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ORIGINAL RESEARCH

Correlations Between Optical Coherence Tomography Angiography Parameters and the Visual Acuity in Patients with Diabetic Retinopathy

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Aim: The aim of this study was to assess the correlation between different optical coherence tomography angiography (OCTA) parameters and the best corrected visual acuity (BCVA) in patients with diabetic retinopathy (DR).

Patients and Methods: Sixty eyes of 60 participants were included in this prospective study: 40 diabetic patients [20 with non-proliferative diabetic retinopathy (NPDR group), 20 with proliferative diabetic retinopathy (PDR group)] and 20 age- and gender-matched normal healthy subjects (control group). After full ophthalmological examination and fundus fluorescein angiography, OCTA was performed for all participants. Quantitative OCTA parameters, such as the foveal avascular zone (FAZ) area, the superficial capillary plexus vessel density (%) (SCP-VD) and the deep capillary plexus vessel density (%) (DCP-VD) in, whole and parafoveal areas were measured. Correlations between BCVA and OCTA parameters were analyzed.

Results: There were no statistically significant differences between groups regarding age, gender, refraction, macular thickness or intraocular pressure. The median (IQR) FAZ area was 0.42 (0.39–0.46) mm^2 in the NPDR group, 0.54 (0.45–0.65) mm^2 in the PDR group and 0.24 (0.21–0.26) mm^2 in the control group ($P<0.001$). The FAZ area increased with increasing severity of DR. SCP-VD and DCP-VD showed significant differences between groups ($P<0.001$). Vessel density (VD) was decreased in both DCP and SCP as DR progressed. There was a significant positive correlation between BCVA (LogMAR) and FAZ area. There were significant negative correlations between BCVA (LogMAR) and VD in both SCP and DCP. Stepwise multiple linear regression analysis demonstrated that SCP-VD in the whole area and DCP-VD in the parafoveal area were the best predictive factors for BCVA in the NPDR and PDR groups.

Conclusion: With progression of DR, the VD decreased and the FAZ area increased, and both parameters were correlated with poor visual acuity. OCTA is a non-invasive tool which can be used to detect diabetic macular ischemia and help in the prediction of visual prognosis.

Keywords: visual acuity, OCT angiography, vessel density, foveal avascular zone, diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is considered the leading cause of defective vision in developed countries.[1] Fluorescein angiography (FA) is commonly used in imaging and monitoring the progression of DR. Currently, with advances in optical coherence tomography angiography (OCTA), it serves as an adjunctive, non-invasive and rapid imaging technique for detecting microvascular diabetic changes, especially

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diabetic macular ischemia, and can help in the prediction of visual prognosis in these patients.[2,3]

Optical coherence tomography (OCT) can provide high-resolution cross-sectional scans of the retinal microstructure and is considered a standard tool for detecting and monitoring diabetic maculopathy.[4,5] OCTA is a novel tool that permits quantitative analysis of retinal and choroidal blood flow, without the need for dye injection, by performing high-contrast repeated scan images of the retinal and choroidal microvascular bed to detect the motion change signals from the red blood cells moving inside the blood vessels.[2,6-8]

The retinal microvascular changes in DR may lead to visually fatal complications, including macular ischemia, neovascularization and macular edema.[9] Recent research has highlighted the potential role of this new imaging modality in assessing the retinal microvascular abnormalities in various retinal diseases, including DR.[7–10] The quantitative OCTA parameters, such as foveal avascular zone (FAZ) area, vessel density, and perfusion density in the superficial and deep capillary plexus, may have a useful role in the early detection of subclinical disease and may also provide valuable biomarkers in monitoring the progression of DR and preventing its severe complications.[11–13]

The aim of the current study was to assess the correlation between best corrected visual acuity (BCVA) and different OCTA parameters in patients with DR.

