DOI:10.14744/bej.2022.92668
Beyoglu Eye J 2022; 7(4): 273-281

Original Article

Sensitivity and Specificity of the Optical Coherence Tomography Angiography for Detection of Neovascularization and Evaluation of Peripheral Ischemia in Diabetic Retinopathy

Sema Tamer Kaderli,[1] Aylin Karalezli,[2] Cansu Kaya,[2] Safak Korkmaz,[3] Sabahattin Sul[2]

[1]Department of Ophthalmology, Mugla Training and Research Hospital, Mugla, Türkiye
[2]Department of Ophthalmology, Mugla Sitki Kocman University, Mugla, Türkiye
[3]Department of Ophthalmology, Giresun Training and Research Hospital, Giresun, Türkiye

Abstract

Objectives: The purpose of this study was to identify the sensitivity and specificity of optical coherence tomography angiography (OCTA) parameters for the presence of neovascularization elsewhere (NVE) and to investigate the relationship between ischemic areas.

Methods: This study included 59 eyes with non-proliferative diabetic retinopathy (NPDR) and 36 eyes with proliferative diabetic retinopathy (PDR). The foveal avascular zone (FAZ), vessel density (VD) for the superficial and the deep capillary plexus (DCP), choriocapillaris flow area (CCP), and non-perfusion area (unit²) were recorded. The area under the curve (AUC) under the receiver operating characteristic curves, sensitivity and specificity were calculated for statistically significant outcomes. Later, based on visual acuity, PDR group was subdivided into group 2A: PDR eyes with VA ≤0.2 logMAR and group 2B: PDR eyes with VA>0.2 logMAR. Non-perfusion area and OCTA features were compared between the subgroups.

Results: The VD in DCP was significantly lower, FAZ and non-perfusion area were larger in PDR group ($p=0.001$, $p<0.001$, and $p<0.001$). The AUC for presence of NVE, for the VD, was 0.710 ($p=0.012$) with sensitivity and specificity of 64% and 65%, for the FAZ was 0.746 ($p<0.001$) with sensitivity and specificity of 72% and 72.7%. There was a significant positive correlation between the FAZ and non-perfusion area (For NPDR, $p=0.025$, for PDR $p<0.001$). There was a significant negative correlation between the VD in DCP and ischemic area in PDR group. ($p<0.001$) In group 2B, non-perfusion area and FAZ were larger than group 2A. The VD and CCP flow area were also lower in group 2B (All, $p<0.05$).

Conclusion: In cases with decreased VD in DCP and increased FAZ, the probability of PDR increases. Despite the sensitivity and specificity of the OCTA indices for the prediction of NVE being moderate, the OCTA is very useful in evaluating the microvascular structure in DR.

Keywords: Non-perfusion area, Optical cohorence tomography angiography, Proliferative diabetic retinopathy, Ultra wide-field angiograhy

How to cite this article: Tamer Kaderli S, Karalezli A, Kaya C, Korkmaz S, Sul S. Sensitivity and Specificity of the Optical Coherence Tomography Angiography for Detection of Neovascularization and Evaluation of Peripheral Ischemia in Diabetic Retinopathy. Beyoglu Eye J 2022; 7(4): 273-281.

Address for correspondence: Sema Tamer Kaderli, MD. Department of Ophthalmology, Mugla Training and Research Hospital, Mugla, Türkiye
Phone: +90 507 411 01 29 **E-mail:** sematamerkaderli@hotmail.com

Submitted Date: May 23, 2022 **Revised Date:** August 18, 2022 **Accepted Date:** September 01, 2022 **Available Online Date:** November 15, 2022

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

Introduction

The novel improvement of ultra-widefield fluorescein angiography (UWFA) imaging systems has provided images with a 200° field of view that can visualize up to 3.2 times more retinal region compared with the conventional 7-standard field imaging realized by the early treatment of diabetic retinopathy (DR) Study (1,2). With this current technology, significant vascular lesions can be obtained in the periphery of retina which was previously missed with standard field fluorescein angiography.

Diagnosing the stage of DR severity is important for evaluating progression risk, considering a therapeutic intervention, and determining optimal follow-up intervals (3). DR severity also has relationships for risk of DR-related complications, such as diabetic macular edema, a cause of vision loss in DR (1). However, funduscopic features alone may not afford a comprehensive image of progression risk and overall DR activity. UWFA has led to provide peripheral panretinal assessment of retinal vascular changes. In the previous studies, the UWFA imaging to capture additional DR features as compared to standard ETDRS felds also provide valuable prognostication information (4,5). Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that can evaluate retinal vasculature and capillary networks. OCTA provides a quantitative measurement of various vascular characteristics in the macula, including the foveal avascular zone (FAZ) and vessel density (VD). It has been shown that as the severity of the disease increases in eyes with DR, the vascular density decreases, and the FAZ expands (6,7).

