



# Optical coherence tomography angiography findings in Behcet patients

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## Abstract

**Purpose** Retinal vasculitis and vein occlusions are common causes of serious visual loss in Behçet's disease. We aimed to evaluate the optical coherence tomography angiography (OCTA) findings of Behçet uveitis (BU) patients.

**Methods** We evaluated 32 eyes of 16 patients with BU and 30 eyes of 15 healthy controls. Superficial capillary plexus (SCP) and deeper capillary plexuses (DCP) were evaluated using OCTA RTVue XR AVANTI.

**Results** On SCP, nonperfusion/hypoperfusion areas (NPA) were seen in 10 eyes, perifoveal capillary arcade disruption (PCAD) was seen in 10 eyes, capillary network disorganization (CND) was seen in 7 eyes and intraretinal cystoid spaces (ICS) were seen in 2 eyes. On DCP, NPA were seen in 13 eyes, PCAD

was seen in 11 eyes, CND was seen in 7 eyes and ICS were seen in 4 eyes.

**Conclusion** We showed that DCP were affected more than SCP in these patients. In addition, capillary vessel density of BU group was significantly lower than control group.

**Keywords** Behçet disease · Optical coherence tomography angiography · Vasculitis · Uveitis · Retinal vein occlusion

## Introduction

Behçet disease (BD) is a chronic, recurrent, multisystem disease characterized by occlusive and necrotizing vasculitis [1, 2]. Ocular involvement, which is seen in up to 70% of patients, is characterized with anterior uveitis, retinitis, retinal vasculitis, vitritis, retinal vein occlusion, macular edema, optic disk hyperemia, and edema [3, 4]. As retinal vasculitis is the leading component of posterior segment involvement and responsible from vision loss, FA has become a gold standard technique for the evaluation of Behçet uveitis [5, 6]. However, only early phase of FA allows the visualization of capillary bed due to dye leakage and it is unable to evaluate the retinal capillary levels separately [7, 8].

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Optical coherence tomography angiography (OCTA) is a novel method that generates three-dimensional images of vasculature in vivo and without dye injection [9, 10]. The OCTA signal describes the pixel-by-pixel changes that occur in the repeated B-scans as a result of erythrocyte movement. Another advantage of OCTA is that it allows resolution of both the superficial and deeper capillary plexuses networks [11]. The effectiveness of the OCTA on retinal microvascular properties was showed in some previous studies [12–14].

Patients with Behçet uveitis require close follow-up, and therefore, we should evaluate these patients' microvascular changes, especially at foveal region, with a noninvasive and effective method. In this study, we aimed to evaluate microvascular changes in BD patients with using OCTA.

## Materials and methods

This study was conducted in Başkent University School of Medicine Zubeyde Hanım Research Hospital. The patients, whose were following with Behçet uveitis, were evaluated using OCTA during the inactive period of disease, retrospectively. Behçet disease was diagnosed, based on diagnostic criteria of the international study group for BD [15]. This study adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants.

Exclusion criteria were significant media opacities, trauma, other retinal diseases such as retinal vascular occlusive disease unrelated to BD, diabetic retinopathy, hypertensive retinopathy, central serous chorioretinopathy, and macular degeneration, and optic nerve diseases such as glaucoma or optic neuropathy.

All patients underwent detailed ophthalmic examination including measurement of Snellen best-corrected visual acuity (BCVA), slit-lamp examination, tonometry, and dilated fundus examination with noncontact or contact lenses. FA and SD-OCT were also performed for all patients.

OCTA images were acquired with OCTA (RTVue XR AVANTI; Optovue Inc, Fremont, CA). The AngioVue OCTA system operated at 70,000 A-scans per second, to acquire 6 mm × 6 mm OCTA images of the posterior pole, consisting of 304 A-scans, using a light source centered on 840 nm and a bandwidth of

50 nm. The OCTA volumes contained 304 A-scans with 2 consecutive B-scans that were captured at each fixed position before proceeding to the next sampling location. Split-spectrum amplitude-decorrelation angiography (SSADA) was used to extract the OCTA information [16]. Each OCTA volume was acquired over 3 s, and 2 orthogonal OCTA volumes were acquired to perform motion correction to minimize the motion artifacts arising from microsaccades and fixation changes [17]. Angiography information is displayed as the average of the decorrelation values when viewed perpendicularly through the thickness being evaluated. The modifications in reflectivity are directly related to blood flow. The horizontal and vertical scans were combined with a motion correction technology algorithm that compensates for the motion of the patient's eyes to create a 3D volume of the retinal vascularization. A qualitative analysis and comparisons of the entire imaging data set were conducted from 3 min to 5 min. The peripapillary region was defined as a 700- $\mu$ m-wide elliptical annulus extending from the optic disk boundary. An en face angiogram of the retinal circulation was obtained by the maximum flow (decorrelation value) projection from the inner limiting layer to retinal epithelial pigment.