Patients and Methods

Patients

Sixty eyes of 60 participants were included in this prospective study, which was conducted between January 2019 and January 2020, with the participants recruited from the outpatient clinics of Benha University Hospital. All participants signed informed consent forms, which were in compliance with the requirements of the Declaration of Helsinki, and approval for the study was obtained from the local ethics committee (Benha Faculty of Medicine Research Ethics Committee). The participants were divided into three groups: 20 eyes of 20 diabetic patients with non-proliferative diabetic retinopathy (NPDR group), 20 eyes of 20 diabetic patients with proliferative diabetic retinopathy (PDR group) and 20 eyes of 20 normal healthy subjects (control group). The controls were matched for age and gender to both the NPDR group and PDR group.

The classification of DR was carried out in compliance with the International Clinical Disease Severity Scale for DR.[14] Inclusion criteria were diabetic patients with type 2 diabetes mellitus (DM), spherical equivalent ranging between −1.5 and +1.5 diopter and intraocular pressure (IOP) <21 mmHg. Exclusion criteria were eyes with a history of laser photocoagulation or any other treatment for DR, the presence of macular edema, tractional retinal detachment, vitreomacular traction, media opacity (eg, cataract,) IOP ≥21 mmHg and a history of other retinal diseases (eg, retinal vein or artery occlusion and choroidal neovascular membrane). The healthy subjects had BCVA better than 6/9, with no evidence of any ocular or neurological diseases.

Ophthalmological Examination

All participants underwent a full ophthalmological examination including slit-lamp examination, refraction, BCVA using the Snellen chart (expressed as LogMAR), IOP measurement by applanation tonometry, dilated fundus examination and fundus fluorescein angiography.

OCTA was performed for all subjects using the RTVue XR OCT Avanti System with AngioVue version 2018.0.0.18 (Optovue, Fremont, CA, USA); AngioVue HD imaging retinal scan size 6×6 mm^2, 400×400 pixels (two repeats/B-scan), scan time 3 s, axial resolution 5 µm and transversal resolution 15 µm. En face, A-scan and B-scan angiography images of both the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were used for analysis. The automated measured OCTA parameters were the FAZ area (mm^2), the superficial capillary plexus vessel density (SCP-VD) and the deep capillary plexus vessel density (DCP-VD), in whole and parafoveal areas. The vessel density was automatically calculated in two circular rings after excluding the FAZ area: the parafoveal area in a circular zone of 3 mm diameter and the whole area in a circular zone of 6 mm diameter. The automated vessel density measurements were applied using the new AngioVue software (Optovue, USA), which includes automated algorithms for mapping capillary density in the SCP and DCP, and the vessel density was demonstrated as a percentage by taking the ratio of the total vessel area to the total area of analyzed region. The central retinal thickness was recorded from a 6×6 mm^2 area on the B-scan map. OCTA images with a signal strength index (SSI) <6 were excluded from the present study.

Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 16 software (SPS, Chicago, IL, USA). Categorical data were presented as number and percentages, and

analyzed using the chi-squared (χ^2) test. Quantitative data were tested for normality using the Shapiro–Wilks test, assuming normality at $P>0.05$. Normally distributed variables were expressed as mean±standard deviation and analyzed by Student's *t*-test for two independent groups or one-way analysis of variance (ANOVA, *F*-test) for three independent groups, while non-parametric data were presented as median and interquartile range (IQR), and analyzed by the Kruskal–Wallis (KW) test. Significant KW findings were followed by post-hoc multiple comparisons using Bonferroni adjusted tests to detect significant pairs. The Spearman correlation coefficient (rho) was used to assess non-parametric correlations. Stepwise multiple linear regression analysis [adjusted for glycated hemoglobin (HbA_{1c}) and DM duration] was run to detect the significant predictors of BCVA. $P\leq0.05$ was considered significant and $P\leq0.001$ was considered highly significant.