In this study, we investigated whether macular OCTA parameters could predict the size of the peripheral ischemic area and the presence of neovascularization. The other question we seek to answer in the present study; in some eyes with PDR, despite peripheral ischemia, the macula is normal and patients can have good visual acuity. Is there a difference between the size of peripheral ischemic areas or OCTA parameters in these patients?

Methods

Cases consisting of 95 eyes (58 patients) who were referred to ophthalmology department from February 2017 to December 2020 were retrospectively reviewed. The cases were divided into two groups as severe non-proliferative DR (NPDR) (group 1) and proliferative diabetic retinopathy (PDR) (group2) according to the International Clinical DR Disease Severity Scale (3). Later, based on visual acuity, PDR group was subdivided into group 2A: PDR eyes with VA≤0.2 logMAR and group 2B: PDR eyes with VA>0.2 logMAR. UWFA and OCTA features were compared between the subgroups. This study adhered to the principles of the Declaration of Helsinki. Approval from the Institutional Review Board/Ethics Committee was obtained (Approval number:10/XI).

Cases with DR and no history of prior treatment (e.g., laser photocoagulation and intravitreal injection) were included in the study. Cases with history or symptoms of chorioretinal diseases (e.g., posterior uveitis, retinal vein occlusion, and choroidal neovascularization), insufficient quality images for UWFA and OCTA, media opacity (e.g., cataract and vitreous hemorrhage), and significant artifacts (e.g., eyelashes and eyelids) were excluded from the study.

Demographic information and clinical data were obtained from all the individuals' records. A detailed ophthalmic examination that included measurement of best-corrected visual acuity (BCVA), slit-lamp examination, dilated fundus examination, optical coherence tomography (OCT), OCTA (RTVue; Optovue, Fremont, CA), and UWFA imaging with either the Optos 200Tx (Optos, Dunfermline, United Kingdom) or California (Optos) systems was performed in all patients. The BCVA was measured with a Snellen chart, and the decimal values were converted to the logarithm of minimal angle of resolution units for statistical analyses.

Ultra-widefield fundus photography and UWFA for each patient were evaluated for image quality and propriety for DR severity grading and quantitative analysis. Montage was not performed. An optimal UWFA image was chosen for an early mid-phase image. Images were processed by dewarping the standard UWFA images through transformation of the image into a stereographic projection of the eye. Images were imported into a novel software platform as previously described for angiographic feature analysis (8). Ischemic areas with capillary non-perfusion were first identified. Following identification, the total region was able to be analyzed and ischemic areas were obtained and manually drawn by an expert retina specialist (Fig. 1). The drawn capillary ischemic areas between the large retinal vessels were added arithmetically, the total non-perfusion area (unit^2) was calculated and recorded given by the optos. Peripheral areas of defocus, artifacts, and poor illumination were excluded. The ischemic index (%) was defined as the percentage area of the ischemic retina computed based on the total retinal region. For each UWFA image, manual imitations of the whole image region, areas of retinal capillary non-perfusion, and buds of neovascularisation were completed and checked by two separate unmasked graders (SS and AK). Interinvestigator reliability (κ) between the 2 observes was assessed. Interinvestigator reliability between two retina specialist was assessed with a κ value, which was 0.980 ($p<0.001$).

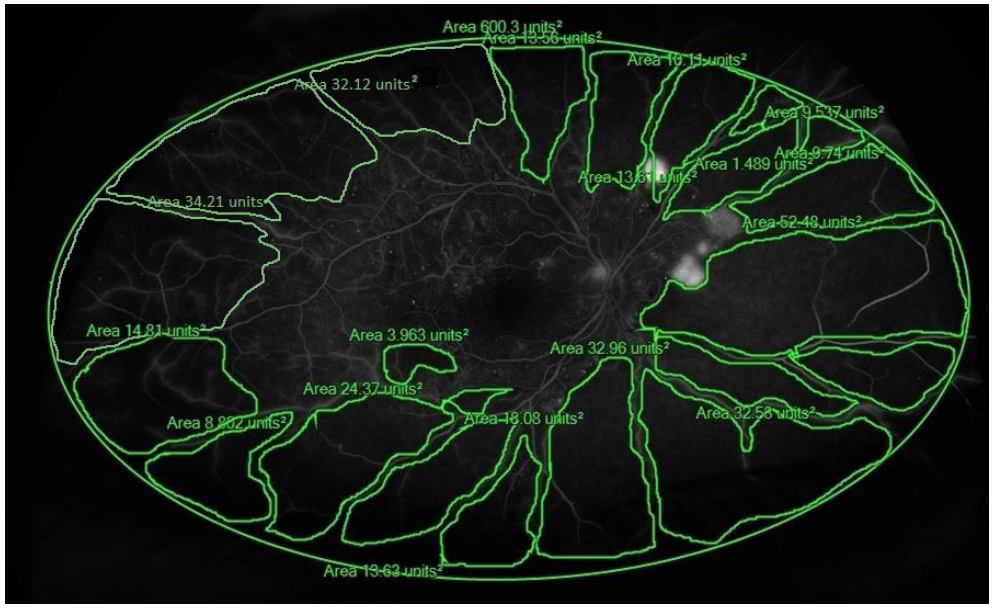

Figure 1. Representative example of quantitative ultra-widefield angiographic analysis, non-perfusion areas in an eye with Proliferative diabetic retinopathy.