Qualitative analysis of the OCT angiograms of the SCP and DCP was then independently performed by two masked examiners (M.O. Ulusoy and S. Emre), at different time points and in different orders, for the following parameters: perifoveal anastomotic capillary arcade disruption in the SCP (when extending over 1 quadrant of the entire length), capillary changes (including telangiectasia and areas of rarefied capillaries), areas of capillary nonperfusion/hypoperfusion (presenting as irregular hypointense grayish areas), disorganization of the superficial and deep capillary network (defined as localized or diffuse loss of the normal architecture of capillary network), and intraretinal cystoid spaces (presenting as well-defined black roundish areas without any signal on OCTA). Capillary vessel density (CVD) was evaluated in the central area with a radius of 1.25 mm from the foveolar center for both retinas, excluding the central foveal area (0.3 mm radius). The following parameters in this region were evaluated: whole image superficial CVD (%), parafoveal superficial CVD (%), superior, inferior, temporal and nasal region superficial CVD (%), whole image deep CVD (%),

parafoveal deep CVD (%), superior, inferior, temporal and nasal region deep CVD (%) The CVD is the percentage of signal positive pixels per total pixels in an area of interest.

### Statistical analysis

Statistical data were analyzed using SPSS version 21.0 (SPSS, Chicago, IL, USA). Values were expressed as mean  $\pm$  standard deviation. Differences between group characteristics were tested using student t test for continuous variables and Chi-squared tests for categorical variables. Correlations between parameters were determined based on the Pearson or Spearman correlation coefficient. Differences were considered significant at  $p < 0.05$ .

### Results

A total of 32 eyes of 16 Behçet's uveitic patients and 30 eyes of 15 healthy control subjects were evaluated. After examination, finally 26 eyes with Behçet uveitis were recruited in the study. Six fellow eyes of Behçet's uveitic patients group were excluded from the study due to poor quality images. Statistical analysis was performed on 26 eyes of 16 Behçet group and 30 eyes of 15 control subjects. The mean age of the patients was  $39.44 \pm 13.56$  years (range 15–70 years) and that of the controls was  $38.1 \pm 6.76$  years (range 30–56). There were 6 (37.5%) men and 10 (62.5%) women in the Behçet group and 5 (33.3%) men and 10 (66.6%) women in the control group. We found no statistically significant differences in age or gender between the groups ( $p = 0.53$  and  $0.79$ , respectively). The mean duration of disease was  $14 \pm 11.7$  years (2–34 years). The mean intraocular pressure was  $14.6 \pm 2.8$  mmHg (Behçet) and  $13.9 \pm 2.5$  mmHg (control) ( $p = 0.52$ ). Ocular involvement was bilateral in 10 patients and unilateral in 6 patients (Table 1).

On the SD-OCT imaging, cystoid macular edema (CME) was detected in 7 eyes, serous macular detachment was detected in 1 eye, foveal atrophy was detected in 2 eyes and epiretinal membrane was detected in 2 eyes (Table 1).

Both superficial (SCP) and deeper capillary plexuses (DCP) of the all eyes were evaluated with using OCTA. On SCP, nonperfusion/hypoperfusion areas were seen in 10 eyes, perifoveal capillary arcade

disruption was seen in 10 eyes, capillary network disorganization was seen in 7 eyes and intraretinal cystoid spaces were seen in 2 eyes (Fig. 1). On DCP, nonperfusion/hypoperfusion areas were seen in 13 eyes, perifoveal capillary arcade disruption was seen in 11 eyes, capillary network disorganization was seen in 7 eyes and intraretinal cystoid spaces were seen in 4 eyes (Fig. 2). On OCTA images of optic nerve head, nonperfusion/hypoperfusion areas were seen in 5 eyes and telangiectatic capillary collaterals were seen in 1 eye (Fig. 3). Although all OCTA findings were seen in DCP more than SCP, the difference was not statistically significant in either pathological condition (nonperfusion/hypoperfusion areas:  $p = 0.4$ ; perifoveal capillary arcade disruption:  $p = 0.77$ ; capillary network disorganization:  $p = 0.92$ ; intraretinal cystoid spaces:  $p = 0.38$ ) (Table 1).

