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Longitudinal changes in parafoveal microvascular structure in diabetic macular edema

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Abstract

Aim: This study aims to investigate retinal microvascular changes according to increases and decreases in macular edema, explain how these changes are associated with different capillary plexuses in diabetic macular edema (DME), and provide evidence for treatment efforts.

Materials and Methods: 21 eyes of diabetic patients with DME who were treated with intravitreal injections were investigated. The control group was assigned age-and sex-matched healthy subjects. The patients were divided into decreased edema and increased edema subgroups to compare microvascular changes before and after treatment. Optical Coherence Tomography Angiography (OCTA) parameters were used for comparison.

Results: There were significant differences in visual acuity and mean OCTA parameters between the main patient group and the control group (all $P<0.05$). There were no significant differences between the two DME subgroups in terms of baseline values (all $P>0.05$). The foveal avascular zone (FAZ) in the deep capillary plexus (DCP) was significantly lower in the decreased edema group; however, there were no significant differences in the other parameters between the two subgroups after 6 months of treatment. The changes in the FAZ in the DCP ranged from 2126.82 ± 1858.59 μm^2 to 711.64 ± 738.55 μm^2 in the decreased edema group ($P = 0.013$) and from 2231.50 ± 2187.66 μm^2 to 2025.50 ± 2020 μm^2 in the increased edema group ($P = 0.575$) after 6 months of treatment.

Conclusion: Deep retinal ischemia can actually recover after proper treatment. However, we were unable to find a significant change in the density of the parafoveal vessel in DME after treatment; the changes in the FAZ of the DCP were the most prominent indicator of that improvement.

Introduction

The most important reason for vision loss in patients with diabetic retinopathy (DR) is diabetic macular edema (DME) [1,2]. Occlusion of the retinal capillaries causes tissue hypoxia and leads to increased levels of vascular endothelial growth factor (VEGF) and inflammatory factor levels resulting in the breakdown of the blood retinal barrier and fluid accumulation [3]. Swept source optical coherence tomography angiography (OCTA) provides simultaneous viewing of structural and blood flow information of the different levels of the retina [4]. Quantitative analysis of the superficial microvascular structure in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) can be performed by measuring the vessel density (VD) and the FAZ (foveal avascular zone), which are OCTA parameters [5]. Capillary loss and microvascular changes were suggested to be associated with DR. Even in diabetic patients without retinopathy, some early microvascular changes were found [6-8]. Especially progressive loss of vessel density has been correlated with progression of DR [9-11]. Microvascular changes and association with DME are still unclear because DME can occur in some eyes with moderate DR while some eyes with severe DR eyes do not have DME. Many studies have evaluated the microvascular structure in DME using OCTA. Some reported that the VD of the SCP was more associated with the development of DME, while others revealed that the OCTA parameters in the DCP were related to DME [9,12]. However, studies on the effect of treatment on microvascular status in DME also revealed conflicting results. Some of them reported improvement in microvascular status in the related plexus [13,14], while others claimed unchanged [15-19]. All the studies mentioned above have

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drawbacks, such as imaging modalities used, the baseline characteristics, and short follow-up time. Many of them used spectral domain OCTA, which means that the clarity of the images is limited due to the weak penetration of light sources, especially under edematous conditions, and some had conflicting results due to the image processing. Although the aforementioned studies have revealed some relevant information, there are still gaps in that area in terms of microvascular structure and its association with the treatment of DME.

Our aim was to investigate microvascular changes according to the increase and decrease in macular edema to contribute to understanding of the pathogenetic mechanisms of DME and treatment efforts, since the association between the microvascular status of the macula and DME has not been fully clarified.

