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ORIGINAL ARTICLE

Can optical coherence tomography angiography be a first line ophthalmological evaluation in patients with Behçet's disease?

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ABSTRACT

Objectives: This study aimed to investigate whether early ocular findings can be demonstrated with optical coherence tomography angiography in patients with Behçet's disease.

Patients and methods: Thirty-seven eyes of 22 patients with Behçet's disease with ocular involvement, 48 eyes of 26 Behçet patients without any ocular involvement, and 44 eyes of 22 healthy controls were included, for a total of 70 patients (39 males, 31 females; mean age: 42.3±11.7 years; range, 18 to 65 years), in the cross-sectional study conducted between September 2019 and April 2020. The parameters analyzed were the foveal avascular zone (FAZ), central macular thickness, total deep capillary plexus vessel density (DCPVD), parafoveal deep capillary plexus vessel density (PaDCPVD), total superficial capillary plexus vessel density (SCPVD), and parafoveal superficial capillary plexus vessel density (PaSCPVD).

Results: Total DCPVD, total SCPVD, PaDCPVD, and PaSCPVD were found to be low in the ocular involvement group compared to the others, and the FAZ area was larger compared to the control group. Capillary plexus densities were positively correlated with the best-corrected visual acuity and negatively correlated with disease duration. No statistically significant difference was found between patients with Behçet without ocular involvement and the control group in terms of the FAZ area, DCPVD, PaDCPVD, SCPVD, and PaSCPVD.

Conclusion: Optical coherence tomography angiography demonstrated decreased vascularity in Behçet patients with ocular involvement; however, it revealed no microvascular differences between patients with Behçet's disease who do not have ocular involvement and the control group.

Keywords: Behçet's disease, capillary plexus density, optical coherence tomography angiography, uveitis.

Behçet's disease is an idiopathic, chronic, inflammatory condition with an unpredictable relapsing and remitting course, which can affect multiple systems. Uveitis is the most common manifestation of ocular involvement, and it presents as an acute, recurrent, nongranulomatous panuveitis associated with retinal vasculitis. Uveitis attacks may cause permanent structural changes and may lead to the loss of vision if left untreated.[1] Therefore, it is crucial to consider the patients followed up with the diagnosis of Behçet's disease in rheumatology practice in this regard.

Optical coherence tomography angiography (OCTA) is a novel imaging modality that requires no exogenous contrast and uses dense volumetric scanning to provide depth-resolved visualization of the retinal and choroidal vasculature.[2] It enables the evaluation of vascular structures layer by layer, including the superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris.[3] OCTA successfully reveals capillary nonperfusion areas in retinal vasculitis. The foveal avascular zone (FAZ) area can be easily measured, which may not be conclusively

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measured in fundus fluorescein angiography (FFA) due to dye leakage.[4]

Early detection of ocular involvement is critical in Behçet's disease.[5] A limited number of studies in the literature have investigated microvascular changes in patients with Behçet's disease without ocular involvement.[6-13]

In this study, Behçet's disease patients with and without uveitis were evaluated for microvascular changes using OCTA, aiming to investigate whether early ocular findings can be demonstrated with OCTA in patients with Behçet's disease.

PATIENTS AND METHODS

This cross-sectional study was performed with a total of 70 participants (39 males, 31 females; mean age: 42.3±11.7 years; range, 18 to 65 years) at the Haseki Training and Research Hospital between September 2019 and April 2020. In this study, 37 eyes of 22 patients (mean age: 41.9±9.4 years) with Behçet's disease who have posterior uveitis or panuveitis, 48 eyes of 26 patients (mean age: 41.0±11.6 years) who were followed in the rheumatology department for Behçet's disease without any ocular involvement, and 44 eyes of 22 healthy controls (mean age: 44.0±14.2 years) were evaluated. Group 1 consisted of patients with Behçet's disease who have posterior or panuveitis. All the patients in this group were in the remission or inactive phase, and none of them had macular edema at the time of examination. Group 2 consisted of patients who were diagnosed with Behçet's disease but had no ocular involvement. These patients had no history of anterior or posterior uveitis, and their biomicroscopic examination and FFA findings revealed no signs of uveitis. Group 3 consisted of healthy subjects who did not have any systemic or ocular disease.