The OCTA (RTVue; Optovue, Fremont, CA) database was reviewed in all patients. An experienced ophthalmic technician performed the OCTA examinations and OCTA data were analyzed. The VD was automatically calculated by the software embedded in the OCTA scanner. The SCP was located between 3 mm below the ILM to 15 mm below the inner plexiform layer and the deep capillary plexus (DCP) extended from 15 mm to 70 mm below the inner plexiform layer. The parafoveal regions of the ETDRS grid (3 mm diameter) were used for the regional analysis of the VD for both the SCP and DCP. The scan area of 6 mm × 6 mm (about 10° angle of a view), centered on the macula, was performed in this study (Fig. 2). "Auto All" function of the device, OCTA signal position, and signal quality were determined and the scan quality below 7/10 was considered an exclusion criterion from the study. Retinal microvasculature was analyzed using the automated retinal layer segmentation algorithm that is available on the device. The OCTA features were compared between the groups.

A table review also was completed for the following data: Age, sex, hemoglobin A1C (HbA1C) level, presence of hypertension, insulin treatment, and smoking status. The HbA1C and blood pressure measurements noted were the closest to the time of the UWFA.

Statistical Analysis

The SPSS 22.0 (SPSS, Inc, Chicago, IL) software program was used for statistical analyses. Continuous variables were given as mean±SD, whereas qualitative variables were shown as frequencies (absolutes) and percentages (%). Variables that were quantitative in the form of measurement were checked by the Shapiro–Wilk test for the normality hypothesis. Student's t-test was used for comparisons between continuous variables (with normal distribution). Comparisons between categorical variables were evaluated using contingency tables and Chi-square test or Fisher's test, when necessary. The receiver operating characteristic (ROC) curves were generated and summary statistics, including area under the curve (AUC), sensitivity, specificity, and cutoff value, were calculated from the ROC curve. Pearson's correlation analyses were used to examine the relationships between the non-perfusion area and OCTA parameters. P value of lower than 0.05 was considered as statistically significant.

Results

This study included 59 eyes with severe NPDR, and 36 eyes with PDR. We found no significant difference between groups with regard to age, duration of disease, the presence of insulin treatment, BCVA, central macular thickness (CMT) the presence of hypertension, glycated hemoglobin, axial length, or spherical equavalent (Table 1). None of the eyes had CMT of greater than 350 μm or any appreciable segmentation errors.

The OCTA and UWFA parameters are summarized and detailed in Table 2. The FAZ was significantly larger in eyes with PDR than in eyes with NPDR ($p<0.001$). There was no significant difference in terms of the VD in SCP between the groups ($p=0.632$). The VD in DCP was significantly lower when comparing eyes with PDR to severe NPDR group ($p=0.001$). Although choriocapillaris flow area (CCP) flow area was lower in eyes with PDR than NPDR, no statistically significant difference was observed