SCP ( $p = 0.007$ ) and DCP ( $p = 0.002$ ) nonperfusion/hypoperfusion areas and DCP intraretinal cystoid spaces (0.048) were seen more prominent in higher duration of diseases. SCP nonperfusion/hypoperfusion areas ( $p < 0.001$ ) and DCP intraretinal cystoid spaces ( $p = 0.001$ ) were seen more prominent in the eyes with higher uveitis attack history. Treatment history and vasculitis history of the eyes did not affect these OCTA findings.

Parafoveal superficial CVD (%), superior, inferior, temporal and nasal region superficial CVD (%), whole image deep CVD (%), parafoveal deep CVD (%), superior, inferior, temporal and nasal region deep CVD (%) were statistically significantly lower in Behçet group than controls (all  $p < 0.001$ ) (Table 2). Whole image deep CVD and central foveal thickness did not differ between two groups ( $p = 0.12$ ,  $p = 0.1$ , respectively). BCVA was positively correlated with whole image deep CVD (%) ( $p = 0.021$ ;  $r = 0.498$ ), whole image superficial CVD ( $p = 0.01$ ;  $r = 0.449$ ), parafoveal superficial CVD ( $p = 0.009$ ;  $r = 0.504$ ), superior superficial CVD ( $p = 0.016$ ;  $r = 0.466$ ), inferior superficial CVD ( $p = 0.003$ ;  $r = 0.56$ ), parafoveal deep CVD ( $p = 0.003$ ;  $r = 0.552$ ), superior deep CVD ( $p = 0.033$ ;  $r = 0.419$ ), inferior deep CVD ( $p = 0.003$ ;  $r = 0.56$ ), temporal deep CVD ( $p = 0.002$ ;  $r = 0.572$ ) and nasal region deep CVD ( $p = 0.017$ ;  $r = 0.464$ ). Superficial (vasculitis (+):  $20.5 \pm 8.7$ (%), vasculitis (-):  $29.3 \pm 7.8$  (%);  $p = 0.036$ ) and deep (vasculitis (+):  $21.3 \pm 9.9$ (%), vasculitis (-):  $31.7 \pm 8.4$  (%);  $p = 0.02$ ) foveal CVD were significantly lower in the eyes with vasculitis

**Table 1** Comparison of baseline clinical characteristics and SD-OCT and OCTA findings in patients with Behçet uveitis and control group