Subjects who had a history of ocular trauma, diseases that may affect macula or optic disc, a systemic disease other than Behçet's disease, poor fixation, and significant media opacity that may affect the quality of OCTA scans were excluded from the study. The refraction errors of the patients were between -1.50 and +1.50 diopters. Scans with a signal quality lower than 7/10 were excluded from the study.

A thorough ophthalmologic examination, including best-corrected visual acuity (BCVA), using the decimal system, slit-lamp biomicroscopy, intraocular pressure measurement, and fundus examination after pupillary dilation, was performed for all subjects. OCTA scans were acquired after pupillary dilation.

The OCTA scans were obtained by the same examiner using the AngioVue imaging system (RTVue-XR; software version 2016.2.035; Optovue, Inc., Fremont, CA, USA). A 6×6 mm scan size was chosen for OCTA, and the measurements of the FAZ area (Figure 1) and retinal vessel density of the selected area of the retina were obtained. Central macular thickness (CMT) was measured using the retina map mode. The vessel density was calculated as the percentage in the whole 6×6 mm image and parafovea (outside of 1×1 mm circle centered on the fovea) in SCP (Figure 2) and DCP.

Statistical analysis

The statistical analyses were performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The comparison of groups with more than two numerical variables was performed with the one-way analysis over variance (ANOVA) if the normal distribution condition was met; otherwise, the Kruskal-Wallis test was used. Subgroup analyses were performed with the Games-Howell test since the homogeneity of the variables' condition was not met in the parametric test. In the nonparametric tests, analyses were performed with the Mann-Whitney U test and evaluated with the Bonferroni correction. When the parametric test condition was met, Pearson's correlation analysis was used to examine relationships between numerical variables, and Spearman's correlation analysis was used when the parametric test condition was not met. Ratios in the groups were compared with the chi-square test. A p value of <0.05 was considered statistically significant.

RESULTS

No statistical significance was detected between the groups in respect of age and sex ($p=0.679$ and $p=0.096$, respectively). The mean duration of the disease was 11.7±7.8 years