Materials and Methods

This study was designed as a single-center longitudinal study. Study participants were selected from the Ophthalmology Department between October 2018 and December 2020. All participants signed informed consent forms. The local ethics committee approved the study (Ref. number= 2021/118). The study was conducted in line with the principles of the Declaration of Helsinki. Patients with DME due to type II diabetes mellitus who had at least a 6-month follow-up were enrolled. DME was defined as central foveal thickness (CFT) greater than 270 µm due to intraretinal and/or subretinal fluid in the B scans. The patients were treated with intravitreal anti-VEGF (bevacizumab, aflibercept, and ranibizumab) or dexamethasone. The control group was assigned age- and sex-matched healthy subjects. The patient records were reviewed for a complete ophthalmologic examination. For statistical analysis, the best-corrected visual acuity (BCVA) was converted into the logarithm of the minimum angle of resolution (logMAR). Participants who had poor OCTA images (quality factor < 60, blinking motion artifacts, significant media opacity), epiretinal membrane, vitreomacular traction, macular scar, macular hole, choroidal neovascularization (CNV), retinal vein occlusion, and uncontrolled glaucoma were excluded from the study. The macular grid photocoagulation and intraocular surgery history (except simple cataract surgery at least 3 months prior to participation) were also considered exclusion criteria.

OCTA imaging

A sweep-source OCT device (DRI OCT Triton; Topcon Inc., Tokyo, Japan) was used for OCTA imaging. A 6 × 6-mm volumetric scan was taken centered on the fovea for all participants. The SCP and DCP were segmented using the built-in automated software IMAGEnet6, v1.25 and OCTARA^{TM} (Topcon Inc., Tokyo, Japan). The SCP slabs were considered 2.6 µm below the internal limiting membrane and 15.6 µm below the junction between the inner plexiform and inner nuclear layers; the DCP slabs were considered 15.6 µm below the junction between the inner plexiform and inner nuclear layers and 70.2 µm below them. An experienced grader (NP) verified the accuracy of the automatic segmentation lines and corrected the segmentation errors. The device's built-in software measures the VD based on the ETDRS grid at the SCP plexus. The average parafoveal VD was calculated as the mean of the four quadrants. The ETDRS grid was manually repositioned to be centralized to the fovea in the decentralized case. The built-in software in the available commercial version of Triton measures the VD just at the superficial plexus frame. To measure VD at the deep plexus, we adapted the superficial plexus frames by modifying slabs equal to the deep plexus. Furthermore, the projection artifact removal (PAR) function was turned on for each frame. The device's area measurement tool was used to manually contour and measure the FAZ at both the SCP and the DCP.

OCT

The built-in software of the OCT (Triton) device was used to measure the central foveal thickness (CFT) and sectoral parafoveal retinal thickness (RT) (İ, S, N, and T) at the 3 mm ETDRS grid. The elipsoid zone (EZ) disruption and the external limiting membrane (ELM) disruption were considered as any clear discontinuation within the 3 mm ETDRS grid in the 12 radial B-scan images.

Statistical analysis

SPSS Statistics software, version 22.0 (IBM Corporation, Armonk, New York, USA), was used for statistical analyses. The Shapiro–Wilk test was used to assess the conformity of univariate data in terms of normal distribution. Quantitative variables were presented as mean ± standard deviation (SD), and categorical variables were presented as n (%) in the tables. Independent groups were compared using the independent-samples t-test and the Mann–Whitney U test. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. For comparison of subgroups of DME eyes according to the treatment response, the paired t test and Wilcoxon signed rank test were used for quantitative variables, and the McNemar test was used for categorical variables. A p value <0.05 was considered as a significance level.

