• Clinical Research •

COVID-19's effects on microvascular structure in a healthy retina: an OCTA study

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Abstract

● **AIM:** To examine the subclinical alterations in the retina and choroid between patients with 2019 coronavirus disease (COVID-19)-related lung involvement and the healthy control group.

● **METHODS:** In this prospective case-control study, 85 cases with lung involvement due to COVID-19 and 50 healthy cases were included. Best-corrected visual acuity, intraocular pressure measurement, and anterior and posterior segment examination were performed on both eyes for each individual. Choroidal and retinal changes were examined and recorded by optical coherence tomography angiography.

● **RESULTS:** All choroidal thickness measurements of the COVID-19 group showed no statistically significant difference when compared to healthy individuals. When vascular density and perfusion density values were compared, there was a decrease in the average of these values in the COVID-19 group, although it was not statistically significant (*P*=0.088, *P*=0.065 respectively). When the fovea avascular zone (FAZ) area values were compared, the average was 0.57±0.38 in the COVID-19 group, while it was 0.54±0.24 in the control group.

● **CONCLUSION:** Although our data are not statistically significant, the decrease in vascularity and perfusion and the accompanying FAZ expansion are detected in the acute period (1st month). These changes may anatomically alter the retina in the long term and affect functional vision. Future ischemia-related alterations in the retina caused by a prior COVID-19 infection may arise in situations without comorbidities and may require concern in the patient's systemic assessment.

● **KEYWORDS:** COVID-19; pneumonia; perfusion density; vascular density; optical coherence tomography angiography
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INTRODUCTION

The World Health Organization recognized the 2019 coronavirus disease (COVID-19), which affects millions of people globally and is brought on by the acute respiratory syndrome coronavirus 19 (SARS-CoV2), to be a pandemic in March of that year. While COVID-19 disease mainly affects the respiratory system, it has the potential to affect other systems as well. Angiotensin-converting enzyme 2 (ACE2), which is expressed in most tissues and located on the surface of the host cell, is the binding site through which SARS-CoV2 enters the cell[1]. In the human body, ACE2 receptors are found in blood vessels, immune system, lungs, central nervous system, nose, cornea, conjunctiva and retina[2-4]. In the retina, ACE2 is present in the vascular endothelium, ganglion cells, Müller glia, and neurons in the inner nuclear layer[5]. Additionally, CD147-spike protein, which is highly expressed in the retina, was identified as the entry pathway of the virus[6]. Cytokine oversecretion and microvascular endothelial damage are thought to be among the mechanisms causing multiorgan failure in patients with COVID-19[7]. The blood-retina barrier's fundamental functions are largely carried out by vascular endothelial cells. Cytokine oversecretion causes ischemia, inflammation, tissue edema and prothrombotic conditions[7-8]. While dilated veins, tortuous vessels, hemorrhages and cotton

wool spots can be observed in the retina due to COVID-19, microvascular changes may continue 6mo after discharge, while the fundus appears normal[9-10].

A non-invasive imaging technique called optical coherence tomography angiography (OCTA) enables the assessment of possible microvascular alterations in the retina by providing high-resolution images of the flow in the deep and superficial capillary plexuses of the retina. It enables the qualitative and quantitative examination of ischemic changes in the macula[11].

This study contrasts age-matched healthy controls with subclinical abnormalities in the retina and choroid of SARS-CoV2 positive patients with lung involvement using OCTA recordings in order to discover potential issues with retinal microcirculation.

This study was aim to examine subclinical retinal microvascular changes with OCTA in patients with COVID-19 lung involvement and no lesions on fundus examination.

PARTICIPANTS AND METHODS

Ethical Approval The ophthalmology and infectious diseases clinics of İzmir Katip Çelebi University Atatürk Training and Research Hospital hosted the prospective study. The research was approved by Izmir Katip Celebi University Ethics Committee (İKC Non-Invasive Clinical Research Ethics Committee Decision Form: 09.07.2020/0041). Every study participant received a comprehensive explanation of the study protocol. Participants provided signed informed consent.