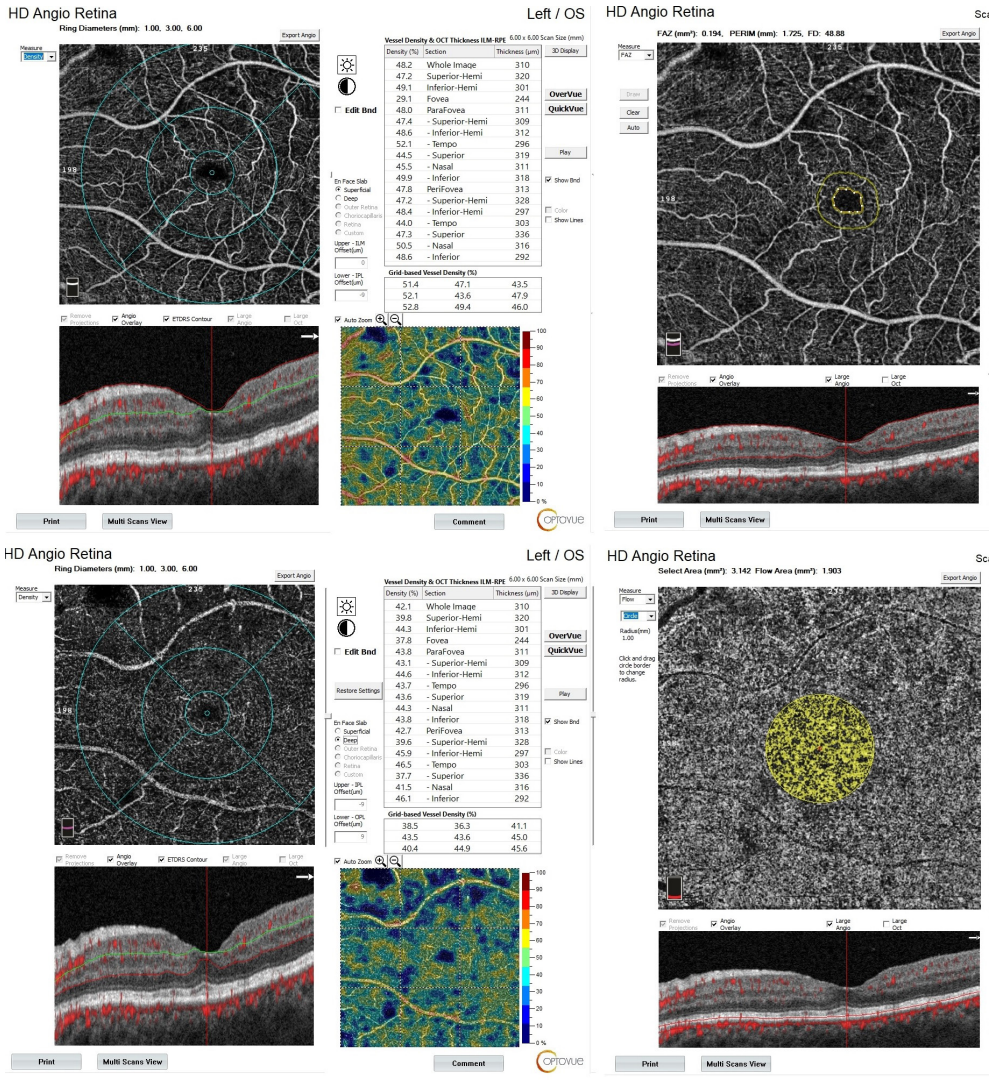

Figure 2. Representative example of optical coherence tomography angiography images, segmentation and measurements of image.

(For NPDR, 1.935±0.15 mm^2; for PDR, 1.884±0.19 mm^2, p=0.102). The mean non-perfusion area was higher in PDR group (For PDR, 184.2±107.7 unit^2 for NPDR, 61.8±43.8 unit^2) (Table 2).

We, then, generated ROC curves for presence neovascularization elsewhere (NVE) using the VD in DCP and FAZ (Fig. 3 and Table 3). The AUC for the VD was 0.710 (p=0.001) with sensitivity and specificity of 64% and 65%, for the FAZ was 0.746 (p<0.001) with sensitivity and specificity of 72% and 72.7%, respectively. We identified 0.302 mm^2 as a possible threshold of FAZ and 50.95% as a possible threshold of VD in DCP for the presence of NVE. Using the same OCTA parameters, we examined the ROC curves for presence of NVD and found comparable results although with a slightly higher specificity for NVD. The AUC for the VD was 0.818 (p<0.001) with sensitivity and specificity of 75% and 72.6%, for the FAZ was 0.847 (p<0.001) with sensitivity and specificity of 81.8% and 78.5%, respectively. We identified 0.324 mm^2 as a possible threshold of FAZ and 49.2% as a possible threshold of VD in DCP for the presence of NVD (Table 3).

The correlation between OCTA parameters and non-perfusion area is shown in table 4. There was a significant positive correlation between the FAZ and non-perfusion area. There was a significant negative correlation between the parafoveal VDs in SCP and DCP and non-perfusion area in NPDR group and a significant negative correlation between the VD in DCP and ischemic area in PDR group (Table 4).

In eyes with PDR with low VA, non-perfused area and FAZ were found to be wider, while VD in DCP and CCP flow area was found to be lower (All, p<0.05) (Table 5).

Table 1. Baseline patient demographics and clinical findings

Clinical characteristics	Mean±SD		p
	NPDR group n=36	PDR group n=22	
Age	57.7±12.2	58.9±9.5	0.677
Sex(F/M)	15/21	8/14	0.724
Duration of disease (years)	12.6±4.4	11.7±5.9	0.368
HbA1c	7.7±1.8	7.8±1.7	0.664
Treatment with insulin, n (%)	16(44.4)	14(63.6)	0.671
Hystory of hypertension, n (%)	24(66.6)	18(81.8)	0.597
Ocular characteristics	**n=59**	**n=36**	
BCVA, logMAR	0.33±0.22	0.32±0.23	0.801
Lens status (Phakic/Pseudophakic)	41/18	27/9	0.786
NVE present, n (%)	-	36(100)	-
NVD present, n (%)	-	16(44.4)	-
CMT, µm	289.1±51.8	305.3±49.3	0.132
Axial length, mm	22.95±0.36	23.05±0.37	0.783
Spherical equivalent, D	0.78±0.28	0.61±0.12	0.682

SD: Standart deviation, NVE: Neovascularisation elsewhere, NVD: Neovascularization disc, CMT: Central macular thickness, IOP, D: dioptri.