Results

21 eyes were assigned to the DME group (Figure 1), and 20 eyes of normal healthy subjects were assigned to the control group. Table 1 shows the BCVA and demographic characteristics. There were no significant differences between the DME group and the control group in terms

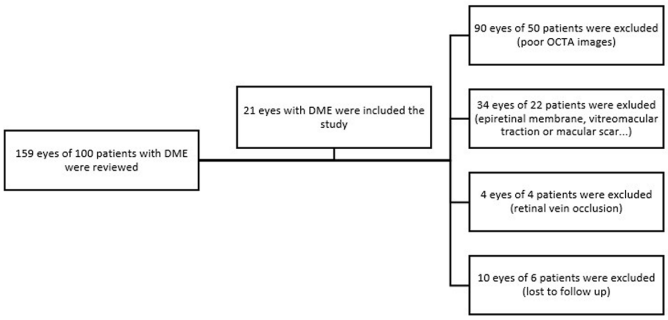
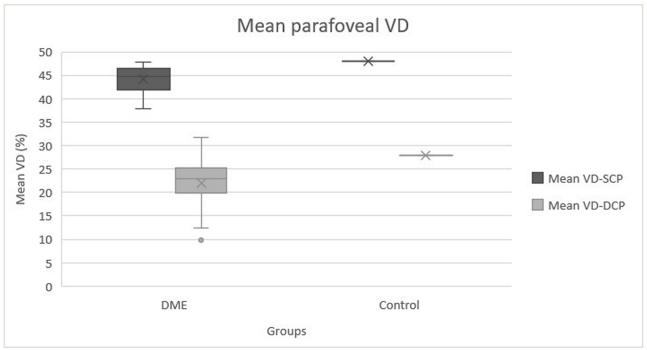


Figure 1. Flow chart of the study population.



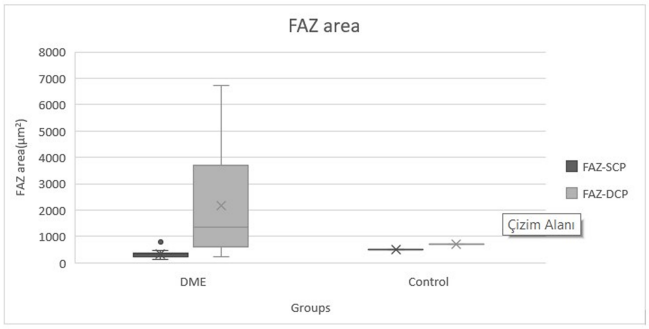
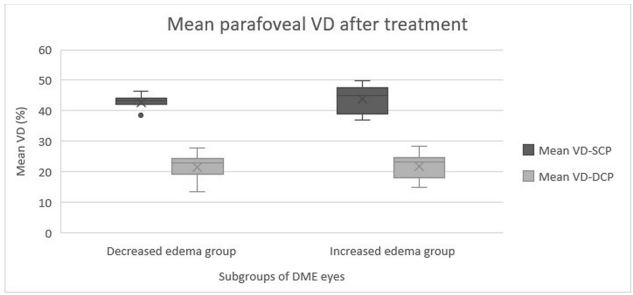


Figure 2. Comparison of the baseline OCTA values of DME eyes with the control group.



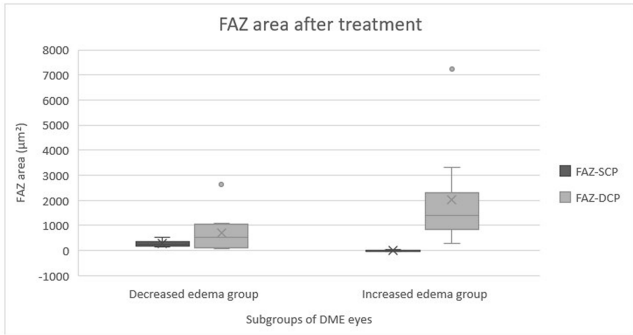


Figure 3. The OCTA parameters of decreased edema group and increased edema group after treatment.

Table 1. The demographic characteristics of the groups.

	DME (n= 21)	Control (n=20)	P
Age (mean±SD), years	59.67±6.78	57.80±7.50	0.408
Sex n(%)(male)	11(52.4)	12(60)	0.623
Eye distrubitions n(%) (Right)	11(52.4)	12(60)	0.623
BCVA (mean±SD), logMar	0.40±0.43	0.04±0.001	**0.0001***

BCVA: Best-corrected visual acuity, * statisticaly significant.