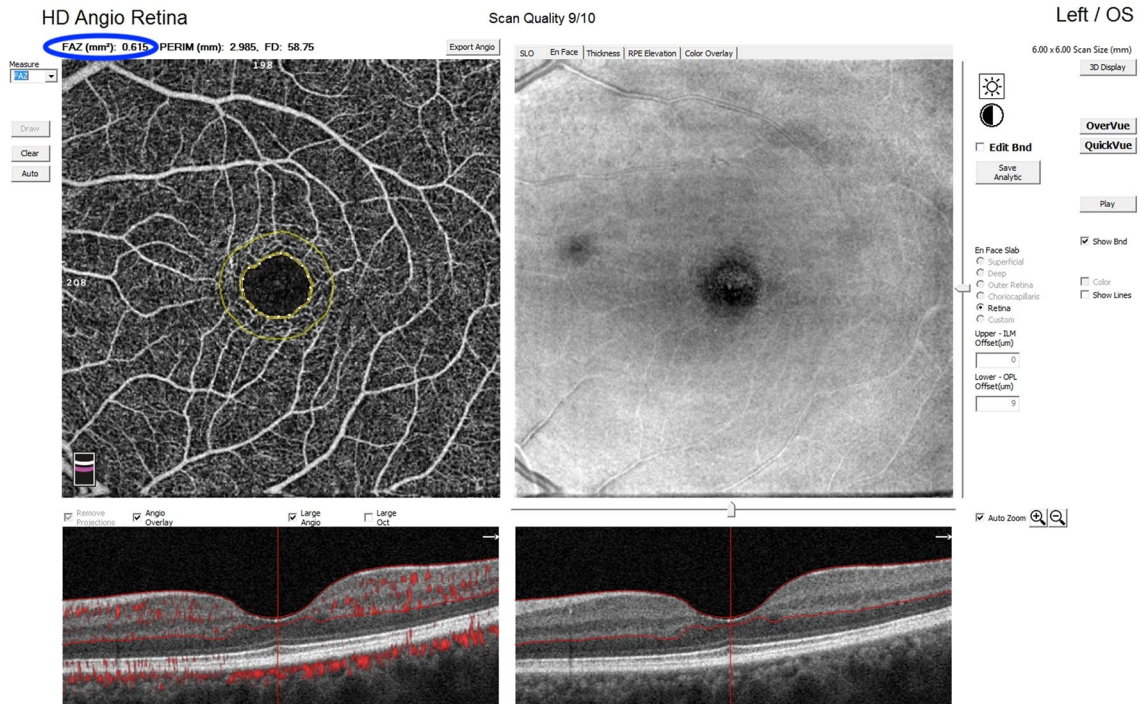

Figure 1. An example of FAZ measurements.
FAZ: Foveal avascular zone.

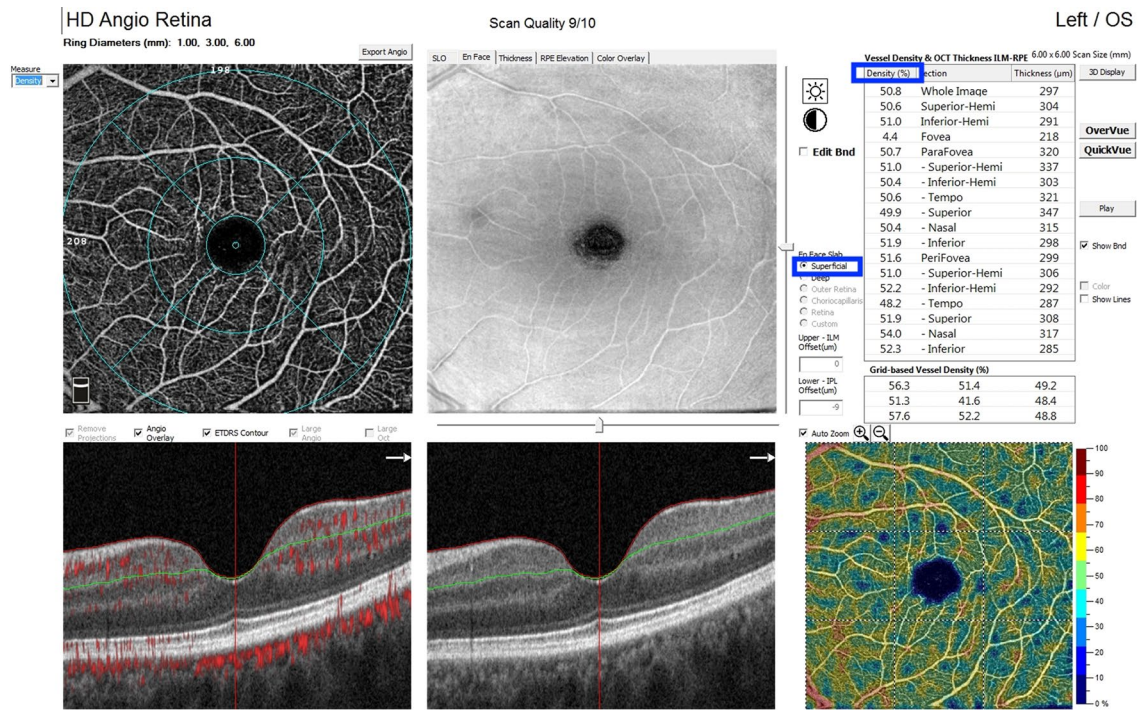

Figure 2. An example of SCPVD measurements, size of 6×6 mm.
SCPVD: Superficial capillary plexus vessel density (whole area).