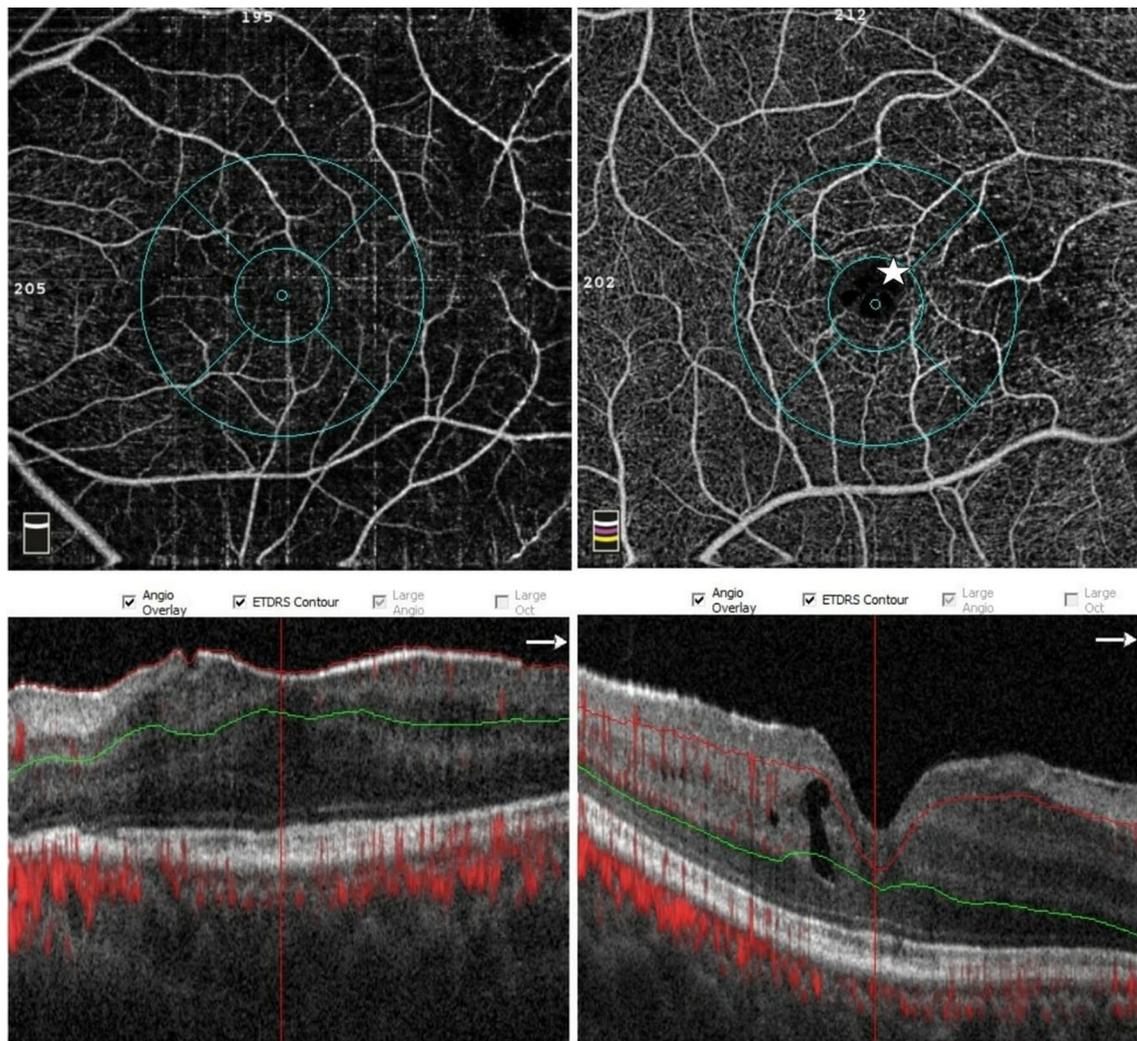
	Behçet	Control	<i>p</i>
Patient ( <i>n</i> /eye)	16/26	15/30	
Age (years)	39.44 ± 13.56	38.1 ± 6.76	0.53
Gender (m/f)	6/10	5/10	0.79
Vo (logmar)	0.2 ± 0.001	0	< 0.001
IOP (mmHg)	14.6 ± 2.8	13.9 ± 2.5	0.61
Duration of disease (months)	79.1 ± 44.04	–	
<b>Laterality</b>			
Unilateral	6/16	–	
Bilateral	10/16	–	
Uveitis attacks in a year	2.9 ± 2.3	–	
<b>Uveitis characteristics</b>			
Panuveitis	26/26	–	
Vasculitis/vein occlusion	10/26	–	
Cystoid macular edema	7/26	–	
Vitreous hemorrhage	2/26	–	
<b>Treatment</b>			
Corticosteroids	6/16	–	
Immunosuppressive therapy	10/16	–	
Biologic agents	7/16	–	
Colchicine	3/16	–	
<b>SD-OCT findings (%)</b>			
CME	7/26 (26.92)	–	
ERM	2/26 (7.69)	–	
Foveal atrophy	2/26 (7.69)	–	
SMD	1/26 (3.84)	–	
<b>OCTA findings (%)</b>			
Nonperfusion	10/26 (38.46)	–	
PCAD	10/26 (38.46)	–	
CND	7/26 (26.92)	–	
Cystoid spaces	2/26 (7.69)	–	
Collaterals	–	–	
Nonperfusion	13/26 (50)	–	
PCAD	11/26 (42.3)	–	
CND	7/26 (26.92)	–	
Cystoid spaces	4/26 (15.38)	–	
Collaterals	1/26 (3.84)	–	

*Sup* superficial, *IOP* intraocular pressure, *SD-OCT* spectral domain optical coherence tomography, *OCTA* optical coherence tomography angiography, *CME* cystoid macular edema, *ERM* epiretinal membrane, *SM* serous macular detachment, *PCAD* perifoveal capillary arcade disruption, *CND* capillary network disorganization

history. None of the CVD parameters was correlated with any OCTA findings, CFT, duration of disease, treatment history, and number of uveitis attacks.