Table 2. Central and parafoveal OCT and OCTA values of the groups.

	DME-baseline (n=21)	Control (n=20)	P
CFT (mean±SD) (µm)	387.81±132.47	248.70±15.80	**0.0001***
Inferior PRT	382.14±84.99	306.40±17.53	**0.0001***
Superior PRT	377.95±72.99	314.80±20.75	**0.0001***
Nasal PRT	362.14±69.48	315.55±19.31	**0.0005***
Temporal PRT	404.14±99.30	301.30±15.51	**0.0001***
ELM disruption (+ eyes)%			
Inferior	6 (28.6)	0	NA
Superior	4 (19)	0	NA
Nasal	4 (19)	0	NA
Temporal	6 (28.6)	0	NA
EZ disruption (+ eyes)%			
Inferior	11 (52.4)	0	NA
Superior	10 (47.6)	0	NA
Nasal	9 (42.9)	0	NA
Temporal	13 (61.9)	0	NA
Mean parafoveal VD-SCP(mean±SD)%	44.09±2.97	46.28±1.67	**0.006***
Inferior	45.39±3.14	47.03±2.76	0.084
Superior	44.20±4.38	47.85±2.42	**0.002***
Nasal	42.46±3.99	44.32±2.14	0.073
Temporal	44.27±3.58	45.93±1.86	0.074
FAZ-SCP (mean±SD) (µm^2)	335.24±14124	277.95±130.95	0.144
Mean parafoveal VD-DCP(mean±SD)%	22.07±5.61	25.11±2.27	**0.030***
Inferior	23.56±5.58	25.63±3.42	0.148
Superior	21.89±8.60	25.59±3.03	0.077
Nasal	23.92±7.36	25.88±3.22	0.774
Temporal	18.90±6.86	23.37±2.86	**0.010***
FAZ-DCP (mean±SD) (µm^2)	2176±1970.71	432.80±172.16	**0.0001***

CFT: Central foveal thickness, PRT: Parafoveal retinal thickness, VD: Vessel density %, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, * statisticaly significant.

of age, sex, or eye distribution. BCVA was significantly lower in the DME group compared to the control group ($p<0.0001$).

Table 2 shows the baseline central and parafoveal OCT and OCTA values and comparisons between the DME group and the control group. The CFT was significantly higher in the DME group compared to the control group ($p<0.0001$). In terms of comparison of baseline microvascular OCTA metrics, the mean parafoveal VD of the SCP and DCP in DME was significantly lower compared to controls ($P = 0.0006$ and $P = 0.030$, respectively) (Figure 2). With the comparison of VD in the parafoveal quadrants, only the superior quadrant in the SPC and the temporal quadrant in the DCP were significantly different between the baseline values of eyes with DME eyes and controls

Table 3. Changes in BCVA, OCT and OCTA values of the DME group after 6 months follow up.