Results

Twenty patients (10 males and 10 females) with a mean age of 50.0±3.4 years (NPDR group), 20 patients (12 males and 8 females) with a mean age of 50.6±2.4 years (PDR group) and a control group of 20 healthy normal subjects (8 females and 12 males) with a mean age of 49.2 ±2.5 years were included in this study. There were no significant differences in the age, gender, refraction, macular thickness or IOP between the studied groups ($P=0.299$, 0.76, 0.75, 0.20 and 0.79, respectively) (Table 1).

DM disease duration was 7.3±1.8 years in the NPDR group and 9.0±2.3 years in the PDR group. Mean BCVA was significantly higher in the control group in comparison to the other groups ($P<0.001$). The mean FAZ area showed significant differences between groups ($P<0.001$). The FAZ area was larger in patients with NPDR and PDR in comparison to the healthy control group (Figure 1), and the FAZ area increased with increasing severity of DR (Figure 2). SCP-VD and DCP-VD showed significant differences between groups ($P<0.001$) in whole and parafoveal areas (Figure 3). The mean vessel density was reduced in eyes with DR in comparison to the control group (Figure 4). The mean vessel density values were shown to decrease in both DCP and SCP as DR progressed (Table 2). There was a significant positive correlation between BCVA (LogMAR) and the FAZ area. Larger FAZ areas were correlated with poorer BCVA. There were significant negative correlations between BCVA (LogMAR) and vessel density in both SCP and DCP. The reduction in vessel density was correlated with poorer visual acuity (Table 3).

The changes in FAZ area and vessel density were found to correlate with systemic indicators such as duration of DM and HbA_{1c} (Tables 4 and 5).

HgA_{1c} and DM duration were adjusted in the regression analysis to demonstrate the actual relationship between BCVA and OCTA parameters. Stepwise multiple linear regression analysis demonstrated that SCP-VD in the whole area and DCP-VD in the parafoveal area were the best predictive factors for BCVA in the NPDR and PDR groups (Table 6).

Discussion

OCTA is a new imaging technique which can assess the retinal and choroidal microvasculature.[2–12] It allows demonstration of the blood flow in both superficial and deep retinal capillary layers, so it can delineate the microvascular changes in DR, such as irregular FAZ, areas of capillary dropout and neovascularization, which have serious effects on visual acuity.[15]

The aim of the current study was to demonstrate the impact of these microvascular changes on the vision of

Table 1 Comparison Between the Studied Groups Regarding Basic Characteristics

Variable		Controls (n=20)	NDPR Group (n=20)	PDR Group (n=20)	Test of Significance	P
Age (years)	Mean±SD (range)	49.2±2.5 (45–53)	50.0±3.4 (45–55)	50.6±2.4 (47–55)	*F*=1.23	0.299
Gender (no., %)	Male Female	12 (60.0) 8 (40.0)	10 (50.0) 10 (50.0)	12 (60.0) 8 (40.0)	χ^2=0.54	0.76
IOP (mmHg)	Mean±SD (range)	13.7±1.8 (11–17)	13.4±2.0 (11–17)	13.8±1.9 (11–17)	*F*=0.24	0.79
Macular thickness (mm)	Mean±SD (range)	242.2±12.4 (221–261)	238.2±14.1 (206–254)	245.1±8.6 (233–260)	*F*=1.65	0.20
DM duration	Mean±SD (range)	–	7.3±1.8 (4–10)	9.0±2.3 (5–12)	St.'*t*'=2.56	0.015 (S)
HbA_{1c} (mmol/mL)	Mean±SD (range)	–	7.1±0.8 (5.8–8.4)	8.9±1.9 (5.8–11.9)	St.'*t*'=3.89	<0.001 (HS)

Abbreviations: St.'*t*', Student's *t*-test; S, significant; HS, highly significant; IOP, intraocular pressure; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; *F*, *F*-test (ANOVA); χ^2, chi-squared test.