Table 1. Clinical and demographic characteristics of the participants

	Group 1 (n=22)				Group 2 (n=26)				Group 3 (n=22)				
	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	*p*
Age (year)			41.9±9.4	23-60			41.0±11.6	19-65			44.0±14.2	18-65	0.679
Sex													0.096
Female	10	45.5			11	42.3			10	45.4			
Male	12	54.5			15	57.7			12	54.6			
BCVA (decimal)													<0.001
<0.05	2	5.4			0	0.0			0	0.0			
0.05-0.4	11	29.7			1	2.1			0	0.0			
0.5-0.9	14	37.9			2	4.1			0	0.0			
1.0	10	27			45	93.8			22	100			
Disease duration			11.7±7.8	2-25			10.6±8.3	0.25-30					0.349
Azathioprine	29	72.5			4	8.3							<0.001
Corticosteroids	7	17.5			2	4.2							0.073
Treatment													
IFN-α	2	5.0			0	0.0							0.204
Colchicine	12	30.0			20	41.7							0.257
Cyclosporine	3	7.5			0	0.0							0.090
Pathergy test													0.036
Positive	19	86.3			18	69.2							
Negative	3	13.7			8	30.8							
Type of uveitis													
Panuveitis	21	56											
Posterior uveitis	16	44											
Number of attacks			2.6±1.5	1-6									

SD: Standard deviation; BCVA: Best corrected visual acuity; IFN-α: Interferon alfa.

(range, 2 to 25 years) in Group 1, and 10.6±8.3 years (range, 0.25 to 30 years) in Group 2.

In Group 1, 72.5% of the patients were under treatment with azathioprine, 30% colchicine, 17.5% corticosteroids, 7.5% cyclosporine, and 5% interferon-alpha 2b. In the Group 2, 41.7% were under colchicine, 8.3% were under azathioprine, and 4.2% were under corticosteroid treatment. In the first group, 86.3% of patients tested positive for pathergy, and 13.7% tested negative. In the second group, positivity was present in 69.2% and negativity in 13.7%.

The patients were divided into four subgroups according to their BCVA. The groups contained subjects with a BCVA of 1.0 (27%), a BCVA between 0.5 and 0.9 (37.9%), a BCVA between 0.05 and 0.4 (29.7%), and a BCVA lower than 0.05 (5.4%). In Group 2, 93.8% of the eyes had a BCVA of 1.0, 4.1% of them had a BCVA between 0.5 and 0.9, and 2.1% between 0.05 and 0.4. The visual acuity was lower than 1.0 in this group due to amblyopia. In the control group, all of the 44 eyes had a BCVA of 1.0. The BCVA was significantly lower in Group 1 compared to the other two groups (p<0,001). In Group 1, two eyes had a BCVA lower than 0.05, 11 had a BCVA between 0.05 and 0.4, 14 eyes had a BCVA between 0.5-0.9, and 10 eyes had a BCVA of 1.0.

In Group 1, ocular involvement was in the form of panuveitis in 56% of the eyes and posterior uveitis in 44%. The mean number of uveitis attacks in Group 1 was 2.6±1.5 (range, 1 to 6). The demographic and clinical characteristics of the patients are listed in Table 1.

There was no statistically significant difference in CMT between the groups (p=0.154). The mean FAZ, total superficial capillary plexus vessel density (SCPVD), parafoveal superficial capillary plexus vessel density (PaSCPVD), total deep capillary plexus vessel density (DCPVD), and parafoveal deep capillary plexus vessel density (PaDCPVD) values statistically significantly varied between the groups (p=0.02 for FAZ; p<0.001 for the others). Table 2 demonstrates the comparison of CMT, FAZ, and vessel density in the SCP and DCP between the groups.

The mean FAZ area of Groups 1 and 2 was significantly larger compared to the control

Table 2. Comparison of CMT, FAZ, and vessel density of the SCP and DCP between the groups

	Group 1			Group 2			Group 3			*p*
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
CMT (µm)	239.0±41.0	245	145-337	242.1±15.9	243	214-275	251.3±22.6	247	214-300	0,154*
FAZ (mm^2)	0.345±0.173	0.349	0.092-0.828	0.277±0.086	0.285	0.07-0.425	0.251±0.107	0.242	072-0.466	0,002*
SCPVD (%)	47.4±5.0	48.3	35-54.4	51.0±2.8	51.4	44-55.8	50.9±3.2	51.5	40.6-55.9	<0,001*
PaSCPVD (%)	49.3±4.6	50	36.2-57	53.0±3.3	53.2	47-58	52.5±3.7	53.35	43.5-59	<0,001*
DCPVD (%)	48.7±7.2	50.6	32.6-59.3	55.6±4.3	56.9	44.2-65.5	55.5±5.8	57.4	43.4-66.5	<0,001†
PaDCPVD (%)	51.8±6.8	53.1	37.5-63.6	58.8±3.4	58.9	51.3-66.4	58.2±4.7	59.2	47.8-66.5	<0,001†