The cohort of patients with COVID-19 comprised 85 willing participants with moderate pulmonary involvement as determined by thoracic computed tomography (CT) among those receiving in-hospital care. The presence of ground glass density less than 3 cm in three or fewer foci in the thoracic CT interpretation, which is utilized as an imaging modality, indicates mild pneumonia. Moderate pneumonia is defined as consolidation, more than three foci, or ground glass density more than 3 cm. Every lobe in both lungs is involved, and at least three lesions measuring more than three centimeters were identified as severe pneumonia. A 5-15 L/min mask was used to provide noninvasive oxygen assistance to the patients. Apart from oxygen support, the patients were administered the following medications: dexamethasone (1×6 mg, intramuscularly for 10d), favipiravir (2×1600 mg on the first day, 2×600 mg for the next 4d), azithromycin (1×500 mg on the first day, 1×250 mg for the next 4d), and enoxaparin sodium (1×0.4 mL, equivalent to 4000 anti-Xa IU, 10d). At that time, the patients were advised to follow this particular regimen of therapy. The control group comprised 50 subjects with no chronic disease and consisted of healthy patients who came to the ophthalmology department for a standard eye checkup and whose blood tests showed negative immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies for COVID-19 and who had not previously been vaccinated against COVID-19. The positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) result validated the diagnosis of SARS-CoV2 infection. PCR analysis was carried out on samples obtained from nasopharynx swabs using the Bio-speedy SARS-CoV2 (2019-nCoV) identification kit (Bioksen, Istanbul, Turkiye). Recovery of the clinical situation, laboratory and radiological improvement, no need for oxygen support on room air, and following two negative oropharyngeal swabs in a row, considered as full recovery. Four weeks following their hospital discharge, the COVID-19 patients were sent to the eye outpatient clinic based on a negative RT-PCR report.

The following criteria were used to exclude individuals from both groups: spherical and cylindrical refractive error greater than ±2 diopters; visual acuity of less than 20/20 (Snellen); keratoconus, corneal opacity, pseudoexfoliation, cataracts, or any media opacity affecting scan or image quality; eyes with an axial length of between 21 and 24 mm; intraocular pressure greater than 21 mm Hg; macular and optic nerve disease, retinal vascular disease, prior ocular surgery, ocular trauma, uveitis, and retinal degenerations. In order to detect subclinical effects, cases with visual acuity of 20/20 (Snellen) and without additional ophthalmological pathology as mentioned above were included in the study. Patients with any chronic disease also excluded from both COVID-19 and the control groups.

Patients with systemic diseases, long-term medication, smoking, or chronic alcohol use-all of which potentially impair the perfusion and vascularization of the retina and choroidal layers-were excluded from both groups.

Every patient received a bilateral ophthalmic examination, which included retinal fundus examination, intraocular pressure measurement (Goldman tonometry), slit lamp biomicroscopy, and best corrected visual acuity. An RS-3000 Advance equipment (NIDEK Co., Ltd., Tokyo, Japan) was used to obtain OCTA images (Figure 1). Macular cube regions measuring 3 mm×3 mm and 6 mm×6 mm, each with 256 B-scans, were generated by using the fovea as the internal fixation source. Next, using the same methodology as the Early Treatment Diabetic Retinopathy Study, the macula was split into inner, outer, central, and full subgroups in a 6 mm×6 mm region. For every subgroup in the superficial capillary plexus layer, automated measurements of vessel density (VD) and perfusion density (PD) were acquired. Furthermore, the area, perimeter, and circularity values of the fovea avascular zone (FAZ) were noted. Three more choroidal measures, 600 μm from the nasal and temporal areas' centers, were obtained in order to ascertain the subfoveal choroidal thickness (Figure 2). Following the collecting of all patient data, a random eye from each patient was chosen and enrolled in the study.