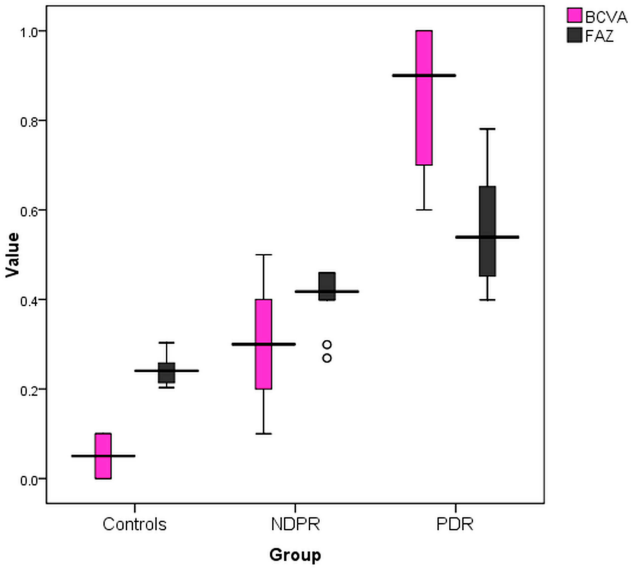

Figure 1 Box plot showing median and IQR of BCVA (LogMAR) and FAZ area among the studied groups.

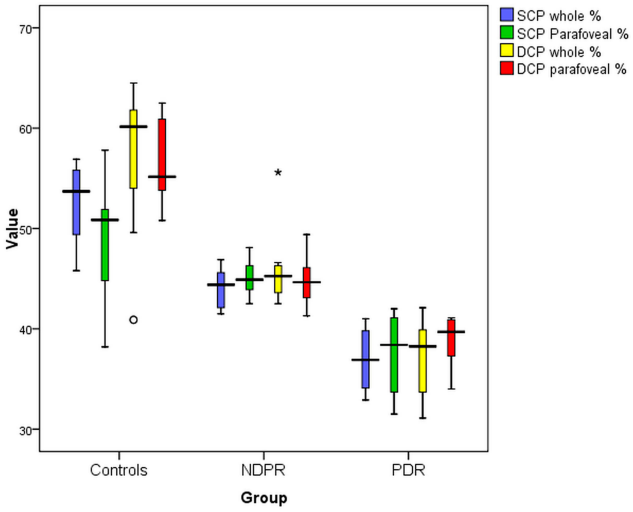

Figure 3 Box plot showing median and IQR of vessel density in superficial capillary plexus (SCP) and deep capillary plexus (DCP) among the studied groups.

patients with DR by analyzing the correlation between visual acuity and retinal vessel density, as well as the area of FAZ, using OCTA.

In our study, the FAZ area shows significant differences between the studied groups. It shows more widening with increasing severity of DM. We found a significant positive correlation between the FAZ area and BCVA (LogMAR) in DR patients; larger FAZ areas were correlated with poorer BCVA (P<0.001). These results concur with previous research by Balaratnasingam et al, who also demonstrated a significant correlation between the FAZ area and BCVA in patients with DR.[16] Our results are also in agreement with a study by Johannesen et al,[17] who stated that the FAZ area was larger in patients with NPDR and PDR in comparison to the healthy control group. The association between DR progression and increased FAZ area may reflect the increased amount of non-perfused areas.[18]

Many previous studies also reported an increase in FAZ area with advancing DR severity;[19–22] however, one study, by Carnevali et al, stated that the FAZ area had not changed as DR progressed.[23]

Controversy regarding the correlation between FAZ size and BCVA in DR is still present; some studies reported a significant correlation between them[16,24,25] while another did not find an association between them.[26] Further research is needed to explicate this correlation.

