, Chan JCK, Chan CKM, Tham CC, Ng DS, Cheung CY. OCT Angiography Metrics Predict Progression of Diabetic Retinopathy and Development of Diabetic Macular Edema: A Prospective Study. Ophthalmology 2019; 126:1675-84. [PMID: 31358386].

15. Mastropasqua R, Toto L, Mastropasqua A, Aloia R, De Nicola C, Mattei PA, Di Marzio G, Di Nicola M, Di Antonio L. Foveal avascular zone area and parafoveal vessel density measurements in different stages of diabetic retinopathy by optical coherence tomography angiography. Int J Ophthalmol 2017; 10:1545-51. [PMID: 29062774].

16. Ghasemi Falavarjani K, Iafe NA, Hubschman J-P, Tsui I, Sadda SR, Sarraf D. Optical Coherence Tomography Angiography Analysis of the Foveal Avascular Zone and Macular Vessel Density After Anti-VEGF Therapy in Eyes With Diabetic Macular Edema and Retinal Vein Occlusion. Invest Ophthalmol Vis Sci 2017; 58:30-4. [PMID: 28114569].

17. Sorour OA, Sabrosa AS, Yasin Alibhai A, Arya M, Ishibazawa A, Witkin AJ, Baumal CR, Duker JS, Waheed NK. Optical coherence tomography angiography analysis of macular vessel density before and after anti-VEGF therapy in eyes with diabetic retinopathy. Int Ophthalmol 2019; 39:2361-71. [PMID: 31119505].

18. You QS, Chan JCH, Ng ALK, Choy BKN, Shih KC, Cheung JJC, Wong JKW, Shum JWH, Ni MY, Lai JSM, Leung GM, Cheung CMG, Wong TY, Wong IYH. Macular Vessel Density Measured With Optical Coherence Tomography Angiography and Its Associations in a Large Population-Based Study. Invest Ophthalmol Vis Sci 2019; 60:4830-7. [PMID: 31747685].

19. Jo YH, Sung KR, Shin JW. Effects of Age on Peripapillary and Macular Vessel Density Determined Using Optical Coherence Tomography Angiography in Healthy Eyes. Invest Ophthalmol Vis Sci 2019; 60:3492-8. [PMID: 31408111].

20. Lin Y, Jiang H, Liu Y, Rosa Gameiro G, Gregori G, Dong C, Rundek T, Wang J. Age-Related Alterations in Retinal Tissue Perfusion and Volumetric Vessel Density. Invest Ophthalmol Vis Sci 2019; 60:685-93. [PMID: 30786280].

21. Bowd C, Zangwill LM, Blumenthal EZ, Vasile C, Boehm AG, Gokhale PA, Mohammadi K, Amini P, Sankary TM, Weinreb RN. Imaging of the optic disc and retinal nerve fiber layer: the effects of age, optic disc area, refractive error, and gender. J Opt Soc Am A Opt Image Sci Vis 2002; 19:197-207. [PMID: 11778725].

22. Curtis TM, Gardiner TA, Stitt AW. Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis? Eye (Lond) 2009; 23:1496-508. [PMID: 19444297].

23. Lorusso M, Milano V, Nikolopoulou E, Ferrari LM, Cicinelli MV, Querques G, Ferrari TM. Panretinal Photocoagulation Does Not Change Macular Perfusion in Eyes With Proliferative Diabetic Retinopathy. Ophthalmic Surg Lasers Imaging Retina 2019; 50:174-8. [PMID: 30893451].

24. Fawzi AA, Fayed AE, Linsenmeier RA, Gao J, Yu F. Improved Macular Capillary Flow on Optical Coherence Tomography Angiography After Panretinal Photocoagulation for Proliferative Diabetic Retinopathy. Am J Ophthalmol 2019; 206:217-27. [PMID: 31078542].

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