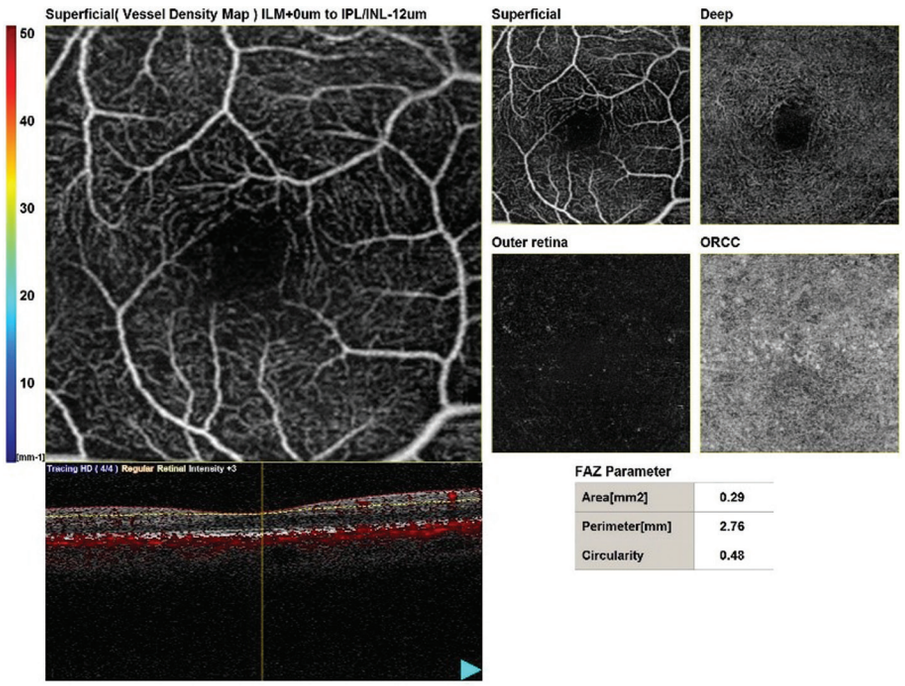

Figure 1 Representative OCTA measurement analysis of COVID-19 patients and control subjects OCTA: Optical coherence tomography angiography; COVID-19: 2019 coronavirus disease.

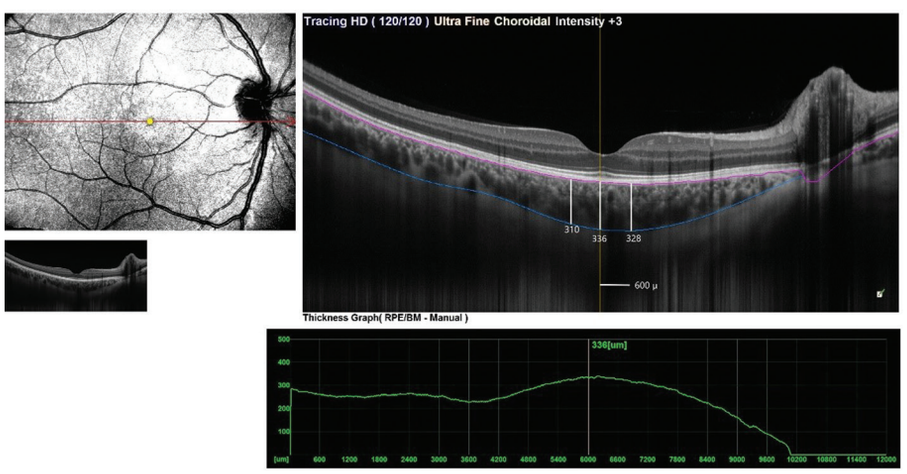

Figure 2 Representative choroidal measurement analysis of COVID-19 patients and control subjects COVID-19: 2019 coronavirus disease.