We found a significant correlation between FAZ size, vessel density and systemic indicators such as duration of DM and HbA_{1c}. Our results are in accordance with

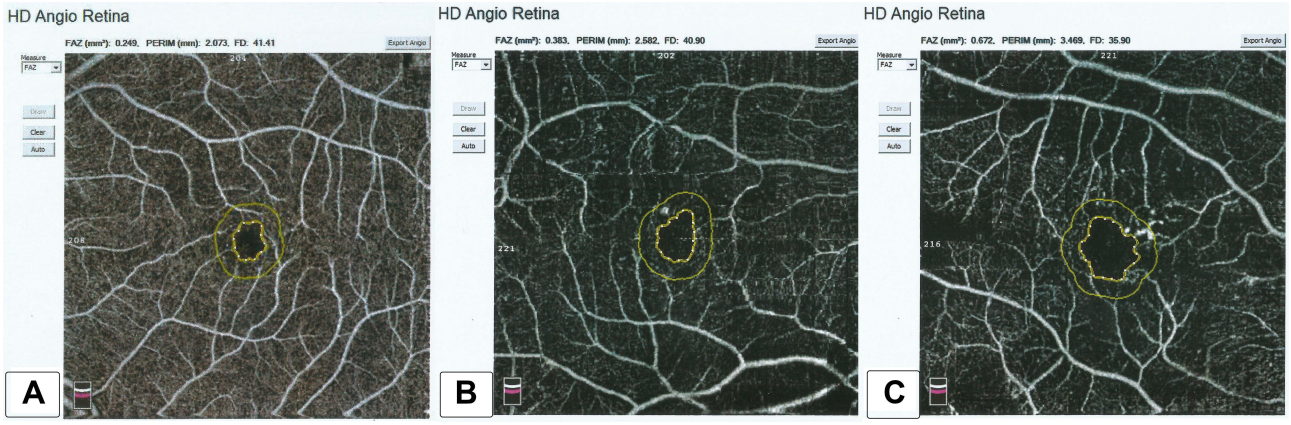

Figure 2 Foveal avascular zone (FAZ) area: (**A**) in a healthy subject (**B**) in a patient with NPDR, and (**C**) in a patient with PDR. There was widening of the FAZ area as DR progressed.

