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Original Article

The Impact of COVID-19 Infection on Macular Capillary Perfusion

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Abstract

Objectives: Thromboembolic complications related to the COVID-19 infection are frequently reported. This study aims to evaluate the impact of a prior non-severe COVID-19 infection on retinal microcirculation with optical coherence tomography angiography (OCTA).

Methods: A total of 83 eyes of 43 patients with a history of non-severe COVID-19 infection confirmed with a positive PCR test (Group 1) and 30 healthy controls (Group 2) underwent detailed eye examination, including optic coherence tomography angiography (OCTA, RTVue-XR Avanti) scanning. Vessel densities (VD) in the superficial capillary plexus (SCP), deep capillary plexus (DCP), and foveal avascular zone were evaluated.

Results: The mean duration between the COVID-19 positive PCR test and ocular examination was 144.6±82.2 days. VD of SCP and DCP in the foveal and perifoveal regions were significantly lower in Group 1 compared to Group 2 ($p<0.05$).

Conclusion: A non-severe COVID-19 infection may cause a decrease in the VD of retinal SCP and DCP.

Keywords: COVID-19, optical coherence tomography angiography, retinal capillary perfusion

Introduction

Since the beginning of the COVID-19 pandemic, hypercoagulability and thromboembolic complications related to the SARS-CoV-2 infection have been frequently reported. Patients with severe COVID-19 are particularly susceptible to pneumonia and sepsis-induced coagulopathy, which may progress to disseminated intravascular coagulation with increased D-dimer and fibrin degradation products if left untreated (1). Retinal capillaries are common sites for thromboembolic complications in many systemic diseases with hypercoagulation. While thromboembolic complications of the COVID-19 infection mainly consist of deep venous thromboembolism, pulmonary embolism, or myocardial infarction, there are also reports of retinal venous and even arterial occlusions associated with this infection (2-6).

Optical coherence tomography angiography (OCTA) is a new, non-invasive, and rapid technique that allows the quantitative evaluation of retinal capillary perfusion by automatically calculating the vessel densities (VD) of retinal superficial and deep capillary plexuses (DCP).

Herein, using OCTA, we aimed to investigate whether a complication-free COVID-19 infection has any impact on macular capillary perfusion in patients who have recovered from non-severe COVID-19.

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Methods

This cross-sectional, observational study was conducted between March 2020 and April 2021 at X Hospital. A total of 73 patients were included in the study, and participants were separated into two groups. The inclusion criteria for Group 1 were the following: (1) being a health care professional working in X Hospital (2) Having a medical history of non-severe and/or asymptomatic COVID-19 infection confirmed with positive PCR tests from nasopharyngeal swabs. Inclusion criteria for Group 2 were: (1) Being a health care professional at the same hospital; (2) No history of any systemic or ocular disease; (3) Not having a history of COVID-19 infection or any contact with someone who had the infection (including under professional circumstances). Group 1 consisted of 43 (58.9%) individuals, while Group 2 consisted of 30 (41.1%) age-matched healthy controls. Exclusion criteria for Group 1 included the presence of COVID-19-related complications (such as thromboembolic complications, need for oxygen support, high-grade fever, etc.), or hospitalizations (including emergency service applications), and the presence of any systemic or ocular diseases.

All patients included in the study underwent a detailed ophthalmological examination that was performed by the same ophthalmologist. The examination included best corrected visual acuity (BCVA) with the Snellen chart, measurement of intraocular pressure (IOP) with the Goldmann applanation tonometer, biomicroscopic anterior segment examination, and posterior segment examination with a 90D lens. Spectral-domain optical coherence tomography (OCT, Topcon, Triton Swept Source, Tokyo, Japan) and OCT angiography (OCTA, Optovue, RTVue-XR Avanti, CA, USA) scans were obtained for all participants.

The age and gender of the patients, the duration between the ophthalmological examination and positive PCR tests, as well as their symptoms and medications used during the infection, were noted. BCVA values were converted to LogMAR for statistical analyses. Subfoveal choroidal thickness (SFCT) was measured from the OCT scans (6 × 6 mm, HD Raster) manually.

