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Original Article

# Optical coherence tomography angiography findings in patients with COVID-19



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***Objective:*** To examine the changes in choriocapillaris and retina caused by coronavirus disease 2019 (COVID-19) by comparing optical coherence tomography angiography (OCTA) findings of COVID-19 patients and healthy controls.

***Methods:*** The study and control groups consisted of 54 eyes of 27 participants, each. Patients and controls underwent OCTA examination. Foveal zone vessel density and parafoveal zone vessel density (for 4 quadrants: nasal, temporal, superior, inferior) were calculated for both superficial and deep capillary plexuses. Additionally, choriocapillaris flow and foveal avascular zone areas were calculated.

***Results:*** For the parafoveal area in the study group, vessel density was significantly lower in the superior and nasal quadrants of the superficial capillary plexus and in all quadrants of the deep capillary plexus compared with controls ($p < 0.05$ for all). The study group had significantly higher choriocapillaris flow area values compared with controls ($p = 0.042$).

***Conclusion:*** Reduced vessel density of the retinal capillary plexus was detected in COVID-19 patients who may be at risk for retinal vascular complications.

***Objectif:*** Cette étude examinait les effets de la COVID-19 sur la choriocapillaire et la rétine en comparant les images obtenues à l'angiographie-tomographie par cohérence optique (OCTA, pour *optical coherence tomography angiography*) chez des sujets ayant été infectés par la COVID-19 à celles de sujets sains.

***Méthodes:*** L'étude comptait 2 groupes de 27 participants chacun (54 yeux). Les patients et les sujets témoins ont subi un examen à l'OCTA. La densité vasculaire de la zone fovéale et la densité vasculaire de la zone parafovéale (dans les 4 quadrants: nasal, temporal, supérieur et inférieur) ont été calculées, tant dans le plexus capillaire superficiel que dans le plexus capillaire profond. On a également calculé l'aire du débit de la choriocapillaire de même que l'aire de la zone fovéale avasculaire.

***Résultats:*** La densité vasculaire de la zone parafovéale chez les patients était significativement moindre dans les quadrants supérieur et nasal du plexus capillaire superficiel et dans tous les quadrants du plexus capillaire profond, comparativement aux sujets témoins ($p < 0,05$ pour l'ensemble des mesures). De même, l'aire du débit de la choriocapillaire était significativement plus élevée chez les patients, comparativement aux sujets témoins ($p = 0,042$).

***Conclusion:*** On a observé une baisse de la densité vasculaire du plexus capillaire rétinien chez des patients qui ont été infectés par la COVID-19, ce qui les expose peut-être à un risque de complications vasculaires rétiniennes.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a subtype of the coronavirus family that can affect both animals and humans causing coronavirus disease 2019 (COVID-19). Different viruses from this family, such as Middle East respiratory syndrome and SARS, are already known to cause severe respiratory diseases. Although COVID-19 may present with a simple upper respiratory tract infection, it can progress to severe respiratory failure. The clinical manifestations can further progress to involve the hepatic, enteric, neurologic, and nephrologic systems. Because of its ability to recognize the angiotensin-converting enzyme 2 (ACE-2) receptor, SARS-CoV-2 can be located on the plasma membranes of epithelial cells in various tissues, including the respiratory tract, cornea, retina, esophagus, ileum, liver, gall bladder, heart, kidney, testicles, and endothelium.[1] Retina in particular has ACE and ACE-2 receptors in the choroid and on different cell types such as the Muller cells, ganglion cells, photoreceptor cells and the retinal vascular endothelial cells.[1,2]

SARS-CoV-2 is a pathogen that can lead to a multisystem inflammatory syndrome. Ocular tissues, like many other tissues, can be affected by this inflammatory process. Polymerase chain reaction (PCR) tests for SARS-CoV-1 and SARS-CoV-2 were able to detect viral proteins in samples taken from the tear film layer of some patients.[3,4]

Optical coherence tomography angiography (OCTA) is a new, noninvasive, and reproducible imaging technique that allows assessment of the choriocapillaris (CC) and retinal vascular structures. OCTA can help detect the presence of local ischemia more accurately by measuring vessel density, foveal avascular zone (FAZ) area, and CC flow area.