	DME-baseline (n=21)	DME-six month follow up (n=21)	P
BCVA(mean±SD), logMar	0.40±0.43	0.45±0.39	0.148
CFT (mean±SD) (µm)	387.81±132.47	351.86±11.22	0.122
Inferior PRT	382.14±84.99	352.67±54.51	0.140
Superior PRT	377.95±72.99	363.24±72.65	0.198
Nasal PRT	362.14±69.48	346.76±51.89	0.175
Temporal PRT	404.14±99.30	378.14±88.67	0.136
ELM disruption (+ eyes)%			
Inferior	6 (28.6)	6 (28.6)	1.000
Superior	4 (19)	5 (23.8)	1.000
Nasal	4 (19)	5 (23.8)	1.000
Temporal	6 (28.6)	3 (14.3)	0.250
EZ disruption (+ eyes)%			
Inferior	11 (52.4)	10 (47.6)	1.000
Superior	10 (47.6)	10 (47.6)	1.000
Nasal	9 (42.9)	9 (42.9)	1.000
Temporal	13 (61.9)	8 (38.1)	0.063
Mean parafoveal VD-SCP(mean±SD)%	44.09±2.97	43.76±3.20	0.548
Inferior	45.39±3.14	46.14±4.74	**0.001***
Superior	44.20±4.38	43.26±2.83	0.099
Nasal	42.46±3.99	41.88±4.83	**0.004***
Temporal	44.27±3.58	43.76±4.54	**0.015***
FAZ-SCP (mean±SD) (μm^2)	335.24±141.24	335.81±194.72	0.689
Mean parafoveal VD-DCP(mean±SD)%	22.07±5.61	23.49±3.64	0.153
Inferior	23.56±5.58	24.96±4.78	0.363
Superior	21.89±8.60	23.45±6.26	**0.0001***
Nasal	23.92±7.36	24.15±6.61	0.986
Temporal	18.90±6.86	21.42±5.75	0.407
FAZ-DCP (mean±SD) (μm^2)	2176±1970.71	1337±1600	0.092

CFT: Central foveal thickness, PRT: Parafoveal retinal thickness, VD: Vessel density %, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, * statisticaly significant.

(P = 0.002 and P = 0.010, respectively). The FAZ was not significantly different at the SPC (P = 0.144) but was significantly higher at the DCP in the DME group (P = 0.0001) (Figure 2).

The longitudinal changes after 6 months of follow-up in the DME eyes are shown in Table 3. The decrease in CFT did not reach significance, despite a trend to decrease after treatment in the main DME group. In terms of BCVA, ELM and EZ disruption, there were no significant changes (all P>0.05). The mean parafoveal VD in the SCP and DCP did not change significantly, but there were significant changes in the quadrants. Although the inferior parafoveal VD in the SPC increased, the nasal and temporal parafoveal VD decreased after 6 months (P = 0.001, P = 0.004, and P = 0.015, respectively). In terms of the parafoveal quadrants in the DCP, only the superior parafoveal VD increased significantly (P = 0.0001). The FAZs did not change at either the SCP or DCP (P = 0.689 and P = 0.092, respectively), but the decrease at the DPC was striking despite not reaching significance (from 2176 ± 1970.71 μm^2 to 1337 ± 1600 μm^2).

DME eyes were divided into two subgroups: increased CFT and decreased CFT, according to the change in initial CFT on the before and after treatments. The changes in CFT ranged from 432.55 ± 152.32 µm to 325.00 ± 119.90 µm in the decreased CFT group (P = 0.003) and from

Table 4. Subgroup analysis of baseline values of DME patients according to treatment response.

	Decreased CFT (n=11)	Increased CFT (n=10)	P
Age	60.82±6.32	58.40±7.38	0.429
BCVA(mean±SD), logMar	0.39±0.40	0.41±0.48	0.859
CFT (mean±SD) (µm)	432.55±152.32	338.60±89.88	0.169
Inferior PRT	405.91±94.93	356±67.74	0.307
Superior PRT	385.45±84.57	369.70±61.23	0.888
Nasal PRT	375.27±76.97	347.70±60.86	0.360
Temporal PRT	424.18±101.31	382.10±97.34	0.231
ELM disruption (+ eyes)%			
Inferior	3 (27.3)	3 (30)	1.000
Superior	3 (27.3)	1 (10)	0.586
Nasal	3 (27.3)	1 (10)	0.586
Temporal	4 (36.4)	2 (20)	0.635
EZ disruption (+ eyes)%			
Inferior	6 (54.5)	5 (50)	1.000
Superior	5 (45.5)	5 (50)	1.000
Nasal	5 (45.5)	4 (40)	1.000
Temporal	6 (54.5)	7 (70)	0.659
Mean parafoveal VD-SCP(mean±SD)%	42.69±2.24	43.56±4.48	0.577
Inferior	45.05±2.72	45.76±3.66	0.616
Superior	45.14±1.71	43.16±6.10	0.315
Nasal	42.57±2.53	42.34±5.31	0.901
Temporal	43.91±3.13	44.76±4.20	0.603
Mean parafoveal VD-DCP(mean±SD)%	21.98±4.04	22.22±4.78	0.902
Inferior	22.76±6.15	24.44±4.28	0.484
Superior	22.49±9.06	21.32±8.51	0.746
Nasal	23.88±6.96	23.96±8.16	0.888
Temporal	17.51±5.36	20.42±8.23	0.346
FAZ-SCP (mean±SD) (μm^2)	282.55±86.93	393.20±169.73	0.113
FAZ-DCP (mean±SD) (μm^2)	2126.82±1858.59	2231.50±2187.66	1.000