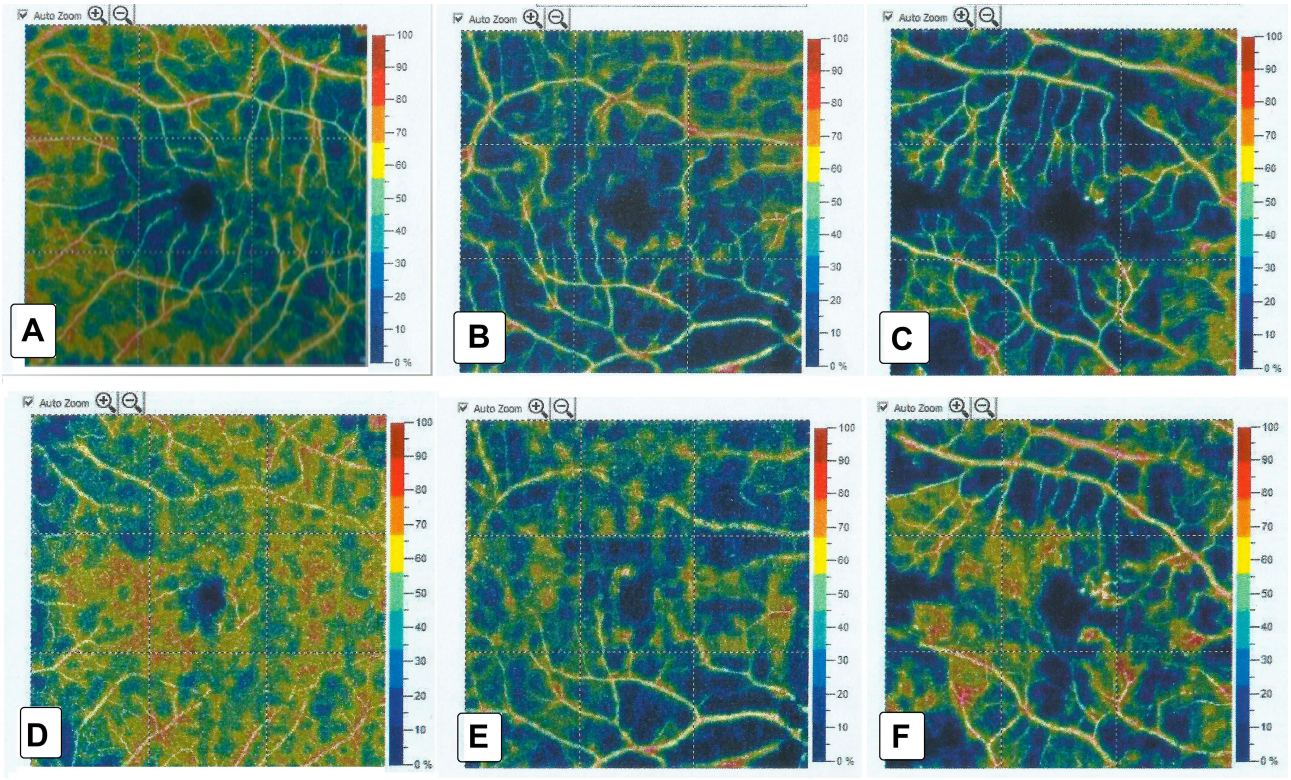

Figure 4 OCTA images (6×6 mm) from SCP and DCP: corresponding color-coded vessel density (VD) mapping with quantitative data. The VD is reduced in eyes with DR in comparison to controls with areas of capillary non-perfusion outside the FAZ. (**A**) SCP-VD in a healthy subject, (**B**) SCP-VD in a patient with NPDR, (**C**) SCP-VD in a patient with PDR, (**D**) DCP-VD in a healthy subject, (**E**) DCP-VD in a patient with NPDR, and (**F**) DCP-VD in a patient with PDR.

previous research;[27–29] however, other studies reported no correlation between them.[19,30]

We also found that poor visual acuity in DR was associated with decreased vessel density in the SCP and DCP. Diminished vessel density reflects low perfusion and the presence of capillary dropout in parafoveal areas. Macular ischemia (inadequate blood supply) may contribute to both macular dysfunction and poor visual acuity.[4]

Past studies concluded that diminished vessel density, irregularity of the FAZ and increased FAZ area were associated with progression and worsening of DR.[24,31,32] Other studies also reported that poorer visual acuity was correlated with diminished vessel density and widening of the FAZ area in DR patients without diabetic macular edema.[25]

In a 2019 study, Hsiao et al[15] concluded that poor visual acuity in diabetic maculopathy was significantly

Table 2 Comparison Between the Studied Groups Regarding Visual Acuity and OCTA Parameters

Variable	Controls (n=20)	NDPR Group (n=20)	PDR Group (n=20)	KW Test	P
	Median (IQR)	Median (IQR)	Median (IQR)		
SE	0.63 (−0.75, 1.0)	0.0 (−0.75, 1.0)	0.63 (−0.5, 1.25)	0.58	0.75
BCVA (LogMAR)	0.05 (0.0, 1.0)	0.3 (0.2, 0.4)*	0.9 (0.7, 1.0)*†	51.05	<0.001 (HS)
FAZ area (mm^2)	0.24 (0.21, 0.26)	0.42 (0.39, 0.46)*	0.54 (0.45, 0.65)*†	44.1	<0.001 (HS)
SCP-VD whole (%)	53.7 (49.4, 55.8)	44.4 (42.1, 45.6)*	36.9 (34.1, 39.8)*†	50.9	<0.001 (HS)
SCP-VD parafoveal (%)	50.8 (44.8, 51.9)	44.9 (43.9, 46.3)*	38.4 (33.7, 41.1)*†	37.2	<0.001 (HS)
DCP-VD whole (%)	60.1 (54, 61.8)	45.2 (43.6, 46.3)*	38.3 (33.7, 39.9)*†	44.6	<0.001 (HS)
DCP-VD parafoveal (%)	55.1 (53.8, 60.9)	44.7 (43.1, 46.1)*	39.7 (37.3, 40.9)*†	52.5	<0.001 (HS)

Notes: *Significant in comparison with controls; †significant in comparison with NDPR.