Statistical Analysis The sample size at the stage of planning of the study was calculated using the G*Power 3.1.9 program. During the planning process; no research was found that was exactly same to our study design, and general presuppositions were used for calculation. When the calculation is made assuming power =80%, effect size =0.5 (medium effect fort test) and alpha error =0.05; it was determined that our study could be conducted with at least 51 patients in each group. Considering possible losses due to missing data, 50% additional patients were included in the case group. For continuous variables, the data were reported as mean±standard deviation (SD), and for categorical variables, as number (*n*, %). The Kolmogorov-Smirnov and Shapiro-Wilk (n<50) tests were used to determine normality. For the purpose of comparing numerical variables, the independent-sample *t* test was utilized if a normal distribution was appropriate, and the Mann-Whitney test if it was not. The Chi-square test was utilized for evaluating categorical variables. Two continuous variables were compared using correlation analysis. A statistically significant result was defined as a *P* value less than 0.05. IBM SPSS Statistics for Windows, version 22.0, was used for statistical analysis (IBM Corp., Armonk, NY; USA).

RESULTS

In our study, the COVID-19 positive group with lung involvement consisted of a total of 85 patients, 34 women and 51 men. The control group consists of a total of 50 patients, 24 women and 26 men. While the average age of the control group is 44.8±5.8, the average age of the COVID-19 group with lung involvement is 44.7±11.7.

When the choroidal thicknesses of both groups were compared, no statistically significant difference was found between the groups, while subfoveal and temporal choroidal

Table 1 Comparison of the choroidal and macular thickness measurements, between the COVID-19 and control groups mean±SD

Parameters	COVID-19 (*n*=85)	Control (*n*=50)	*P*
Age (y)	44.7±11.7	44.8±5.8	0.919
Subfoveal choroidal thickness (μm)	336.11±68.64	335.66±80.78	0.973
Nasal 600 μm choroidal thickness	327.08±66.92	330.52±78.18	0.787
Temporal 600 μm choroidal thickness	334.28±68.45	328.92±81.87	0.684
Foveal macular thickness (μm)	264.37±21.05	261.84±19.73	0.490
Avarage macular thickness (μm)	316.34±13.60	317.00±13.15	0.785

COVID-19: 2019 coronavirus disease; SD: Standard deviation.

thickness was found to be higher in the COVID-19 group (*P*=0.973, *P*=0.684). While the central macular thickness was 261.84±19.73 in the control group, it was found to be 264.37±21.05 in the COVID-19 group (Table 1).

When the VD values were compared, the whole VD average of the COVID-19 group was recorded as 8.06±1.98, while the control group was found to be 8.55±1.30 (*P*=0.088). Similarly, VD values of the COVID-19 group were found to be lower than the control group in the inner, outer and central quadrants.

When the average PD values of the COVID-19 group and the control group were examined, it was observed that perfusion decreased in the group with COVID-19. While the whole PD value was 38.22±9.36 in the COVID-19 group, this value was recorded as 40.62±5.56 in the control group (*P*=0.065; Table 2). PD values in other quadrants were similarly found to be lower in the COVID-19 group than in the control group, but no statistically significant difference was detected.

When the FAZ area values were compared, it was determined that it was wider in the COVID-19 group than the average of control cases. When the correlation between the whole PD-FAZ area and the whole VD-FAZ area was examined, it was determined that there was a moderate and negative correlation in both (Table 2; *P*<0.001, spearman correlation coefficient: -0.467; *P*<0.001, spearman correlation coefficient: -0.478).