In the present study, we aimed to examine the changes caused by COVID-19 in the CC and retina. To do this, we

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compared OCTA findings of cases with a recent history of PCR-positive COVID-19, in whom widespread microangiopathy and inflammation may have occurred, with the findings of healthy individuals.

## Methods

### Patients

The study group consisted of 54 eyes of 27 patients with a history of recent PCR-positive COVID-19 who were treated between May and June 2020. The control group included 54 eyes of 27 age-matched healthy individuals. Hospital database was screened for PCR-confirmed COVID-19 cases recently treated at the hospital who recovered completely as confirmed by a negative PCR test. Patients were excluded upon the search of medical records if they were nonhospitalized, admitted to the intensive care unit or received mechanical ventilation, had no ocular symptoms during the active COVID-19 infection, and received high-flow oxygen support within 24 to 48 hours before their discharge. Patients were contacted after completion of their treatment and eligible patients were invited for study assessments. Patients willing to participate and admitting for assessments and eligible after initial examination were included in the study. Study measurements were done within 1 week of discharge after complete recovery as indicated with conversion to PCR-negative status. The control group consisted of volunteers who admitted to our clinic for routine ophthalmologic examination.

Additionally, the following exclusion criteria were applied upon initial examination of all participants: presence of eye symptoms, systemic diseases that could have affected the retinal vascular morphology (diabetes, hypertension, carotid artery disease, etc.), ocular pathologies, intraocular pressure >21 mm Hg, an axial length <20 mm or >24 mm, and those receiving systemic treatment that could lead to retinal toxicity. The best-corrected visual acuity, anterior and posterior segment examination, intraocular pressure measurements, colored fundus photographs, and OCTA data were recorded for all participants.

The study protocol was approved by the Ethical Committee of the Sisli Hamidiye Etfal Training and Research Hospital and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

### OCTA assessments

The same technician performed all scans using the same device at the same time during the day (between 10 AM and 2 PM) following pupil dilation with tropicamide. Thus, the same technician scanned patients and controls using the same device under the same conditions. Assessments of controls were done after completing assessments of all patients with COVID-19, for infection control purposes. OCTA images were obtained using the AngioVue Imaging System version 2017.1 (Optovue, Inc, Fremont, Calif). A previously described algorithm was used for OCTA, which included OCT 3-dimensional macular images of 6 × 6 mm, with activation of the eye-tracking system.[5–7] Low-quality scans were excluded (signal strength index <7/10) and repeated until satisfactory image quality (≥7/10) was obtained.

Foveal zone vessel density (VD)and parafoveal zone vessel density (for 4 quadrants: nasal, temporal, superior, inferior) were calculated for both superficial (SCP) and deep capillary plexuses (DCP). Additionally, CC flow area and FAZ were calculated.

Previously defined retinal and choroidal layers, which were automatically identified by the software algorithm, were used.[8] Upper and lower boundaries of the SCP were 3 $\mu$m below internal limiting membrane and 15 $\mu$m below inner plexiform layer, respectively. DCP was defined as the region between 15 to 70 $\mu$m below inner plexiform layer. Upper and lower boundaries of the CC layer were as follows: 30 and 60 $\mu$m below retinal pigment epithelium, respectively.

Foveal zone VD was defined as the percent density of vessels in a small circle with a 1-mm diameter. The parafoveal zone VD was defined as the percent density of vessels in the area within the 3-mm diameter circle excluding foveal zone. For the calculation of VD, binary image of the blood vessels was extracted from the greyscale OCTA image by AngioVue Analytics software. Then, the percentage of pixels with flow signal greater than a specific threshold was calculated for the related region and layer. The zones were automatically divided into quadrants (temporal, nasal, inferior, and superior).

FAZ area was defined as the area without vessels within the fovea and automatically calculated by the device. CC flow area was defined as the area in the 6 × 6 mm macular angiogram within CC layer with evidence of flow, which was also calculated by the device.

### Statistical analysis

Statistical analysis was carried out using Number Cruncher Statistical System 2007 Statistical Software package program (NCSS, LLC, Kaysville, Utah). Continuous data are presented as mean (±standard deviation), while categorical data is presented as percentage. Shapiro–Wilk test was used to test the normality of continuous variables. Continuous variables with normal distribution were compared using Student's $t$ test for independent samples. $\chi^2$ test was used to compare qualitative data. A $p < 0.05$ was considered statistically significant.