CMT: Central macular thickness; FAZ: Foveal avascular zone; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; SD: Standard deviation; SCPVD: Superficial capillary plexus vessel density (whole area); PaSCPVD: Parafoveal superficial capillary plexus vessel density; DCPVD: Deep capillary plexus vessel density (whole area); PaDCPVD: Parafoveal deep capillary plexus vessel density; * One Way Anova; † Kruskal Wallis.

Table 3. Comparison of the subgroups in respect of FAZ area and vessel densities

		FAZ	SCPVD	PaSCPVD	DCPVD	PaDCPVD
		*p***	*p***	*p*#	*p**	*p**
Group 1 *vs.*	Group 2	0.094	0.001	<0.001	<0.001	<0.001
	Group 3	0.013	0.001	0.001	<0.001	<0.001
Group 2 *vs.*	Group 3	0.317	0.990	1.000	0.716	0.944

FAZ: Foveal avascular zone; SCPVD: Superficial capillary plexus vessel density (whole area); PaSCPVD: Parafoveal superficial capillary plexus vessel density; DCPVD: Deep capillary plexus vessel density (whole area); PaDCPVD: Parafoveal deep capillary plexus vessel density; # Bonferroni; *Mann-Whitney U test; ** Games-Howell.

group (p=0.013). The mean values of SCPVD, PaSCPVD, DCPVD, and PaDCPVD of Group 1 were significantly lower compared to the other groups. The mean FAZ area, SCPVD, DCPVD, and PaDCPVD values of the patients in Group 2 was not statistically different from the ones in the control group. The comparison of the subgroups in respect of FAZ, SCPVD, PaSCPVD, DCPVD, and PaDCPVD is listed in Table 3.

The CMT values of the groups were not statistically different from each other (p=0.154); however, statistically significant differences existed in respect of the mean SCPVD, PaSCPVD, DCPVD, and PaDCPVD values between the groups (p=0.02 for FAZ; p<0.001 for the others).

In Group 1, the BCVA and the FAZ area were inversely correlated, whereas the SCPVD, PaSCPVD, DCPVD, and PaDCPVD were positively correlated (p=0.001, p=0.004, p<0.001, and p=0.001). The SCPVD, PaSCPVD, DCPVD, and PaDCPVD values were inversely correlated in the same group (p<0.001, p<0.001, p=0.001, and p=0.003). There was no statistically meaningful correlation between the duration of the disease and the FAZ area. The correlations between the FAZ area and the capillary plexus densities with BCVA and the duration of the disease are listed in Table 4. Group 2 was not included in this correlation table since most of the patients in this group had a BCVA of 1.0.

In Group 1, CMT was inversely correlated with the FAZ area (p<0.001), whereas it was positively correlated with the SCPVD and PaSCPVD (p<0.001 and p=0.006).

In Group 2, CMT was inversely correlated with the FAZ area, total DCPVD, and PaDCPVD (p<0.001 for each). Similarly, the CMT was inversely correlated with the FAZ area, DCPVD, and PaDCPVD (p<0.001, p=0.034, p=0.002).