Abbreviations: SE, spherical equivalent; HS, highly significant; BCVA, best corrected visual acuity; FAZ, foveal avascular zone; SCP-VD, superficial capillary plexus vessel density; DCP-VD, deep capillary plexus vessel density; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; KW, Kruskal–Wallis.

Table 3 Correlations Between BCVA and the Studied Variables Among the Studied Groups

	BCVA (LogMAR)					
	NPDR Group		PDR Group		Control Group	
	Rho	P	Rho	P	Rho	P
Age	−0.188	0.42	−0.06	0.82		
DM duration	0.683	0.001 (HS)	0.886	<0.001 (HS)	–	–
HbA_{1c}	0.985	<0.001 (HS)	0.846	<0.001 (HS)	–	–
IOP	−0.037	0.87	0.168	0.47	0.351	0.129
Macular thickness	−0.055	0.81	0.095	0.69	−0.314	0.177
SE	0.272	0.24	0.369	0.11	0.244	0.299
FAZ	0.975	<0.001 (HS)	0.963	<0.001 (HS)	0.244	0.299
SCP-VD whole (%)	−0.985	<0.001 (HS)	−0.963	<0.001 (HS)	0.383	0.096
SCP-VD parafoveal (%)	−0.985	<0.001 (HS)	−0.963	<0.001 (HS)	0.219	0.35
DCP-VD whole (%)	−0.960	<0.001 (HS)	−0.963	<0.001 (HS)	0.304	0.19
DCP-VD parafoveal (%)	−0.985	<0.001 (HS)	−0.963	<0.001 (HS)	−0.313	0.179

Abbreviations: SE, spherical equivalent; HS, highly significant; BCVA, best corrected visual acuity; FAZ, foveal avascular zone; SCP-VD, superficial capillary plexus vessel density; DCP-VD, deep capillary plexus vessel density; IOP, intraocular pressure; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4 Correlations Between DM Duration and OCTA Parameters

	DM Duration			
	NPDR Group		PDR Group	
	Rho	P	Rho	P
FAZ	0.660	0.002 (S)	0.951	<0.001 (HS)
SCP-VD whole (%)	−0.691	0.001 (HS)	−0.951	<0.001 (HS)
SCP-VD parafoveal (%)	−0.691	<0.001 (HS)	−0.951	<0.001 (HS)
DCP-VD whole (%)	−0.624	0.003 (S)	−0.951	<0.001 (HS)
DCP-VD parafoveal (%)	−0.691	0.001 (HS)	−0.951	<0.001 (HS)

Abbreviations: S, significant; HS, highly significant; FAZ, foveal avascular zone; SCP-VD, superficial capillary plexus vessel density; DCP-VD, deep capillary plexus vessel density; DM, diabetes mellitus; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 5 Correlations Between HbA_{1c} and OCTA Parameters

	HbA_{1c}			
	NPDR Group		PDR Group	
	Rho	*P*	Rho	*P*
FAZ	0.985	<0.001 (HS)	0.869	<0.001 (HS)
SCP-VD whole (%)	−0.988	<0.001 (HS)	−0.868	<0.001 (HS)
SCP-VD parafoveal (%)	−0.988	<0.001 (HS)	−0.870	<0.001 (HS)
DCP-VD whole (%)	−0.976	<0.001 (HS)	−0.869	<0.001 (HS)
DCP-VD parafoveal (%)	−0.988	<0.001 (HS)	−0.870	<0.001 (HS)

Abbreviations: HS, highly significant; FAZ, foveal avascular zone; SCP-VD, superficial capillary plexus vessel density; DCP-VD, deep capillary plexus vessel density; HbA_{1c}, glycated hemoglobin; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

correlated with decreased DCP-VD, and no correlation was found with SCP-VD.