## Discussion

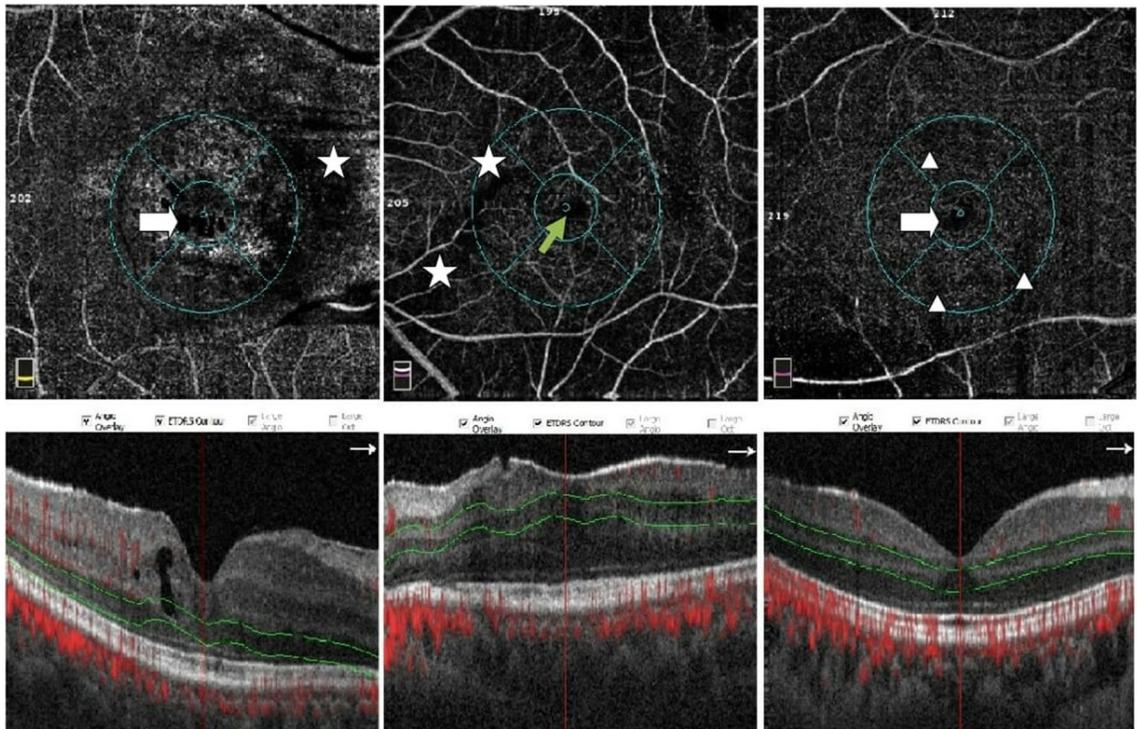
The main sight threatening mechanism of BU is retinal vasculitis and its complications. Most of these ocular manifestations can be easily detected with FFA. The hallmark of retinal vasculitis is vascular leakage on FFA, and it is the most frequent angiographic finding [18]. In addition to this, disk leakage, cystoid macular



**Fig. 1** In the left superficial capillary plexus OCTA image, capillary rarefaction and wide nonperfusion/hypoperfusion areas are seen under epiretinal membrane. In the right image, well-defined dark cystoid spaces and perifoveal capillary disruption (arrow) are seen