The OCTA analysis divided the macular area (6 × 6 mm quadrant centered on the fovea) into the whole image, foveal, parafoveal, and perifoveal regions, and then automatically calculated the VD of the superficial capillary plexus (SCP) and DCP. The foveal avascular zone (FAZ) was also automatically calculated by the OCTA system. Scans were assessed for flow area of the choriocapillaris and outer retina at 1 mm radius, FAZ, central retinal thickness (CRT), and VD in the SCP and DCP.

All OCT and OCTA examinations were performed by the same technician (NA). Eyes with low-quality OCTA images (7/10 and higher were accepted as good quality) due to dense cataracts or high refractive errors were excluded from the study. All OCTA and OCT images were examined by the same ophthalmologist (MEB).

Informed consent was obtained from all study participants, and institutional review board approval was gathered from the Ege University Medical Studies Ethical Committee (approval number: 20-8.1T/37). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using SPSS software (Version 20; SPSS Inc., Chicago, Illinois, USA). All data are reported as mean±standard deviation (SD), and demographic data were compared with a chi-square test. An independent t test was used to compare data between groups with a normal distribution, while a Mann–Whitney U test was used for data without a normal distribution. $P<0.05$ was considered to be statistically significant.

Results

A total of 83 eyes of 43 patients (29 [67.4%] female, 14 [32.6%] male) assigned to Group 1 and 60 eyes of 30 patients (15 [50%] female, 15 [50%] male) assigned to Group 2 were included, in the study. Both eyes of all patients were included with the exception of 3 patients in Group 1. Only one eye of each of those 3 patients was included due to the low image quality of the OCTA obtained from the other eye. The reasons for the low quality of imaging were keratoplasty in one eye, cataracts in one eye, and corneal scars in one eye. The mean age was 40.29±10.08 (range, 24–70) years in Group 1 and 40.36±8.67 (range, 31–53) years in Group 2 (p=0.2). All the eyes included in the study had a BCVA of 20/20 (0 LogMAR), and none of them had high refractive errors (cylinder correction range was −1.50–+1.00; spherical correction range was corre). There were no significant differences in BCVA and refractive errors between the groups (p=1.9 and p=1.5, respectively). The demographics of the two groups and the symptoms of the patients in Group 1 during the acute phase of the SARS-CoV-2 infection are summarized in Table 1.

Biomicroscopic anterior segment examination revealed that 4 eyes in Group 1 and 2 eyes in Group 2 had Grade 1 nuclear sclerosis. No other anterior segment pathologies were observed. Fundus examinations were also normal in all patients in both groups; no lesions were detected.

No statistically significant differences could be identified in SFCT (310.5±161.7 μm vs. 298.9±165.0 μm; p=0.7) and CRT (249.2±19.3 μm vs. 253.1±15.9 μm; p=0.3) between Group 1 and Group 2. The mean outer retinal flow area also showed no significant difference between the two

Table 1. The demographics of study participants and the symptoms of patients in Group 1 during the acute phase of the infection

	Group 1 (COVID-19 Group)	Group 2 (Control Group)	p
Demographics			
Number of patients, n (%)	43 (58.9)	30 (41.1)	
Mean age±SD	40.29±10.08	40.36±8.67	0.2*
Gender			
Female, n (%)	29 (67.4)	19 (63.3)	1.2**
Male, n (%)	14 (32.6)	11 (36.6)	
Symptoms, n(%)			
Fever (<39.0°C),	4 (9.3)	-	
Headache	16 (37.2)	-	
Myalgia	24 (55.8)	-	
Anosmia	25 (58.1)	-	
Cough	5 (11.6)	-	
Asymptomatic	18 (41.8)	-	

*Independent samples t test; **Chi-square test.

groups (0.62±0.4 mm^2 vs. 0.7±0.3 mm^2; p=0.3). The mean choriocapillaris flow area was significantly larger in Group 1 (2.14±0.1 mm^2), compared to Group 2 (2.04±0.2 mm^2; p=0.01).

FAZ was significantly larger in Group 1 (0.29±0.12) compared to Group 2 (0.24±0.07; p=0.01). VD of the deeper capillary plexus (DCP) in the whole image was significantly lower in Group 1 than Group 2 (54.8±6.4% vs. 58.9±4.3%; p=0.01); the same was observed in superior (54.5±6.7% vs. 58.6±4%; p=0.02) and inferior (55.0±6.5% vs. 59.2±5.2%; p=0.01) hemi-retinal quadrants as well as the foveal (42.1±6.1% vs. 57.8±5.8%; p=0.02) and perifoveal (51.1±6.6% vs. 53.6±3.3%; p<0.01) regions. The VD of DCP in the parafoveal region was slightly lower in Group 1 compared to Group 2 (57.8±5.8 vs. 59.9±4.5), but the difference did not reach statistical significance (p=0.06).