**Table 1—Age and sex distribution of the groups**

| | Control group (n = 27) | | COVID-19 group (n = 27) | | $p$-value |
|---|---|---|---|---|---|
| Age | 37.44 ± 10.04 | | 38.74 ± 10.70 | | 0.648* |
| Sex | | | | | |
| Male | 14 | 51.85% | 14 | 51.85% | 1† |
| Female | 13 | 48.15% | 13 | 48.15% | |

*$t$ test for independent samples.
†$\chi^2$ test.

**Table 2—OCTA measurements of the groups**

| | Control group (n = 27) | COVID-19 group (n = 27) | *p*-value* |
|---|---|---|---|
| Parafoveal superficial superior VD (%) | 51.82 ± 3.37 | 49.85 ± 4.88 | **0.017** |
| Parafoveal superficial inferior VD (%) | 51.52 ± 4.00 | 50.16 ± 4.20 | 0.089 |
| Parafoveal superficial nasal VD (%) | 49.99 ± 4.01 | 47.75 ± 4.29 | **0.006** |
| Parafoveal superficial temporal VD (%) | 48.80 ± 4.18 | 47.32 ± 3.90 | 0.064 |
| Parafoveal deep superior VD (%) | 55.16 ± 3.70 | 52.40 ± 4.38 | **0.001** |
| Parafoveal deep inferior VD (%) | 54.44 ± 3.73 | 52.42 ± 4.28 | **0.011** |
| Parafoveal deep nasal VD (%) | 55.08 ± 3.89 | 53.16 ± 3.92 | **0.012** |
| Parafoveal deep temporal VD (%) | 54.78 ± 3.73 | 53.10 ± 3.60 | **0.021** |
| Superficial foveal VD (%) | 17.64 ± 5.51 | 17.70 ± 7.33 | 0.963 |
| Deep foveal VD (%) | 33.91 ± 7.03 | 32.44 ± 8.39 | 0.323 |
| CC flow area ($mm^2$) | 2.08 ± 0.11 | 2.15 ± 0.23 | **0.042** |
| FAZ ($mm^2$) | 0.29 ± 0.11 | 0.30 ± 0.14 | 0.493 |

OCTA, optical coherence tomography angiography; VD, vessel density; CC, choriocapillaris; FAZ, foveal avascular zone.
Bolded *p*-values below 0.05 were considered statistically significant.
**t* test for independent samples.

## Results

Fifty-four eyes of 27 recently treated COVID-19 patients were included in the study group, and 54 eyes of 27 healthy volunteers were included in the control group. All contacted COVID-19 patients accepted to participate and were admitted for initial study assessments. The 2 groups did not differ regarding mean age and sex distribution (Table 1). All patients had signal strength index (SSI) ≥7. Additionally, the 2 groups did not differ regarding SSI values: 8.2 ± 0.7 for controls versus 8.3 ± 0.7 for patients ($p = 0.514$).

The foveal and parafoveal VD percentage values of the SCP and DCP, FAZ measurements, and CC flow area values are presented in Table 2. For the parafoveal area in the study group, VD was significantly lower in the superior and nasal quadrants of the SCP and in all quadrants of the DCP, compared with controls ($p < 0.05$ for all). The study group had significantly higher CC flow area values than controls ($p = 0.042$).

## Discussion

This study demonstrated that patients with a recent history of COVID-19 had lower VD in the parafoveal SCP at the superior and nasal quadrants and lower VD in the parafoveal DCP at all 4 quadrants compared with controls. On the other hand, CC flow area values were higher in these patients.

Studies on OCTA findings in patients infected with SARS-Cov-2 are relatively scarce. In a recent study by Abrishami et al., OCTA was performed at least 2 weeks after recovery from systemic COVID-19 and mean SCP VD and DCP VD were significantly reduced in the COVID-19 cohort versus the age-matched controls.[2] FAZ area was also greater in the COVID group, but this did not reach statistical significance. In the present study, where all patients were hospitalized in contrast to the study by Abrishami et al., parafoveal SCP VD (nasal and superior quadrants) and DCP VD (all 4 quadrants) values were significantly lower compared with controls, whereas an increase in CC flow area was evident, but the 2 groups were similar in terms of FAZ. Sousa et al. reported that changes in oxygen saturation did not cause significant changes in foveal VD values as assessed by OCTA.[9]