Table 2. OCTA and UWFA parameters of eyes with diabetic retinopathy

	Mean±SD		p
	NPDR group n=59	PDR group n=36	
Non-perfusion area, unit^2	61.8±43.8	184.2±107.7	<0.001
Ischemic index, %	10.3±7.3	30.7±17.9	<0.001
FAZ, mm^2	0.263±0.07	0.325±0.08	<0.001
Parafoveal VD in SCP, %	48.1±4.15	47.3±3.34	0.632
Parafoveal VD in DCP, %	51.3±3.23	48.4±4.15	0.001
CCP flow area, mm^2	1.935±0.15	1.884±0.19	0.102

SD: Standart deviation, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, FAZ: Foveal avascular zone, VD: Vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, CCP: Choriocapillary plexus. Bold values are statistically significant (P<0.05).

Discussion

In this study, we attempted to demonstrate that a set of select OCTA parameters develops the overall efficacy for discriminating eyes with NPDR from those with PDR. We determined that VD in DCP and FAZ, among the OCTA parameters, could significantly contribute to suspicion of the neovascularization and peripheral ischemia. We observed that decreased VD in DCP and enlarged FAZ are associated with an increase in peripheral ischemic areas. This could suggest a pre-evaluation with OCTA that was a non-invasive and reproducible technique in DR in clinical applicability, and the attention on diabetic patients with decreased VD and enlarged FAZ to focus on identifying the neovascularisation. However, VD in DCP and FAZ values has moderate sensitivity and specificity when determining the neovascularization. Eyes with PDR with poor visual acuity had lower VD, CCP flow area, and higher FAZ and non-perfusion area.

Macular ischemia and changes of FAZ in DR have been reported (9). Sim et al. showed that FAZ increases in cor-

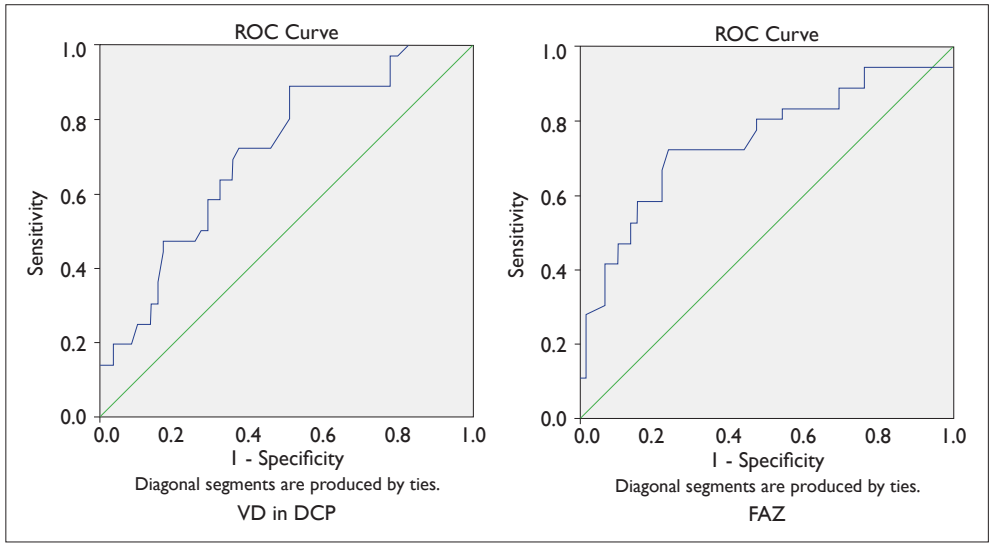

Figure 3. Area under the receiver operating characteristic curves for presence Neovascularisation elsewhere using the Foveal avascular zone and Vessel density in Deep capillary plexus.

Table 3. AUC values for developing NVE and NVD

Parameter	AUC (95%CI)	Cutoff	p	Sensitivity(%)	Specificity(%)
For NVE					
VD in DCP,%	0.710 (0.605–0.815)	50.95	0.001	64	65
FAZ, mm^2	0.746 (0.637–0.854)	0.302	<0.001	72	72.7
Non-perfusion area,$unit^2$	0.877 (0.799–0.955)	90.5	<0.001	72	72.7
Ischemic index, %	0.877 (0.799–0.955)	15.08	<0.001	72	72.7
For NVD					
VD in DCP,%	0.818 (0.712–0.924)	49.2	<0.001	75	72.6
FAZ, mm^2	0.847 (0.723–0.972)	0.324	<0.001	81.1	78.5
Non-perfusion area,$unit^2$	0.958 (0.913–1.000)	142	<0.001	87.5	88.6
Ischemic index, %	0.958 (0.913–1.000)	23.6	<0.001	87.5	88.6

FAZ: Foveal avascular zone, VD: Vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, CCP: Choriocapillary plexus.