VD of SCP in the whole image area (5.0±3.4% vs. 53.0±3.5%), superior (51.0±3.4% vs. 52.9±3.4%) and inferior (51.1±3.7% vs. 53.1±3.7%) hemi-retinal quadrants, and the foveal (20.7±9.1% vs. 24.6±6.6%) and perifoveal (51.1±6.6% vs. 53.6±3.3%) regions were significantly lower in Group 1, compared to Group 2. The VD of SCP in the parafoveal region was slightly lower in Group 1 compared to Group 2, but the difference was not statistically significant (p=0.07). The OCT and OCTA findings and the P values are summarized in Table 2.

The mean duration since the first positive PCR test for SARS-CoV-2 and the ocular examination was 144.6 ± 82.2 days (range: 30–270 days). All patients in Group 1 received 100 mg of acetyl salicylic acid once daily for 1 month. As an antiviral treatment, all patients received favipiravir 1.8 mg twice daily on day 1, then 600 mg twice daily for 14 days, as per local health care guidelines.

Patients in Group 1 were also investigated for the effect of gender and the duration between the positive PCR test and the day of examination on the ocular findings. There were no significant differences in VD and FAZ as a function of gender; however, CRT was significantly lower in females compared to males. No correlations were observed between the duration since the SARS-CoV-2 infection and the VD of DCP and SCP in any region.

Since the study participants were chosen from health care professionals working at a university hospital, OCTA images of nine eyes of five patients in Group 1 were already present in the hospital's database. Therefore, we were able to compare the pre-COVID-19 and post-COVID-19 OCTA images captured with the same device (Table 3). The mean duration between the two OCTA images was 26±8.4 months (range: 18–40). VD of SCP was reduced in 5 (55.5%) eyes in the whole image, in the superior hemiretinal and inferior hemiretinal quadrants; the same was reduced in 4 (44.4%) eyes in the foveal, parafoveal, and perifoveal regions. VD of DCP was decreased in 4 (44.4%) eyes in the whole image, in the superior hemiretinal and inferior hemiretinal quadrants, in 1 (11.1%) eye in the foveal region, in two eyes (22.2%) in the parafoveal region, and in 4 (44.4%) eyes in the perifoveal region. The low sample size precluded any reliable statistical analyses.

Table 2. OCT and OCTA parameters of COVID-19 patients (Group 1) and healthy controls (Group 2)

	Group 1	Group 2	p*
SFCT	310.5±161.7	298.9±165.0	0.7
CRT	249.2±19.2	253.0±15.9	0.3
FAZ area	0.294±0.123	0.245±0.077	**0.03**
VD of SCP			
Whole image	51.0±3.4	53.0±3.5	**0.008**
Superior hemiretinal	51.0±3.4	52.9±3.4	**0.01**
Inferior hemiretinal	51.1±3.7	53.1±3.7	**0.01**
Foveal	20.7±9.1	24.6±6.6	**0.02**
Parafoveal	53.5±4.3	55.2±5.1	0.07
Perifoveal	51.1±6.6	53.6±3.3	**0.04**
VD of DCP			
Whole image	54.8±6.4 (%)	58.9±4.3 (%)	**0.001**
Superior hemiretinal	54.5±6.7	58.6±4.0	**0.002**
Inferior hemiretinal	55.0±6.5	59.2±5.2	**0.001**
Foveal	37.7±10.0	42.1±6.1	**0.02**
Parafoveal	57.8±5.8	59.9±4.5	0.06
Perifoveal	55.6±9.2	60.5±4.8	**0.005**

SFCT: Subfoveal choroidal thickness; CRT: Central retinal thickness; FAZ: Foveal avascular zone; VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; *Independent samples t test.