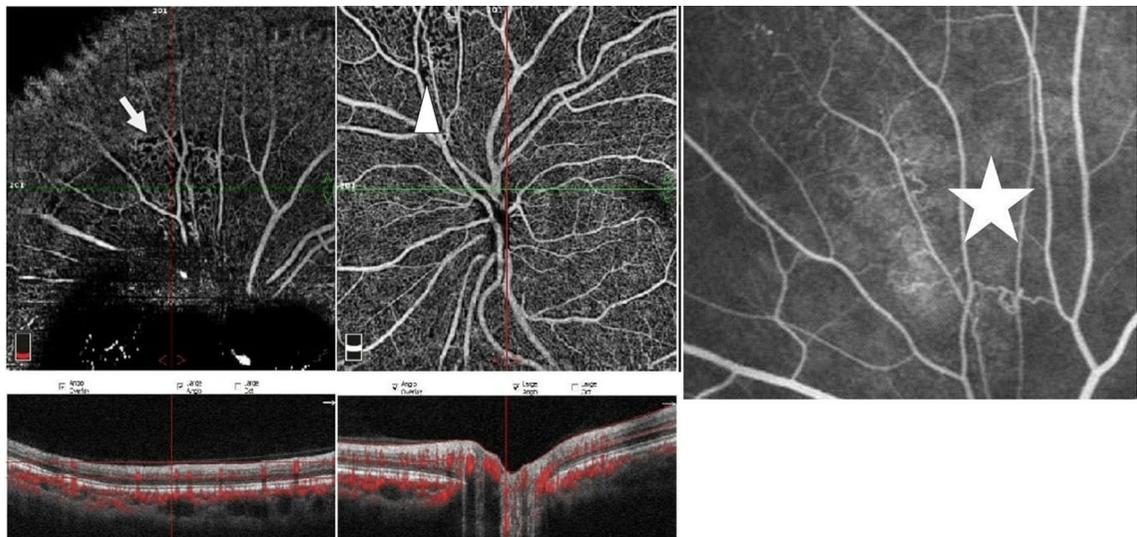
edema, periphery capillary nonperfusion, macular ischemia and disk neovascularization are angiographic findings that can be identified. Nevertheless, a recent study showed the superiority of OCTA on FFA. The authors suggested that, after the early phase of FFA, which is the best time to get an image, it was difficult to obtain perifoveal microvascular alterations, especially due to early dye leakage from the capillaries [7]. The most common OCTA findings were nonperfusion/hypoperfusion areas in both SCP and DCP. In addition, these areas were more prominent in DCP than in SCP, in consistent with the previous studies [7, 8]. This predominance was also observed in other retinal pathologies such as retinal vein occlusion,

diabetic retinopathy, and sickle cell retinopathy [12–14]. In our study, in 10 eyes (10/26; 38.4%) nonperfusion/hypoperfusion areas were seen on SCP and in 13 eyes (13/26; 50%) were seen in DCP. In Khairallah's study, they found in 63.6% of 44 eyes on SCP and 81.8% on DCP [7]. They also reported that the capability of OCTA to detect these areas is superior to FFA, because while OCTA can identify in 38 eyes (86.4%), FFA was able to identify only in 15 eyes (34.1%). In another recent study, with FFA, nonperfusion/hypoperfusion areas were identified in 15 of 37 eyes, however, with OCTA in 26 of 37 eyes. Similarly, mean hypoperfusion area was found to be significantly greater on DCP than SCP [8]. The reason



**Fig. 2** In the left deeper capillary plexuses OCTA image, well-defined dark cystoid spaces (arrow) and nonperfusion/hypoperfusion areas (asterisk) are seen. In the middle image, perifoveal capillary disruption (arrow) and nonperfusion/hypoperfusion

areas (asterisks) were seen, under epiretinale membrane. In the right image, perifoveal capillary disruption (arrow) and capillary rarefaction (triangle) were seen



**Fig. 3** In the left and middle OCTA image of optic nerve head, capillary telangiectatic collaterals (arrow) and perivascular nonperfusion/hypoperfusion areas (triangle) are seen. In the

right late stage fluorescein angiography image, capillary collaterals (asterisks) are seen; however, perivascular nonperfusion/hypoperfusion areas were absent