Table 4. Correlation between OCTA parameters and quantitative UWFA findings in both groups

	Non-perfusion area			
	NPDR group		PDR group	
	r	p	r	p
FAZ	0.291	0.025	0.602	<0.001
VD in SCP	–0.387	0.002	–0.067	0.700
VD in DCP	–0.799	<0.001	–0.871	<0.001
CCP	–0.196	0.136	0.16	0.928

r: Pearson's correlation coefficient. FAZ: foveal avascular zone, VD: Vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, CCP: Choriocapillary plexus. Bold values are statistically significant.

relation with disease severity and is most profound in PDR (10). Previously, the relationship between peripheral retinal ischemia and central macular microcirculatory dropout was investigated in the literature. Oliver et al. reported that the peripheral ischemia on UWFA was associated with an increased risk of retinal neovascularization and macular ischemia, and these associations were statistically significant (11). With standart fluorescein angiography, only the superficial microvasculature structure could be evaluated and it is not possible to describe FAZ alterations in the deep network (12). However, OCTA allows the evaluation of both the superficial and deep microvasculature networks of the FAZ. In the previous studies with OCTA, the FAZ has been shown to be significantly larger in eyes with PDR compared to NPDR and it had a positive correlation with the severity of the disease (9,13,14). Ashraf et al. reported that the FAZ with high sensitivity and specificity for discriminating PDR or NPDR, recommending the possible clinical application for OCTA as a screening tool for DR (15). Similar to their results, we found that the FAZ was significantly larger in eyes with PDR compared to eyes with NPDR and the FAZ was valuable for detecting neovascularisation (For NVE, AUC was 0.746, for NVD AUC was 0.847). Obtained by the OCTA, eyes close to 0.302 mm which is the upper limit of the 95% CI of FAZ in the NPDR cohort, are presumably at higher risk than eyes with a much lower FAZ despite both being classified clinically as severe NPDR.

Similar to the FAZ enlargement, it has been shown that VD in DCP also decreases as the severity of the disease increases (16). Moreover, the parafoveal VD was recently shown to be a crucial prognostic parameter of capillary changes in early DR (17). The VD in SCP and DCP significantly decreased in DR compared to healthy eyes (18). With the increasing severity of DR (in severe NPDR and PDR),

Table 5. The comparison of OCTA and UWF angiography parameters in eyes with proliferative diabetic retinopathy

	Mean±SD		
	Group 2A n=11	**Group 2B n=25**	**p**
BCVA, logMAR	0.10±0.05	0.51±0.13	<0.001
Non-perfusion area, unit^2	125.1±55.3	211.6±114.6	0.024
Ischemic index, %	20.8±9.2	35.2±19.1	0.024
FAZ, mm^2	0.278±0.09	0.355±0.08	0.02
Parafoveal VD in SCP, %	48.2±2.6	47.2±3.2	0.428
Parafoveal VD in DCP, %	50.6±3.23	47.4±4.4	0.01
CCP flow area, mm^2	1.952±0.09	1.804±0.194	0.02

Group 2A: Eyes with PDR and visual acuity ≤0.20 logMAR, Group 2B: Eyes with PDR and visual acuity >0.20 logMAR. SD: Standart deviation, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, FAZ: Foveal avascular zone, VD: Vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, CCP; choriocapillary plexus. Bold values are statistically significant. (P<0.05).

the deep capillary network manifests more significant alterations, opposed to the SCP (15,16,19). The VD in DCP has been previously shown to be significantly lower in eyes with NPDR compared with eyes with PDR (15). Similarly, in our study, the VD in DCP was significantly lower and FAZ was larger in eyes with PDR than in eyes with NPDR. The reduction of VD in the DCP provides a suspicion for the peripheral ischemia of the retina and a parameter to discriminate the stages of retinopathy in the present study.

There was no significant difference in terms of VD in SCP between in eyes with severe NPDR and PDR in our study. Ashraf et al. shown that the VD in SCP was significantly lower in NPDR than in eyes with PDR (15). However, only 14.8% of their NPDR group was severe NPDR, most of them were mild and moderate NPDR. Li et al. reported that the VD in SCP was significantly higher in PDR than severe NPDR group. Furthermore, they supported that the increase of the VD in PDR group might result from the presence of compensatory dilated IRMA and decompensated neovascularization due to VEGF secretion in the non-perfusion areas (20). Possibly, it is for this reason that there is no difference between the two groups in terms of SCP in our study.

The retinal circulation supplies about 15% of the metabolic activities of the outer retina and when choroid circulation is compromised in response to hypoxia, the oxygen supply to the outer layer from the retinal circulation increases (21,22). Since the choroid capillary does not autoregulate itself, when choroid circulation drops, further inner retinal capillary plexus compromises lead to photoreceptor damages. Li et al. reported that the CCP flow area was significantly lower in patients with DR and decreased with severity of DR. Similar to our results, they also did not find a significant difference in terms of CCP between the severe NPDR and PDR (20). In our subanalysis, we also observed that the CCP flow area was higher in PDR eyes with better VA.