Discussion

Thromboembolic complications of SARS-CoV-2 infection are a major problem, especially in severe cases. Pulmonary embolism is the most common thromboembolic complication related to SARS-CoV-2 infection, and it is also one of the causes of mortality. In severe cases, the prevalence of pulmonary embolism is reported as 2.6%, the prevalence of stroke is reported to be up to 3%, and venous thromboembolism is reported to be up to 20% (7,8). Herein, we investigated the impact of non-severe SARS-CoV-2 infection on retinal microcirculation by OCTA, 144.6±82.2 days after the first positive PCR test.

The study group (Group 1) and control group (Group 2) were age and sex matched and revealed no significant differences in BCVA and refractive errors. Corroborating these data, Costa et al. (9) did not report any significant difference in the prevalence of myopia and hyperopia among infected and non-infected individuals, compared to prevalence studies in the general population.

Regarding the anterior segment findings, Costa et al. (9) reported the presence of cataracts in two eyes with the diagnosis known before the infection; no other pathologies or signs of uveitis were observed. In the current study, cataract was the only anterior segment change detected in both groups; additionally, there was no significant difference in the incidence of cataracts between the groups.

In the current study, IOP measurements were similar in both groups. Costa et al. (9) reported a modest but statistically significant higher IOP in critical COVID-19 patients compared to severe and moderate cases (approximately 14.00 mmHg vs. 12.00 mmHg). However, a large proportion of patients with critical infections received systemic corticosteroid treatment (48% of the cases evaluated), (9) potentially leading to such a low difference in IOP.

None of the eyes evaluated in the current study showed any pathologies in fundus evaluation in both groups. Since none of the participants in the study or control groups had any systemic diseases, this was foreseeable. Bypareddy et al. (10) also reported the lack of any fundus pathologies in non-severe COVID-19 patients, except for a single streak of retinal hemorrhage in one eye. Costa et al. (9) reported the frequency of diabetic retinopathy as 52.7%. As mentioned previously, all of our cases had a history of non-severe COVID-19 infection, and none of them had any chronic diseases such as diabetes or hypertension. Costa et al. (9) reported the presence of yellowish-white dots in the outer retinal layers in two patients, both of whom had critical disease (9). Zago Filho et

Table 3. Vessel Densities of superficial capillary plexus and deep capillary plexus before and after the COVID-19 infection

P. No	A	G	Eye	VD of SCP											
				Whole image		Superior hemiretinal		Inferior hemiretinal		Foveal		Parafoveal		Perifoveal	
				Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.
1	30	F	R	48.2	46.3	47.8	46.1	48.7	46.4	18	17.9	49.2	51.2	48.3	47.2
			L	46.7	50.9	46.5	50.3	46.9	51.6	17.5	23.2	46.2	51.6	47.8	51.7
2	33	M	R	56.1	51.9	56.2	51.3	55.9	52	26.3	21.9	57.2	50.2	57	52.7
			L	58.9	54.7	59	54.5	58.8	55	26.7	21.6	61.3	56.6	60.6	56.4
3	31	M	R	54.2	52.3	53.8	51.7	54.6	52.9	23.8	23.1	57	56.2	54.7	52.7
4	50	F	R	50.1	52.2	50.2	51.8	50.1	52.6	12.8	16.5	51.6	53.8	50.4	53.4
			L	54.6	51.2	53.8	51.0	55.3	51.4	20.9	14.5	56.3	52.8	55.4	51.9
5	48	F	R	54	53.9	53.3	52.4	54.6	55.4	20.8	28.2	55.8	55.9	54.7	54.0
			L	55.1	55.2	54.6	54.7	55.4	55.6	26.3	27.3	58	57.5	56.1	56.3
P. No	**A**	**G**	**Eye**	**VD of DCP**											
				Whole image		Superior hemiretinal		Inferior hemiretinal		Foveal		Parafoveal		Perifoveal	
				Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.
1	30	F	R	43.4	59.9	42.8	59	44.1	61.2	29.5	41.1	52.4	60.7	43.1	59.8
			L	50	59.2	50.3	59.2	49.7	59.2	35.4	43.8	53.2	60	50.7	60.7
2	33	M	R	56.7	53	56.6	53.9	56.8	52.1	40.4	53.8	59	58.8	57.2	52.8
			L	59.8	56.5	59.3	56.5	60.2	56.6	41.8	40.8	59.6	57.3	61.3	59.1
3	31	M	R	60.6	58	59.2	56.6	62.1	59.5	41.8	41.9	61.6	60.9	62.7	60.4
4	50	F	R	57.5	60.7	58.9	59.8	56.2	61.7	27.4	29.3	61.4	62.5	58.1	63.2
			L	59.3	63.8	58.9	63.5	59.7	64.1	28.5	31.5	60.8	64.2	61.9	66.4
5	48	F	R	57.5	57.7	54.9	55.3	60.2	60.3	36.3	44.7	60.9	60.9	59.7	62
			L	60	57.8	60	58.2	60.1	57.4	39.6	39.1	62.2	60.7	62.2	60.3