CFT: Central foveal thickness, PRT: Parafoveal retinal thickness, VD: Vessel density %, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, * statisticaly significant.

Table 5. Subgroup analysis of last follow up results of DME patients according to treatment response.

	Decreased CFT (n= 11)	Increased CFT (n=10)	P
BCVA(mean±SD), logMar	0.46±3.39	0.44±0.41	0.777
CFT (mean±SD) (µm)	325.00±119.90	381.40±112.74	0.105
Inferior PRT	336.18±55.28	370.80±50.09	0.151
Superior PRT	349.09±78.68	378.80±65.85	0.139
Nasal PRT	340.45±61.58	353.70±40.85	0.245
Temporal PRT	355.45±81.60	403.10±93.54	**0.045***
ELM disruption (+ eyes)%			
Inferior	4 (36.4)	2 (20)	0.635
Superior	3 (27.3)	2 (20)	1.000
Nasal	3 (27.3)	2 (20)	1.000
Temporal	2 (18.2)	1 (10)	1.000
EZ disruption (+ eyes)%			
Inferior	5 (45.5)	5 (50)	1.000
Superior	5 (45.5)	5 (50)	1.000
Nasal	5 (45.5)	4 (40)	1.000
Temporal	4 (36.4)	4 (40)	1.000
Mean parafoveal VD-SCP(mean±SD)%	42.73±2.35	43.86±4.51	0.472
Inferior	45.24±2.71	47.13±6.29	0.398
Superior	43.84±1.71	42.63±3.71	0.343
Nasal	41.22±2.07	42.61±6.78	0.527
Temporal	43.07±4.14	44.53±5.06	0.478
Mean parafoveal VD-DCP(mean±SD)%	21.51±3.86	21.79±4.42	0.878
Inferior	24.92±3.58	25.01±6.05	0.968
Superior	24.39±6.22	22.42±6.47	0.486
Nasal	22.67±5.11	25.77±7.91	0.091
Temporal	23.86±4.13	18.74±6.26	0.038
FAZ-SCP (mean±SD) (μm^2)	280.36±117.13	396.80±247.24	0.260
FAZ-DCP (mean±SD) (μm^2)	711.64±738.55	2025.50±2020	**0.017***
Injection (mean±SD)	2.73±1.84	1.10±1.10	**0.025***

CFT: Central foveal thickness, PRT: Parafoveal retinal thickness, VD: Vessel density %, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, * statisticaly significant.