**Table 2** Comparison of the capillary vessel densities between two groups

		Behçet	Control	<i>p</i>
	Whole image CD (%)	48.9 ± 4.8	55.4 ± 4.7	0.12
	Parafoveal CD (%)	48.4 ± 7.01	59.04 ± 3.5	< 0.001
S	Superior region CD (%)	48.17 ± 8.3	61.2 ± 4.6	< 0.001
U	Inferior region CD (%)	48.79 ± 6.4	54.1 ± 4.03	< 0.001
P	Temporal region CD (%)	49.16 ± 8.4	59.8 ± 3.9	< 0.001
	Nasal region CD (%)	47.5 ± 9.6	59.1 ± 3.4	< 0.001
	Whole image CD (%)	50.7 ± 10.02	56.09 ± 2.9	< 0.001
	Parafoveal CD (%)	53.2 ± 11.5	68.05 ± 4.7	< 0.001
D	Superior region CD (%)	52.8 ± 12.7	67.8 ± 5.8	< 0.001
E	Inferior region CD (%)	53.06 ± 13.2	64.3 ± 8.2	< 0.001
E	Temporal region CD (%)	53.1 ± 14.2	68.2 ± 6.2	< 0.001
P	Nasal region CD (%)	53.7 ± 12.7	66.5 ± 7.2	< 0.001
	CFT	251.1 ± 61.7	232.4 ± 24.1	<i>p</i> = 0.1

*Sup* superficial, *CD* capillary density, *CFT* central foveal thickness

of why the DCP is more sensitive might be the result of being more vulnerable to ischemia due to being not directly connected to arterioles [19]. It is thought that, due to severity of vasocclusion, density of grayish areas differs from gray to black. However, black nonperfusion areas should be discriminated from cystoid spaces which are due to total absence of flow signal. In our study, 15.3% (4/26) of patients had intraretinal cystoid spaces on OCTA, consistent with the other study which was found in 13.6% of eyes (6/44) [7]. SD-OCT images can be useful for this discrimination.

Due to dye leakage, FFA does not allow foveal avascular zone (FAZ) measurement in both eyes; thus, the investigators have to choose one eye. However, OCTA is a very useful tool to evaluate and measure the FAZ. FAZ areas of the BU patients were reported to be significantly larger than in healthy patients [7, 8]. Another common OCTA finding in our study was perifoveolar capillary disruption. On SCP, 38.4% (10/26) and on DCP 42.3% (11/26) of the eyes had perifoveolar capillary disruption in our study. These results were consistent with the recent study that has reported 40.9% (18/44) of eyes had this situation. These OCTA findings might be the objective indicator of the macular ischemia which is one of the major causes of permanent visual loss in retinal diseases.

As chronic results of these situations, we also can detect retinal manifestations such as cystoid macular edema, epiretinal membrane, foveal atrophy with using FFA or SD-OCT. Despite the lack of visible pathology, there is a possibility of the sequelae of the

vasculitis on the retinal microvasculature. Another important feature of the OCTA is being capable of the visualization of these probable microvasculature changes. In our study, in 6 eyes, although there were no detectable pathology in fundus either with FFA, SD-OCT or 90D fundus examination, in either periphery or central retina, nonperfusion/hypoperfusion areas, perifoveal arcade disruptions, and capillary network disorganization were found with using OCTA. Besides, we found that, SCP and DCP nonperfusion/hypoperfusion areas and DCP intraretinal cystoid spaces were seen more prominent in higher duration of diseases. It is noteworthy that these findings can show the severity of disease and refute the hypothesis that retinal vascular involvement begins from periphery. In addition, follow of the disease and regulation of the treatment can be changed according to these findings.

We also evaluated superficial and deep capillary CVD of these patients and compared with controls. This device gives these CVDs as percentage rate. All parameters were significantly lower in Behçet patients than in controls, except deep whole image CVD. In a previous study, it was showed that percentage of superficial and deep retinal CVD of parafoveal was decreased in diabetic retinopathy patients compared to healthy subjects [20]. Khairallah et al. have been evaluating the capillary CVD, and they reported that superficial and deeper CVD of Behçet uveitis were lower than controls; however, the measurements were taken manually and the results were given as  $\text{mm}^{-1}$ . In addition, they have found a correlation between

capillary CVD and BCVA [7]. In our study, none of the CVD parameters was correlated with any OCTA findings. Similarly, BCVA was correlated with all CVD parameters except superficial temporal and nasal CVD. In other words, better CVD gets better vision. In addition, superficial and deeper foveal CVD were significantly lower in the eyes with vasculitis history.

One of the limitations of our study was the small sample size. In addition, we did not measure and evaluate the FAZ area of these patients.

In conclusion, OCTA can visualize microvascular structures in BU. Also, OCTA can be useful to detect similar changes in other uveitis forms [21]. These microvascular changes can be seen in patients with any retinal pathology that was detected with any other examination method. In addition, measurement of CVD can help to explain the unobservable effects of this disease. Further studies with larger number of patients are required for better benefit from this recent diagnostic technique.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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