P: Patient, A: Age, G: Gender, VD: Vessen density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, F: Female, M: Male.

al. (11) also previously reported yellowish-white lesions in the macular area of a COVID-19 patient in both eyes; however, these lesions were located in the posterior hyaloid surface, inner plexiform, and ganglion cell layers.

We observed significantly lower macular VD of both SCP and DCP in all quadrants, except for the parafoveal region, in Group 1 (recovered non-severe COVID-19 patients) compared to Group 2 (healthy controls). In parafoveal regions of SCP and DCP, VD was slightly lower in Group 1 compared to Group 2; this difference approached but did not reach statistical significance (p=0.07 for SCP and p=0.06 for DCP). None of the patients in the current study were hospitalized during the acute phase of the infection, and many of them were asymptomatic (41.8%). Guemez-Villahoz et al. (12) also reported that VD was reduced in COVID-19 patients compared to healthy controls. The same study also reported that COVID-19 patients with and without thromboembolic events related to infection did not show any significant difference in VD. Interestingly, Turker et al. (13) reported that VD was significantly lower in the parafoveal region of COVID-19 patients compared to controls, but the foveal region was not reported to be affected. Of note, the study included patients who were hospitalized during the acute phase of the infection, which suggests the presence of moderate or severe disease. Cennamo et al. (14) reported that VD was significantly lower in both the foveal and parafoveal regions of SCP and DCP. This study also included patients who were hospitalized for COVID-19 pneumonia,

which again might indicate a moderate to severe infection.

The parafoveal region was found to be either not affected or the least affected in the current study, while the foveal and perifoveal regions were found to be significantly affected. The parafoveal region is richest in VD of SCP and DCP; therefore, it is likely to be relatively better preserved (15,16). The choriocapillaris flow area was significantly larger in COVID-19 patients in the current study, similar to other studies in the literature (13).

In the current study, all patients were evaluated after a mean duration of 144.6±82.2 days (range, 30–270 days) of the acute phase of the infection and a positive PCR test. In statistical analysis, we did not observe any correlations between the VD of SCP or DCP and the duration from SARS-CoV-2 infection to ocular examination. This suggests that the impact of COVID-19 on macular capillary perfusion might be permanent. To the best of our knowledge, this is the first study to investigate this correlation.

SARS-CoV-2 infection causes immune dysfunction and vascular endothelial injury, resulting in systemic microangiopathy. SARS-CoV-2-related inflammation was thought to be the primary cause of endothelial dysfunction; however, studies suggest that endothelial cells lack ACE2 expression, which is required for the virus to infect a cell directly (17,18). On the other hand, studies also indicate that the virus itself can directly infect endothelial cells in the lungs (19,20). More recent studies have shown that SARS-CoV-2 can directly infect mature vascular endothelial cells, both in vivo and ex vivo (21). It was also reported that infection with SARS-CoV-2 can lead to the degradation of the glycocalyx, the protective layer of vascular endothelial cells, and cause increased levels of hyaluronan, a major component of glycocalyx in the systemic circulation (22). Significant damage to the glycocalyx layer was reported to correlate with the severity of the disease, and increased levels of hyaluronan were reported to be associated with endothelial barrier dysfunction (22).

Conclusion

Irrespective of whether the etiology is related to infection-associated inflammation or a direct entry of the virus into the vascular endothelial cells, data from the current study suggests that COVID-19 can lead to a reduction in the VD of the retinal capillary plexus, even when the disease is mild or asymptomatic. Studies with longer follow-up times are needed to confirm whether this reduction in VD is irreversible or not.

Disclosures

Ethics Committee Approval: Informed consent was obtained from all study participants, and institutional review board approval was gathered from the Ege University Medical Studies Ethical Committee (approval number: 20-8.1T/37). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

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