338.60 ± 89.88 µm to 381.40 ± 112.74 µm in the increased CFT group (P = 0.005) after 6 months of treatment. In terms of BCVA, ELM and EZ disruption, there were no significant changes in either subgroup (all P>0.05). All parafoveal VDs in the SCP and DCP did not change in the decreased CFT group (all P > 0.05). All parafoveal VDs in the SCP and DCP did not change in the increased CFT group (all P>0.05). The FAZ in the SCP did not change in the decreased or increased CFT group (all P>0.05). The FAZ in the DCP was significantly decreased in the decreased CFT group (P = 0.013), but not significantly changed in the increased CFT group (P = 0.575). The increased CFT group and the decreased CFT group were compared in terms of baseline and last follow-up values (Tables 4 and 5). There were no significant differences between the two subgroups in all baseline values (all p>0.05) (Table 3). There were no significant differences in terms of BCVA, CFT, ELM disruption, EZ disruption, parafoveal VDs in the SCP and DCP, and the FAZ in the SCP between both subgroups in the 6-month follow-up results (all P>0.05). The FAZ in the DCP in the decreased CFT group was significantly lower than in the increased CFT group after 6 months of treatment (Figure 3). Changes in the FAZ in the DCP were found between 2126.82 ± 1858.59 μm^2 to 711.64 ± 738.55 μm^2 in the decreased CFT group (P = 0.013) and from 2231.50 ± 2187.66 μm^2 to 2025.50 ± 2020 μm^2 in the increased CFT group (P = 0.575) after 6 months of treatment. The injections administered were 2.73 ± 1.84 in the decreased CFT group and 1.10 ± 1.10 in the increased CFT group at 6 months (P = 0.025) (Table 5).

Discussion

In the present study, we found significantly lower VDs in both the SCP and DCP in DME eyes at baseline compared to the controls. When we looked at the FAZs, significantly higher values were evident just at the DCP. After 6 months of treatment, the mean parafoveal VD and the FAZs did not change. When we divided patients with DME into decreased CFT and increased CFT groups, the changes in CFT were found to range from 432.55 ± 152.32 µm to 325.00 ± 119.90 µm in the decreased CFT group (P = 0.003) and were found to range from 338.60 ± 89.88 µm to 381.40 ± 112.74 µm in the increased CFT group (P = 0.005) after 6 months of treatment. There were no significant differences between the two subgroups in terms of baseline values. There was a significant difference in the FAZ in the DCP but not in the other parameters between the two subgroups after 6 months of treatment. Changes in the FAZ in the DCP ranged from 2126.82 ± 1858.59 μm^2 to 711.64 ± 738.55 µm2 in the decreased CFT group (P = 0.013) and from 2231.50 ± 2187.66 μm^2 to 2025.50 ± 2020 μm^2 in the increased CFT group (P = 0.575) after 6 months of treatment. The present study highlights the longitudinal changes in these OCTA metrics and the usefulness of these as follow-up criteria for the response to treatment in patients with DME.

Capillary loss and microvascular changes have been suggested to be associated with DR. Even in diabetic patients without retinopathy, some early microvascular changes were found [6-8]. Especially progressive loss of vessel density has been correlated with the progression of DR [9-11]. Microvascular changes and association with DME are still unclear because some studies that investigated the microvascular status in DME by OCTA reported that VD of the SCP was more associated with the development of DME, while some pointed out the importance of OCTA metrics in the DCP rather than the SCP [9,12,16]. We think that the most important reason for the different results in different studies is image processing and calculation. The 3 3-mm volumetric scans that some studies used may give overestimated results [9]. The overestimation of the density of the DCP vessel in eyes with DME that many studies reported may be due to the effect of suspended scattering particles in motion (SSPiM). The SSPiM effects are more prominent in 3-mm OCTA scans than in 6-mm

scans [20]. Properly uncorrected segmentation errors and unremoved projection artifacts affect the measurement of OCTA metrics and give rise to incorrect values, especially at the DCP. For example, most of the above-mentioned studies have reported parafoveal VD of the DCP about 40% to 50%, which is close to the VD of the SCP. Coscas et al [21]. conducted a study that investigated the normative data on OCTA metrics in healthy patients. They found a higher VD at the DCP and admitted that overestimated values might be due to the superficial layer. Furthermore, even in our healthy controls, we never found values like those in the DCP because we meticulously corrected the segmentation errors and paid attention to using the PAR function. In the present study, we found significantly lower VD in both the SCP and the DCP, but the FAZ was just higher at the DCP in eyes with DME compared to healthy controls. As a result, the microvascular structure decreased in both plexuses, but the FAZ widened only strikingly at the DCP in the eyes with DME. These results may reflect that the capillaries in both plexuses drop out, but the end capillaries in the DCP around the central part are more vulnerable and result in an evident FAZ in the DCP in eyes with DME. Another striking result of our study was that the decrease in sectoral parafoveal VD was not homogenous between quadrants. While the VD in the superior quadrant was significantly lower in the SCP, the VD in the temporal quadrant in the DCP was significantly lower. We were unable to explain the reason for this result.