Table 2 Comparison of the macular optical coherence tomography angiography measurements, between the COVID-19 and control groups

Parameters	COVID-19 (*n*=85)	Control (*n*=50)	*P*
Vessel density (mm^{-1})			
Center	3.38±1.88	3.95±1.75	0.084
Inner	7.71±2.29	8.17±1.73	0.223
Outer	9.58±1.92	9.98±1.00	0.114
Full	8.06±1.98	8.55±1.30	0.088
Perfusion density			
Center	14.21±8.59	15.54±7.66	0.366
Inner	35.80±10.70	38.50±7.09	0.115
Outer	46.60±9.26	48.19±5.24	0.206
Full	38.22±9.36	40.62±5.56	0.065
FAZ			
Area (mm^2)	0.57±0.38	0.54±0.24	0.546
Perimeter (mm)	4.53±2.02	4.26±1.70	0.421
Circularity index	0.36±0.11	0.37±0.10	0.800

COVID-19: 2019 coronavirus disease; FAZ: Foveal avascular zone.

DISCUSSION

A growing number of research indicates that retinal microcirculation is impacted by SARS-CoV2 infection through thrombosis and vasculitis[12-13]. Non-anastomotic terminal vessels make up the retinal plexuses. Furthermore, the retina is especially vulnerable to ischemia since it is an extension of the central nervous system and has a high energy requirement[14-15]. According to earlier reports, COVID-19 patients may experience central retinal vein occlusion, central retinal artery occlusion, vein branch occlusion, and artery branch occlusion[16-18]. Moreover, studies utilizing an electron microscope on the enucleated eyes of patients who died from COVID-19 have demonstrated that the virus can harm retinal structures by piercing the blood-retinal barrier[19].

This study was conducted to examine subclinical, microvascular changes with OCTA in patients with COVID-19 lung involvement and no lesions on fundus examination. There are very few studies in the literature examining patients with COVID-related pulmonary involvement and no comorbidities. Since VD, PD and FAZ data vary depending on age and gender, a control group with no difference in these characteristics was created in this study and its findings were compared with the COVID-19 group[20]. Patients with comorbidities were not included in the COVID-19 group. Thus, it was aimed to reveal the relationship of the findings with COVID-19 more clearly.

When the choroidal thicknesses of the patients are compared, we see that the subfoveal choroidal thickness and the choroidal thickness 600 microns temporal to the fovea increased in the group that had COVID-19. Prior research has demonstrated that hypoxia and inflammation cause an increase in choroidal thickness in COVID-19 patients during the acute phase[21]. However, this change is not statistically significant in our study. Since we examined COVID-19 in the acute phase, we think that the inflammation it causes may contribute to the minimal, statistically non-significant alteration. In longer-term studies, results showing thinning of the choroid are also available in the literature. Sumer and Subasi[22] reported

decrease in choroidal thickness of COVID-19 patients in the 6-month follow-up. We think that while inflammation developing in the acute phase may lead to thickening of the choroid, thinning of the choroid may occur with the regression of inflammation in the long term.

Damage to endothelium cells and the thrombotic microangiopathy that follows induce microvascular occlusion, which can lead to hypercoagulation and multiple organ failure. Previous study indicates that the thrombotic microangiopathy associated with COVID-19 may lead to impairment to vascular perfusion in both the superficial and deep capillary plexus. In their investigation, Dipu *et al*[23] observed a decrease in VD and PD values in individuals experiencing severe systemic symptoms due to COVID-19, while Zapata *et al*[24] discovered a relationship between the decrease in VD and the severity of systemic disease due to COVID-19. There may be a correlation between the severity of lung involvement and the decrease in PD and VD. In a study conducted with pediatric COVID-19 cases, it was shown that there was a decrease in vascularity and perfusion even though there was no pulmonary involvement[25]. Another study showed that there was a decrease in these values in patients with mild and moderate COVID-19[20]. Even in the acute period, macular vascularity and perfusion may be impacted. The results of our investigation showed that the COVID-19 group had lower VD and PD in each quadrant. This finding adds to the evidence that COVID-19 affects the retina during the acute phase. When we examined COVID-19 in the acute period, we observed that it had an effect on VD, although it was not statistically significant. Like in our study, Hazar *et al*'s[26] revealed that VD dropped after one month, and this decrease was determined to be statistically significant. Furthermore, VDs in the deep and superficial plexuses decresed in the third follow-up month, just as they had in the first month, according to a study by Abrishami *et al*[27]. Bilbao-Malavé *et al*[9] performed follow-ups up to the 6th month and revealed that the decrease in the foveal superficial capillary plexus densities was still observed. Nevertheless, Savastano *et al*[28] found no significant decrease in PD and VD by the first month of control and suggested that capillary plexus damage in the macula was reversible.