There was no statistically significant correlation (correlation coefficient, r=0.274) between the

Table 4. The correlation of the FAZ area and the capillary plexus densities with BCVA and duration of the disease

		BCVA		Duration of the disease	
Group		r	*p*	r	*p*
Group 1	FAZ	-0.539	<0.001	0.164	0.340
	SCPVD	0.464	0.004	-0.790	<0.001
	PaSCPVD	0.549	<0.001	-0.560	<0.001
	DCPVD	0.538	0.001	-0.514	0.001
	PaDCPVD	0.543	0.001	-0.479	0.003

FAZ: Foveal avascular zone; BCVA: Best-corrected visual acuity; SCPVD: Superficial capillary plexus vessel density (whole area); PaSCPVD: Parafoveal superficial capillary plexus vessel density; DCPVD: Deep capillary plexus vessel density (whole area); PaDCPVD: Parafoveal deep capillary plexus vessel density.

width of the FAZ and the number of ocular attacks in patients with Behçet uveitis (p=0.106).

DISCUSSION

Behçet's disease is a systemic vasculitis of unknown cause. Musculoskeletal, neurologic, gastrointestinal, and dermatologic involvement can be encountered. It typically presents as peripheral oligoarthritis that does not cause deformity or erosion. Since the most important ocular presentation is uveitis, it is important to know how to evaluate ocular involvement in rheumatology practice as it causes significant vision problems, which may result in a significant increase in the existing disability. Vasculitis is the most common type of posterior segment involvement in Behçet's disease, and it is an occlusive necrotizing vasculitis, affecting both arteries and veins.[14] Fundus fluorescein angiography is the gold standard imaging modality in Behçet uveitis since it detects the occlusions and leakage due to vasculitis.[15] OCTA has several advantages, such as being noninvasive, providing a high-resolution image and blood flow information of both the retina and the choroid, and being capable of giving quantitative data about macula and optic nerve perfusion.[2]

In this study, we aimed not only to observe capillary changes in the macula in Behçet patients with ocular involvement but also to investigate if there was any vascular change in patients without ocular involvement. These patients were further compared with the control group to determine OCTA's capacity for detecting posterior segment involvement before the clinical signs become evident.

We observed no difference between the mean CMT of the groups (p=0.154) in our study. In a study conducted by Koca et al.,[16] patients with Behçet's disease with and without ocular involvement were compared with the control group, similar to our study, and no statistically significant difference was found between the groups in respect of macular thickness.

We observed a statistically significant difference between the mean SCPVD, PaSCPVD, DCPVD, and PaDCPVD values of the three groups (p<0.001 for each). The mean SCPVD, PaSCPVD, DCPVD, and PaDCPVD values of the Behçet uveitis group was lower than the Behçet patients with no ocular involvement. Pei et al.[17] compared 120 eyes of 60 patients with Behçet uveitis with 124 healthy eyes using OCTA, and they observed that both SCP and DCP densities were lower in the Behçet uveitis group (p<0.001, p<0.001). These results reflect the microvascular impact of the disease, as expected.

We did not find any statistically significant difference between Behçet patients without ocular involvement and the control group in respect of SCPVD, PaSCPVD, DCPVD, and PaDCPVD. In a similar study published by Değirmenci et al.,[8] 23 Behçet patients and 29 healthy subjects with no ocular involvement were compared, and the mean capillary density and the mean flow area were found to be lower in both the SCP and DCP, although the results were not statistically significant.

In an OCTA study by Goker et al.,[7] in which 22 eyes of Behçet patients with no ocular involvement were compared with 28 eyes of the control group, SCPVD and DCPVD in the fovea were found to be lower in the Behçet group than in the control group. They concluded that the low capillary densities detected could be considered a subclinical form of ocular involvement in Behçet's disease, particularly in the foveal area. Similarly, Karalezli et al.[9] evaluated perifoveal and peripapillary microvascular structure in nonocular Behçet patients and found decreased vessel density in the deep plexus and an enlarged FAZ area in nonocular Behçet patients when compared to healthy controls.

Küçük et al.[10] compared the microvasculature in the eyes of Behçet patients without ocular involvement with healthy controls and investigated the relationship with systemic vascular involvement. Deep capillary plexus density and foveal vessel densities were lower in the nonocular Behçet group, and there was a reduction in peripapillary and macular vessel densities in Behçet's patients without systemic vascular involvement. Therefore, they concluded that patients may exhibit subclinical ocular involvement even in the absence of clinical ocular symptoms.