Many studies that have investigated longitudinal changes in VD after intravitreal injections have reported conflicting results. Some of them did not find a significant change in VD after treatment despite a decrease in edema [17-19,22]. However, some studies have mentioned an increase and some a decrease with treatment [14,23,24]. According to our results, it should be noted that the mean parafoveal VD in both plexuses did not change, but when we looked at the sectoral parafoveal quadrants, the VD in the DCP quadrants tended to increase, but still to decrease in the SCP quadrants after 6 months of treatment. The reason for the decreasing trend in the SCP may be that the blood flow-reducing effect of anti-VEGF drugs was greater in the SCP due to its proximity to the vitreous [25,26]. Therefore, it can be considered that sectoral parafoveal VD in the DCP after treatment can contribute to the resolution of edema in DME. The increase in the DCP may be a relative increase, not an actual increase, due to the resolution of the fluid, which is evident in deep layers [10,19]. To discriminate against that effect, we divided patients into decreased edema and increased edema groups. Although there were no significant differences in terms of baseline values between the groups, there were no significant changes in all values except the FAZ in the DCP in the increased CFT or decreased CFT groups. The FAZ of the DCP was significantly decreased in the decreased CFT group. This result may show that edema does not have an effect on microvascular density. We speculated that deep capillaries close to the foveal center may reflow with treatment, in agreement with the study by Dastiridou et al [14]. That is, ischemic damage of retinal vessels in the area close to the FAZ border can recover after treatment. The reason why this situation did not cause a significant difference in the mean parafoveal VD may be due to treatment-related narrowing in the other parafoveal telangiectatic vessels, compensating for the increase in VD. The vasoconstrictive effect of intravitreal anti-VEGF injections has previously been demonstrated by studies conducted with retinal vessel analyzer and laser speckled flowgraphy [27,28]. Of course, our patients were undertreated due to less compliance due to pandemic conditions. However, relief of macular edema by more injections resulted in a decrease in the FAZ in the DCP, while the other parameters did not change significantly with treatment. Therefore, the results of the present study are in contrast to previous studies that reported no recovery in the FAZs after anti-VEGF treatments in DME [15,19].

The other parameters that we investigated were the ELM and EZ disruptions. Moon et al [23]. reported that the VD and FAZs of the DCP had a vital effect on the health of the ELM and EZ. In their 12-month results, the integrity of the EZ and ELM regained significantly according to the baseline. We did not find any significant changes in these layers before or after treatment. This different result may be due to our short follow-up period and the undertreated participants.

Limitations

1. The retrospective nature of the study may have caused biases.
2. Due to strict inclusion and exclusion criteria, the sample size of the study was small.
3. The study included both previously treated and untreated patients.
4. The inclusion of patients treated with both anti-VEGF and Dexamethasone implant.
5. There were heterogeneity in the treatment of the patients throughout the study period.
6. Manual adjustment of the grid and drawing of the FAZ may cause unintended errors in terms of calculations.

Conclusion

In conclusion, this longitudinal study has shown that deep retinal ischemia may actually recover after proper treatment. Although we were unable to find a significant change in parafoveal vessel density in eyes with DME after treatment, changes in the FAZ of the DCP were the most prominent indicator of that improvement. Larger prospective studies with longer follow-ups are required.

Declaration of interest

The authors report there are no competing interests to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, NP, upon reasonable request.

Ethical approval

Approval was received for the study from Malatya Clinical Research Ethics Committee (no:2021/118).

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