Invernizzi et al. found retinal hemorrhages, cotton wool spots, dilated veins, and an increase in vascular tortuosity in patients with COVID-19.[10] Although the authors stated that such findings indicating microangiopathy might be secondary to COVID-19 or incidental, they also speculated that the virus itself or the systemic treatments used might have triggered microangiopathy in patients with systemic vascular disease.[10] Virgo et al. found paracentral acute middle maculopathy and acute macular neuroretinopathy lesions in 2 cases who recently had COVID-19 infection, which may indicate ischemic events in different retinal capillary beds.[11]

A disseminated intravascular coagulation–like hypercoagulable state and a vasculitis–like process caused by direct viral infection of the endothelial cell leading diffuse endothelial inflammation appear to be the 2 main mechanisms resulting in vascular damage in COVID-19.[12] COVID-19 patients seem to have a tendency for embolism caused by intravascular coagulation and hypoxia, which may result in end-organ failure.[13] Additionally, tissue damage also may be caused by microvascular alterations due to the inflammatory response to COVID-19.[14] Although the lungs are considered the main target organ of COVID-19, the virus can affect many other organs, including the heart, blood vessels, kidneys, intestines, and the brain, through a variety of mechanisms.[15]

Potential involvement of internal/external retinal layers and the vitreous by COVID-19 has also been previously reported.[16] Viral RNA of SARS-CoV-2 has been detected in the retina.[17] In a study in which PCR analysis was performed on the tears of SARS-CoV-2-infected individuals, 3 of 12 patients showed virus fragments during the active phase of the disease.[3] These findings suggest that COVID-19 may lead to retinal vasculitis and ischemia. Systemic ischemic effects of COVID-19 and demonstration of the virus in retina suggest that multiple mechanisms may be responsible for the decreased VD found in this study. Retina and choroid are the tissues with the highest vascularization per area unit in the body. Therefore, the effects of pathophysiologic processes of systemic diseases such as inflammation and ischemia can be locally observed in these 2 tissues. COVID-19 is associated with widespread microangiopathy; thus, it has the potential to cause impairment of blood flow in retina and CC.

So far, many studies have been done on the effects of systemic diseases on retinal and choroidal perfusion. The effects of the changes in oxygen and carbon dioxide values on retinal vessel diameter have been studied in many studies. Several Doppler studies reported vasoconstriction of

retinal vessels in association with hyperoxia.[18,19] A decrease in flow area in response to hyperoxia has been found in studies using the new technique OCTA.[20] Additionally, hypercapnia, which is known to have vasodilator effect has been shown to effect choroidal perfusion in the study by Hayreh et al.[21] The increase in CC flow found in this study seems to be a reactive vasodilation response to hypoxia due to the ischemia of the choroid tissue supplying external retinal layers. Additionally, systemic factors of inflammation might have resulted in increased choroidal blood flow since the choroid is not autoregulated like the retina; therefore, it is more susceptible to systemic changes.

This study had several limitations including the limited number of patients included in the study. The cohort may not have been representative of the larger population of COVID-19 patients and the small sample size may have reduced generalizability of the findings. Our data was collected immediately after the active infection following recovery but without any longitudinal follow-up. Examining the changes during the acute phase would also be valuable. Additionally, lack of longitudinal follow-up precludes the validation of the findings and the long-term changes that the infection might cause in the CC and retina remain unknown. OCTA has some technical limitations. OCTA technology can evaluate only a limited area of the retinal posterior pole. Although not critical, once wide-angle OCTA is developed, new studies can be performed to assess more peripheral retinal regions. Additionally, OCTA cannot measure oxygen saturation in retinal and choroidal vessels; however, examining the correlation between vascular density/flow area changes and changes in saturation would provide valuable information. On the other hand, this is the first study to make such a comparison between hospitalized PCR-positive COVID-19 patients and healthy controls, similar in characteristics such as age and sex.

## Conclusion

The present study found that the VD percentages of the parafoveal SCP in the superior and nasal quadrants and the DCP in all 4 quadrants were lower in patients with PCR-positive COVID-19, whereas CC flow area values were higher. Multicenter and long-term studies with multiple subgroups of patients are required to understand the pathogenesis of the systemic and local changes caused by COVID-19.

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## Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

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