In another study that investigates subclinical ocular features in pediatric Behçet's disease,

OCTA revealed decreased vessel density and decreased outer retinal flow, supporting the idea that OCTA can demonstrate the microvascular changes in patients without detectable ocular involvement.[11] The different results of these studies could be attributed to differences in disease durations and participant numbers.

In our study, we detected a statistically significant difference between the FAZ areas of the three groups (p=0.002). The FAZ area was larger in the Behçet uveitis group compared to the other two groups. However, there was no statistically significant difference between Groups 2 and 3. There was a significant difference between Group 1 and the control group (p=0.013). While there are different results related to this in the scientific literature, it is reasonable to think that uveitis attacks cause ischemia in the macula, thus resulting in the expansion of the FAZ area in Behçet patients. In our study, there was no statistically significant difference between Groups 1 and 3 in respect of the FAZ area. In another study, 42 eyes of Behçet patients without ocular involvement and 40 eyes of a control group were compared, and no difference was found between the two groups for both superficial and deep FAZ areas (p=0.165, p=0.477).[6] However, the FAZ area was found to be larger in Behçet patients in a study comparing 22 eyes of Behçet patients with no ocular involvement and 28 eyes of healthy subjects (p=0.008).[7] The FAZ area measurements show variability between different studies. This can be attributed to differences in study demographics, study instruments, software, or measurement methods.[12]

The BCVA was inversely correlated with the FAZ area and positively correlated with the SCPVD, PaSCPVD, DCPVD, and PaDCPVD in our study; however, these correlations were present only in the Behçet uveitis group (p=0.001, p=0.004, p<0.001, p=0.001, and p=0.001, respectively). This result showed us that OCTA is a promising imaging tool to investigate microvascular changes in Behçet uveitis patients whose BCVA decreased.

The mean SCPVD, PaSCPVD, DCPVD, and PaDCPVD values were also inversely correlated with the duration of the disease in the Behçet uveitis group (p<0.001, p<0.001, p=0.001, and p=0.003, respectively). Similar results were obtained in the study of Koca et al.,[16] which compared the eyes of Behçet patients with and without ocular involvement. The visual acuity was inversely correlated with the FAZ area and positively correlated with the capillary plexus densities of all layers.[16] These correlations were observed only in the group with ocular involvement. The duration of disease activity in nonocular Behçet's disease patients was found to be not correlated with retinal vasculature abnormalities in a recent study investigating parafoveal microvascular alterations in ocular and nonocular Behçet's disease patients, which was explained by vessel densities decreasing with age.[13]

Somkijrong et al.[4] evaluated the results obtained from the OCTA and FFA of 37 eyes of 21 patients with Behçet uveitis. They showed that DCP loss existed even in the patients who had a normal FAZ area in the FFA. They emphasized that the disruption in the perfusion could occur at any stage of the disease in ocular Behçet and that the disruption that occurred in the DCP, in particular, was responsible for central vision loss. Our results were similar to the earlier studies, as both the DCPVD and SCPVD were positively correlated with visual acuity. As expected, occlusive attacks reduced the capillary plexus densities, inducing macular ischemia and decreasing visual acuity.

The limitations of this study are the cross-sectional design and the relatively small number of patients. The mean number of attacks in our study was low and may have caused a restriction when searching for a correlation within the parameters being evaluated.

In conclusion, our findings revealed that while OCTA is a beneficial tool in the evaluation and follow-up of Behçet uveitis, it does not make an additional contribution to the standard eye examination in terms of early detection of ocular involvement in Behçet's patients. Therefore, the standard eye examination is still the primary method for investigation of ocular involvement in Behçet's disease. Currently, it does not seem necessary for rheumatologists to refer patients to centers with OCTA in the follow-up of eye involvement in Behçet's disease. Nevertheless, as there are conflicting results on this topic, further research on larger patient groups is required.

Ethics Committee Approval: The study protocol was approved by the Haseki Training and Research Hospital Clinical Studies Ethical Committee (date/no: 4.09.2019/2019-28). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All three authors have contributed to the study in conception and design, acquisition of data, analysis and interpretation of data, supervision, drafting the manuscript.

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