Previous studies also reported significant effects on DCP-VD, more than on SCP-VD, in DR patients, and concluded that DCP-VD may be a useful tool for the prediction of DR severity and identifying subjects at high risk, even in the absence of any signs of DR.[23,33–35] These results disagree with other studies, which stated

Table 6 Stepwise Multiple Linear Regression Analysis for the Predictors of BCVA

Model Summary (NPDR Group)	R^2		Adjusted R^2	SEE	*F*	*P*-value
	0.981		0.978	0.021	276.9	<0.001 (HS)
Variable	**Unstandardized Coefficients**		**Standardized Coefficients**	**95% CI of *B***	**t**	***P***
	B	**Std. Error**	**Beta**			
(Constant)	3.25	0.13	–	2.97, 3.52	25.0	<0.001 (HS)
SCP-VD whole	−0.039	0.008	−0.52	−0.06, −0.023	5.17	<0.001 (HS)
DCP-VD parafoveal	−0.035	0.006	−0.62	−0.05, −0.021	5.53	<0.001 (HS)
DCP-VD whole	−0.007	0.002	−0.18	−0.012, −0.002	2.88	0.011 (S)
Model Summary (PDR Group)	R^2		Adjusted R^2	SEE	*F*	*P*-value
	0.908		0.897	0.051	84.1	<0.001 (HS)
Variable	**Unstandardized Coefficients**		**Standardized Coefficients**	**95% CI of *B***	**t**	***P***
	B	**Std. Error**	**Beta**			
(Constant)	2.41	0.18	–	2.99, 8.5	13.2	<0.001 (HS)
SCP-VD whole	−0.073	0.01	−1.38	−0.095, −0.052	7.08	<0.001 (HS)
DCP-VD parafoveal	−0.030	0.012	−0.485	−0.056, −0.004	2.48	0.024 (S)

Abbreviations: SCP-VD, superficial capillary plexus vessel density; DCP-VD, deep capillary plexus vessel density; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; R^2, Regression coefficient; SEE, standard error of estimate; *F*, *F*-ratio; S, significant; HS, highly significant.

that DR severity and BCVA were significantly correlated with SCP-VD rather than DCP-VD.[27–36]

We found a significant negative correlation between the BCVA (LogMAR) and vessel density in both DCP and SCP. Our results are comparable to a study by Samara et al;[25] however, no correlation was found between them in another study.[26] Further research is still needed to elucidate these controversial issues.

In the present study, the stepwise multiple linear regression analysis demonstrated that the SCP-VD in the whole area and the DCP-VD in the parafoveal area were the best predictive factors for BCVA in the NPDR and PDR groups. OCTA is an objective measure of the microvascular changes, while visual acuity (BCVA) is a subjective measure. Therefore, the changes in OCTA vascular parameters may be used as a surrogate for changes in visual acuity in patients with DR. These OCTA quantitative vascular measurements may be used as biomarkers to detect changes in visual acuity with progression of DR.

One limitation of this study is the relatively small sample size. Future research involving bigger numbers and studying the correlation between microvascular OCTA parameters and the functional changes in macular area using other technologies, such as multifocal electroretinography, are needed to assess the relative sensitivity between microvascular damage and macular dysfunction.

Conclusion

With progression of DR, the vessel density is decreased and the FAZ area is increased, and these parameters are correlated with poor visual acuity. OCTA may be a useful imaging tool not only for the diagnosis of DR but also in monitoring disease progression. OCTA is a non-invasive tool which can be used to detect diabetic macular ischemia and help in the prediction of visual prognosis.

Disclosure

The authors report no funding and no conflicts of interest in this work.

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