Severe NPDR, treatment management, and follow-up are alarming due to the risk of progression to PDR and are variable for each retina specialist. ETDRS suggested that panretinal photocoagulation could be performed in severe NPDR, considering the risks and benefits (23). While panretinal laser treatment is considered in eyes with NPDR, evaluating these OCTA parameters in addition to wide-field angiography may also be helpful in treatment selection in clinical practice.

UWFA provides the documentation of a large retinal area and is more valuable in recognizing PDR as opposed to standard 7-field, 30-degree angiography (24). Wessel et al. in a study comparing UWFA with standard ETDRS fields angiography in patients with PDR, UWF angiography detected 3.9 times more non-perfusion and 1.9 times more NVE, both of which were statistically significant (25). Furthermore, they showed that 16.7% of retinal neovascularization was only detected outside of the standard 7-field imaging (25). Nicholson et al. have published reports on quantitative wide-field angiography parameters, identifying a possible threshold with a good specificity for the identification of proliferative changes (26). The same authors also reported that the total area of retinal non-perfusion is higher eyes with PDR than among eyes with severe NPDR and the significance of peripheral non-perfusion as a factor for neovascularization. In addition to the results of Nicholson et al., our study identified the importance of OCTA parameters as a risk factor for proliferative changes in NPDR.

Another aim of the study was to compare the UWFA and macular OCTA parameters in the eyes with PDR regard to visual acuity. We know that PDR can often be found in a patient with a normal macula and good visual acuity without FAZ abnormalities. The macular ischemia may not be found in all eyes with PDR. In our study, we observed that VD and CCP flow area were higher and the non-perfused area was relatively less in these cases. VEGF concentrations in the aqueous humor and vitreous fluid were significantly correlated with the severity of DR. The larger the non-perfused area, the higher the concentration of VEGF is observed (27). In PDR eyes with good visual acuity, VEGF concentrations may be less and/or the choriocapillary circulation may be better in our study.

Limitations to this study include the small sample size and the retrospective nature of the analysis that only captured a single point in time for each eye. In addition, the study was limited by the presence of eyelid and eyelash artifacts in the

UWFA images, which could have affected the exact measurements of the total angiographic image area and of peripheral areas of non-perfusion. Native UWFA images from the Optos 200Tx have inherent warping and peripheral distortion due to the projection of a 3D spherical shape onto a 2D plane. Images were processed by dewarping the standard UWFA images through transformation of the image into a stereographic projection of the eye, as previously described (28,29). We relied on automatic segmentation to distinguish the SCP and DCP with the possibility of segmentation errors. Furthermore, we did not estimate the influence of focal DME on the model; none of our cases had center-involving macular edema. The sensitivity and specificity values are not adequate to make certain inferences. Hence, with larger studies with more participants, more massive more accurate results are needed.

Conclusion

We observed that macular OCTA parameters (enlarged FAZ, decreased VD in DCP) could moderately predict the size of the peripheral ischemic area and the presence of neovascularization and OCTA is very useful in evaluating the microvascular structure in DR. The reduction of VD in the DCP provides a suspicion for the peripheral ischemia of the retina and a parameter to discriminate the stages of retinopathy. Furthermore, we also obtained that eyes with PDR with better visual acuity had lower FAZ and non-perfusion areas. VD and CCP flow area were higher were relatively higher in these eyes. These results may shed light on far-reaching studies that will be used in clinical practice and OCTA may contribute valuable data for the understanding of disease pathogenesis.

Disclosures

Ethics Committee Approval: This study adhered to the principles of the Declaration of Helsinki. Approval from the Institutional Review Board/Ethics Committee was obtained (Approval number:10/XI).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.T.K., A.K., Ş.K., C.K.; Design – S.T.K., C.K.; Supervision – S.T.K., C.K.; Resource – Ş.K., S.S.; Materials – S.S., Ş.K.; Data collection and/or processing – S.T.K., A.K.; Analysis and/or interpretation – S.T.K., S.S.; Literature search – S.S., Ş.K.; Writing – S.T.K., A.K.; Critical review – A.K., S.S.