The decrease in VD may be due to microangiopathy that develops as a result of the direct invasion of the virus into the endothelial cells in the blood vessels[27]. In a study with postmortem examination, it was observed that there was a combination of viral involvement and inflammatory response in the organs[29]. Previous studies have also shown that VD increases in response to hypoxia and decreases as a result of hyperoxemia[30-31]. While oxygen support given in the acute period may be a possible mechanism for the decrease in VD, the fact that this situation continues after discharge weakens the hyperoxia mechanism theory suggested in previous studies[9,27].

In our study, VD values decreased in the COVID-19 group at the 1st month examination compared to the control group, but this decrease was not statistically significant. In order to show whether the changes in the acute period are reversible, studies recording longer-term results are necessary.

We believe that the FAZ area expands as a result of the decrease in PD of the retina as a result of the decrease in systemic saturation as a result of lung involvement due to COVID-19. In our study, the PD recorded in each quadrant decreased compared to the control group, although it was not statistically significant. Upon comparing the FAZ area averages at the superficial capillary plexus level, it was seen that the patients in the COVID-19 group had a larger FAZ area; however, this difference did not reach statistical significance. When we look at the relationship between VD and FAZ area and between PD and FAZ area, we see that there is a moderate negative correlation in both.

While there are studies in the literature in which the FAZ expansion in patients with COVID-19 is statistically significant[24,32-34], there are also publications in the literature in which there is no change in the FAZ area[26,35-37]. There are also conflicting results in studies showing long-term follow-up of FAZ expansion. Studies showing more significant FAZ expansion at the 6th month reveal the long-term effect of ischemia in the acute period[9].

Vasoconstriction, procoagulant activity, and endothelial dysfunction may cause retinal ischemia, which could lead to decrease of VD and expansion of the FAZ area. A perfusion deficit may develop in the fovea due to overall hypoxia and inflammation. Postmortem studies confirm these mechanisms we have mentioned[29]. The endothelium of tiny capillaries in numerous organs was shown to have inflammatory cells, viral components, apoptotic bodies, endotheliitis, and microvascular thrombosis, according to postmortem investigations[29].

One potential strenght of the study is that it excluded patients with comorbidities, which made it easier to interpret the results about COVID-19. Even if our analysis of the short-term findings shows noticeable improvements, this has the disadvantage of not showing the long-term effects. Chronic morphological changes in the retina could impact functional vision due to decreased vascularity, perfusion, and FAZ enlargement.

Our study has certain limitations, primarily due to the limited number of participants, a consequence of the constraints posed by the COVID-19 pandemic. Additionally, follow-up durations were relatively short, restricting the evaluation of long-term outcomes. Future studies could benefit from a larger cohort and extended follow-up periods to better assess the

evolution of examination findings over time, providing a more comprehensive understanding of the subject matter.

In conclusion, COVID-19 may disrupt the retinal microvascularity at a subclinical level in patients with lung involvement even in the acute period due to retinal ischemia resulting from vasoconstriction, procoagulant activity, and endothelial dysfunction. In the future, intravitreal or systemic vasodilator and anticoagulant treatments may be on the agenda to prevent vision loss due to retinal damage caused by COVID-19 in the chronic phase. Given that the pandemic continues, albeit quietly, and there is debate around the consequences of long COVID-19, such research is inevitably necessary also from an ophthalmology perspective.

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