References

1. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98:823–33.
2. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie house classification. ETDRS report number 10. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98:786–806.
3. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–82.
4. Kong M, Lee MY, Ham DI. Ultrawide-field fluorescein angiography for evaluation of diabetic retinopathy. Korean J Ophthalmol 2012;26:428–31.
5. Aiello LP, Odia I, Glassman AR, Melia M, Jampol LM, Bressler NM, et al. Comparison of early treatment diabetic retinopathy study standard 7–field imaging with ultrawide–field imaging for determining severity of diabetic retinopathy. JAMA Ophthalmol 2019;137:65–73.
6. Sun Z, Tang F, Wong R, Lok J, Szeto SK, Chan JC, et al. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: A prospective study. Ophthalmology 2019;126:1675–84.
7. Wang F, Saraf SS, Zhang Q, Wang RK, Rezaei KA. Ultra-wide-field protocol enhances automated classification of diabetic retinopathy severity with OCT angiography. Ophthalmol Retina 2020;4:415–24.
8. Ehlers JP, Wang K, Vasanji A, Hu M, Srivastava SK. Automated quantitative characterisation of retinal vascular leakage and microaneurysms in ultra–widefield fluorescein angiography. Br J Ophthalmol 2017;101:696–9.
9. Conrath J, Giorgi R, Raccah D, Ridings B. Foveal avascular zone in diabetic retinopathy: Quantitative vs qualitative assessment. Eye (Lond) 2005;19:322–6.
10. Sim DA, Keane PA, Zarranz-Ventura J, Fung S, Powner MB, Platteau E, et al. The effects of macular ischemia on visual acuity in diabetic retinopathy. Invest Ophthalmol Vis Sci 2013;54:2353–60.
11. Oliver SC, Schwartz SD. Peripheral vessel leakage (PVL): A new angiographic finding in diabetic retinopathy identified with ultra wide–field fluorescein angiography. Semin Ophthalmol 2010;25:27–33.
12. Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JI, et al. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. Ophthalmology 2017;124:235–44.
13. La Mantia A, Kurt RA, Mejor S, Egan CA, Tufail A, Keane PA, et al. Comparing fundus fluorescein angiography and swept–source optical coherence tomography angiography in the evaluation of diabetic macular perfusion. Retina 2019;39:926–37.
14. Bhanushali D, Anegondi N, Gadde SG, Srinivasan P, Chidambara L, Yadav NK, et al. Linking retinal microvasculature features with severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthalmol Vis Sci 2016;57:OCT519–25.

15. Ashraf M, Nesper PL, Jampol LM, Yu F, Fawzi AA. Statistical model of optical coherence tomography angiography parameters that correlate with severity of diabetic retinopathy. Invest Ophthalmol Vis Sci 2018;59:4292–8.
16. Nesper PL, Roberts PK, Onishi AC, Chai H, Liu L, Jampol LM, et al. Quantifying microvascular abnormalities with increasing severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthalmol Vis Sci 2017;58:BIO307–15.
17. Simonett JM, Scarinci F, Picconi F, Giorno P, De Geronimo D, Di Renzo A, et al. Early microvascular retinal changes in optical coherence tomography angiography in patients with Type 1 diabetes mellitus. Acta Ophthalmol 2017;95:e751–5.
18. Mastropasqua R, Toto L, Mastropasqua A, Aloia R, De Nicola C, Mattei PA, et al. 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.
19. Onishi AC, Nesper PL, Roberts PK, Moharram GA, Chai H, Liu L, et al. Importance of considering the middle capillary plexus on OCT angiography in diabetic retinopathy. Invest Ophthalmol Vis Sci 2018;59:2167–76.
20. Li L, Almansoob S, Zhang P, Zhou YD, Tan Y, Gao L. Quantitative analysis of retinal and choroid capillary ischaemia using optical coherence tomography angiography in Type 2 diabetes. Acta Ophthalmol 2019;97:240–6.
21. Scarinci F, Jampol LM, Linsenmeier RA, Fawzi AA. Association of diabetic macular nonperfusion with outer retinal disruption on optical coherence tomography. JAMA Ophthalmol 2015;133:1036–44.
22. Yi J, Liu W, Chen S, Backman V, Sheibani N, Sorenson CM, et al. Visible light optical coherence tomography measures retinal oxygen metabolic response to systemic oxygenation. Light Sci Appl 2015;4:e334.
23. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98:766–85.
24. Liu TY, Arevalo JF. Wide–field imaging in proliferative diabetic retinopathy. Int J Retina Vitreous 2019;5:20.
25. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra–wide–field angiography improves the detection and classification of diabetic retinopathy. Retina 2012;32:785–91.
26. Nicholson L, Ramu J, Chan EW, Bainbridge JW, Hykin PG, Talks SJ, et al. Retinal nonperfusion characteristics on ultra–widefield angiography in eyes with severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. JAMA Ophthalmol 2019;137:626–31.
27. Noma H, Funatsu H, Yamashita H, Kitano S, Mishima HK, Hori S. Regulation of angiogenesis in diabetic retinopathy: Possible balance between vascular endothelial growth factor and endostatin. Arch Ophthalmol 2002;120:1075–80.
28. Lange J, Hadziahmetovic M, Zhang J, Li W. Region–specific ischemia, neovascularization and macular oedema in treatment–naive proliferative diabetic retinopathy. Clin Exp Ophthalmol 2018;46:757–66.
29. Tan CS, Chew MC, van Hemert J, Singer MA, Bell D, Sadda SR. Measuring the precise area of peripheral retinal non–perfusion using ultra–widefield imaging and its correlation with the ischaemic index. Br J Ophthalmol 2016;100:235–9.